EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy School

on Immunotherapy in children for the treatment of respiratory and food allergy

20 - 22 September 2018
Barcelona, Spain

ABSTRACT BOOK

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

ISAF 2018

8 - 10 November 2018
Madrid, Spain

INTERNATIONAL SEVERE ASTHMA FORUM
ISAF

4th International Severe Asthma Forum

www.eaaci.org/isaf2018

WELCOME

Dear Colleagues and Friends,

It is a great pleasure for me to host you in my home city, Barcelona for the Allergy School on Immunotherapy in Children for the Treatment of Respiratory and Food Allergy. We have prepared a programme which I hope you will enjoy. The Pediatric Section, the Immunotherapy and Food Allergy Interest Groups and the Working Group on Eosinophilic Esophagitis with the great collaboration of the juniors, have been and are continuously going to work hard for the success of the upcoming days.

Some of the best speakers within EAACI and, for sure, the most current topics in food allergy will be "dissected". Immunotherapy, our differential treatment, will be addressed by some of the best specialists in Europe. We are interested in the mechanisms of action which will lead to immunomodulation and immunotolerance, tolerance not only being one of the nicest words related to allergy but also to life. We shall be dealing with the new insights in immunotherapy for respiratory diseases, including its role in prevention, and for food allergy. Eosinophilic Esophagitis will be also treated as an adverse event in food allergy immunotherapy.

An important part of our course will be the workshops in reduced groups. We hope that you can all ask questions and make contributions in a relaxed atmosphere. Innovation and research are the cornerstones in medicine and immunotherapy is one of the subjects' most explored nowadays. The oral presentations and posters offered by our young researchers will add new concepts to our knowledge.

I want to sincerely thank you all for coming to Barcelona to take part in the Allergy School on Immunotherapy in Children for the Treatment of Respiratory and Food Allergy, to our speakers who have been chosen not only for their scientific background but also for their personal communication skills. Thank you for accepting! Also a big thank to our headquarters specialists who have been working very hard for the success of this Allergy School, not only from the scientific point of view but also from the social perspective.

And last but not least I would like to thank the industry who has collaborated with us in a very friendly way. Kind thank you to our diamond sponsor, Merck, our platinum collaborators Aimmune and DBV, to our gold sponsors Inmunotek and Diater, and to our silver sponsors Hal Allergy, Stallergenes, ALK, Leti and Allergy Therapeutics.

Montserrat Alvaro
Local Organising Chair

UPCOMING EAACI EVENTS

Annual Congress 2019

Focused Meetings

Food Allergy and Anaphylaxis Meeting (FAAM 2018)
18 – 20 October 2018
Copenhagen, Denmark
www.eaaci.org/faam2018

European Consortium on Application of Flow Cytometry in Allergy (EUROBAT 2018)
18 October 2018
Copenhagen, Denmark
www.eaaci.org/eurobat2018

International Severe Asthma Forum (ISAF 2018)
8 – 10 November 2018
Madrid, Spain
www.eaaci.org/isaf2018

European Rhinallergy Meeting (RHINA 2019)
21 – 23 March 2019
Eastbourne, United Kingdom
www.eaaci.org/rhina2019

Skin Allergy Meeting Joint meeting with ESCD (SAM 2019)
4 – 6 April 2019
Munich, Germany
www.eaaci.org/sam2019

Pediatric Allergy and Asthma Meeting (PAAM 2019)
17 – 19 October 2019
Florence, Italy
www.eaaci.org/paam2019

Allergy Schools www.eaaci.org/allergy-schools

17th EAACI Immunology Winter School
"Basic Immunology Research in Allergy and Clinical Immunology"
24 – 27 January 2019
Trysil, Norway

For more information visit www.eaaci.org or contact events@eaaci.org

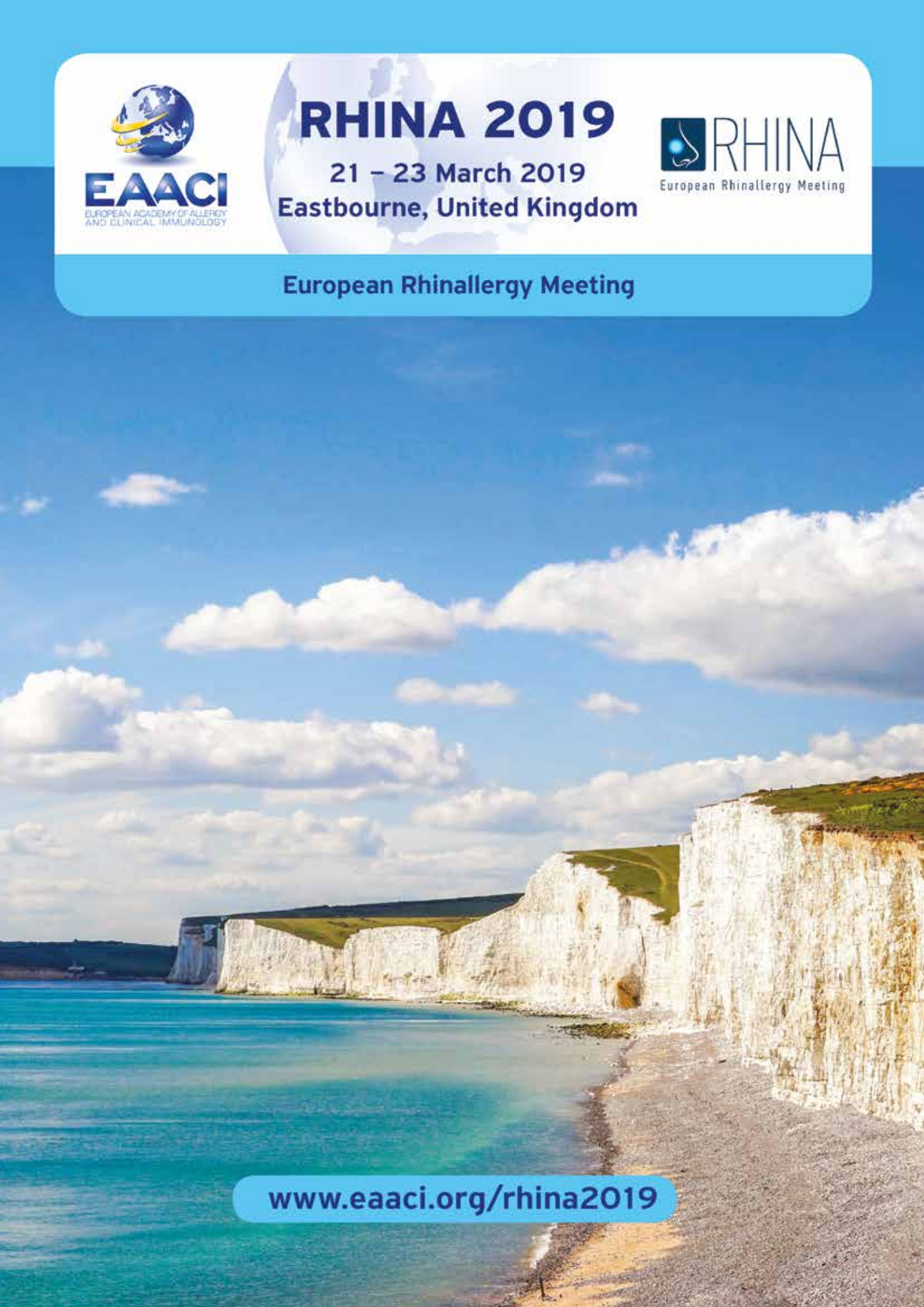
EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

RHINA 2019

21 – 23 March 2019
Eastbourne, United Kingdom

RHINA
European Rhinallergy Meeting

European Rhinallergy Meeting



www.eaaci.org/rhina2019

CONTENTS

GENERAL INFORMATION

CME Accreditation

An application has been made to the UEMS-EACCME® for CME accreditation of this EAACI Allergy School. The CME letter and the Certificate of Attendance can be downloaded after completing the survey which will be sent to you by e-mail after the school. **Please make sure you scan your badge before entering each session room, in order to obtain the CME credits.**

Potential Conflicts of Interest Declaration

Please refer to the relevant event page under the "Meetings" tab on www.eaaci.org for a full conflict of interest declaration, provided by the organising committee and faculty members.

Organising Committee

Montserrat Alvaro Lozano, Organising Chair
Carmen Riggioni, Organising Secretary
Lars Jacobsen, IG Immunotherapy Chair
Margitta Worm, IG Food Allergy Chair
Antonella Cianferoni, WG Eosinophilic Esophagitis Secretary

Poster Information

Posters can be mounted from 11:00 on Thursday, 20 September 2018 and should be removed after the last poster session on Saturday, 22 September 2018.

Please make sure to remove the poster and all poster-mounting material from the board. The organisers will remove posters not taken down on time and will not take any further responsibility for the material.

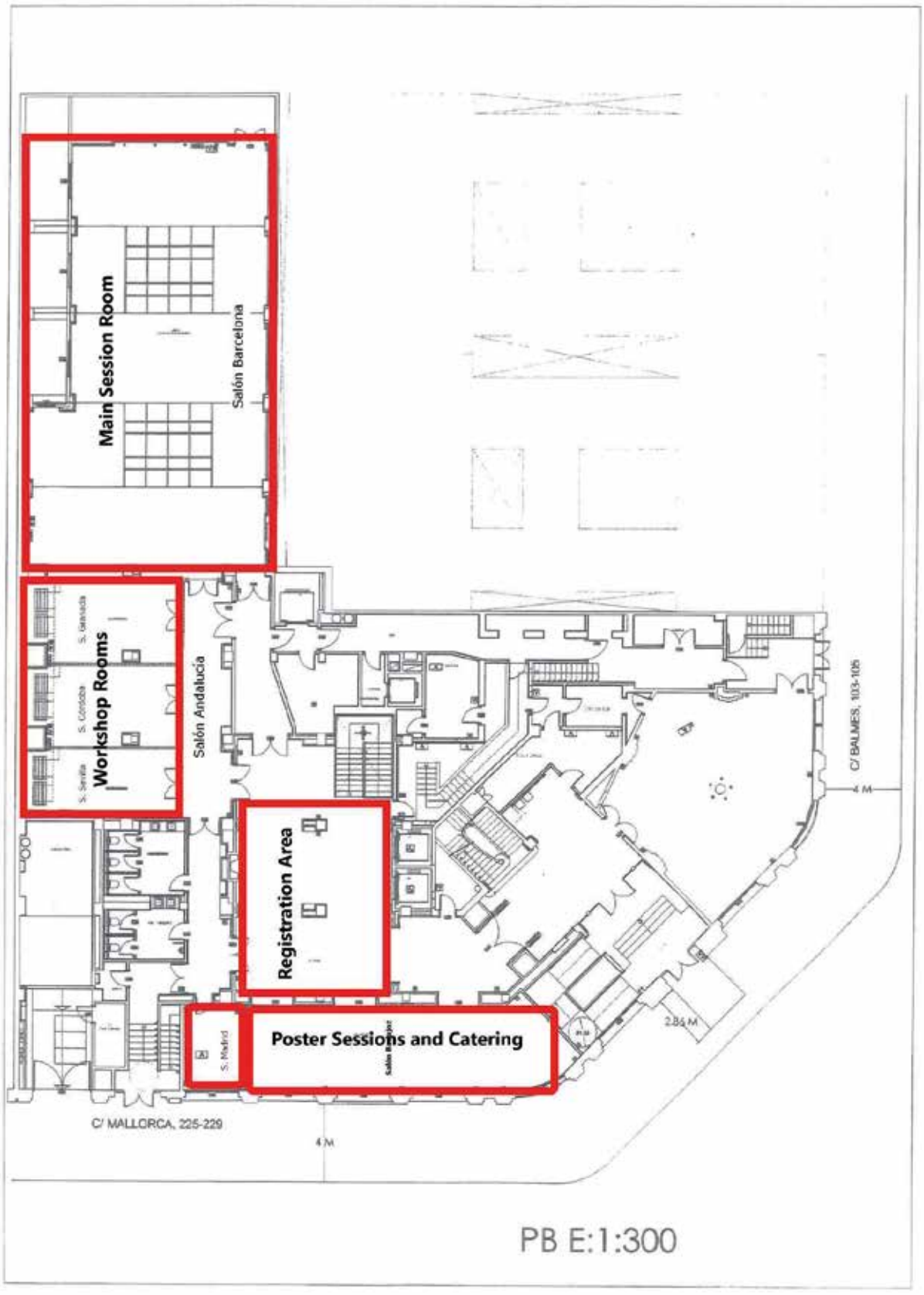
Meeting venue and accommodation

Hotel Barcelona Center
Calle de Balmes, 103-105
08008 – Barcelona
Spain
Phone: +34 93 273 00 00
Website

Contact Details

EAACI Headquarters
Hagenholzstrasse 111, 3rd Floor
8050 Zurich
Switzerland
Email: events@eaaci.org
Thomas Greif, M +41 76 383 06 51
Enna Heller, M +41 79 892 88 41

FLOOR PLAN


Main Session Room
Salón Barcelona
Workshop Rooms
S. Granada
S. Córdoba
S. Sevilla
Salón Andalucía
Registration Area
Poster Sessions and Catering
S. Madrid
C/ BALMES, 103-105
4 M
2.84 M
C/ MALLORCA, 225-229
4 M
PB E:1:300

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

SAM 2019

4 – 6 April 2019
Munich, Germany

sam
SKIN ALLERGY MEETING

Skin Allergy Meeting

Joint meeting

EUROPEAN SOCIETY OF CONTACT DERMATITIS

www.eaaci.org/sam2019

SCIENTIFIC PROGRAMME

Thursday, 20 September 2018

13:00 - 15:00	Registration
15:00 - 15:05	Welcome address *Montserrat Alvaro, Spain*
15:05 - 16:30	**Session I - Basic science in allergen immunotherapy (AIT)** *Chairs: Montserrat Alvaro, Spain / Lars Jacobsen, Denmark*
15:05 - 15:25	Immunotherapy: are there any differences between adults and children? *Mohamed Shamji, United Kingdom*
15:25 - 15:45	New strategies in AIT biomarkers based on metabolomics *Domingo Barber, Spain*
15:45 - 16:05	Biomarkers of desensitation/tolerance in food allergy AIT *Carmen Riggioni, Spain*
16:05 - 16:30	Open debate with speakers
16:30 - 17:00	Coffee break
17:00 - 18:30	**Session II - Uses of AIT in respiratory allergy** *Chairs: Oliver Pfaar, Germany / Mohamed Shamji, UK*
17:00 - 17:20	Preventive effect of AIT over the atopic march *Susanne Halken, Denmark*
17:20 - 17:40	What is the evidence in AIT for allergic rhinitis in children? *Graham Roberts, United Kingdom*
17:40 - 18:00	What is the evidence in AIT for asthma in children? *Pablo Rodríguez del Río, Spain*
18:00 - 18:30	Open debate with speakers
20:00 - 23:00	Welcome reception

Friday, 21 September 2018

08:30 - 10:00 **Session III - Present and future of respiratory AIT**
Chairs: Graham Roberts, United Kingdom / Carmen Riggioni, Spain

08:30 - 08:50 Advances in adjuvants for AIT
Mohamed Shamji, United Kingdom

08:50 - 09:10 The role of placebo effect in AIT
Lars Jacobsen, Denmark

09:10 - 09:30 Current standards in AIT clinical trial design and future needs
Oliver Pfaar, Germany

09:30 - 10:00 Open debate with speakers

10:00 - 10:30 Coffee break

10:30 - 12:20 **Practical workshops I**

Sevilla Topic 1: Mixing allergens / Treating the polysensitized patient
Chairs: Domingo Barber, Spain; Lars Jacobsen, Denmark

Cordoba Topic 2: Provocation tests to inhalant allergens
Chairs: Oliver Pfaar, Germany; Ozlem Cavkaytar, Turkey

Granada Topic 3: How to set up an inhalant immunotherapy service
Chairs: Graham Roberts, United Kingdom; Alberto Alvarez-Perea, Spain

12:20 – 13:45 Lunch

13:45 - 14:45 **Poster discussion Session I**
Chairs: Margitta Worm, Germany / Pasquale Comberiati, Italy

P01 - Fraction Of Exhaled Nitric Oxide In Children Undergoing Allergen Immunotherapy For IgE-Mediated Food Allergy: Towards Precision Medicin
Stefania Arasi, Italy

P02 – Macroarray Diagnostic And Sublingual Allergen Specific Immunotherapy Of Polysensitization Children
Olena Viktorivna Sharikadze, Ukraine

P03 – Adherence To Sublingual Immunotherapy In Real-Life
Polina Y. Shahid, Bulgaria

P04 - Oral Immunotherapy On Children With Cow's Milk Allergy
Alexandra Rodrigues, Portugal

P05 – Sublingual Immunotherapy with Pru P 3 – Review of 7 Cases
Maria Joao Vasconcelo, Portugal

P06 – Steroid Sparing Effect Of Sublingual Immunotherapy: Real Life Study In Mono/Polisensitized Children With Asthma
Nilufer Galip, Cyprus

P07 – Sensitization Pattern To Aeroallergens And Food Allergens Among Pediatric Patients With Common Allergic Diseases
Pauline Florence Robles Santos Estrella, Spain

14:45 - 16:15 **Session IV - Strategies for treating food allergy**
Chairs: Antonella Muraro, Italy / Montserrat Alvaro, Spain

14:45 - 15:05 The five Ws in food AIT: who, what, when, where and why?
Marta Vazquez-Ortiz, United Kingdom

15:05 - 15:25 Challenges in developing IT in Non-IgE mediated food allergies
Antonella Cianferoni, United States

15:25 - 15:45 Food AIT, beyond the oral route
Giovanni Pajno, Italy

15:45 - 16:15 Open debate with speakers

16:15 - 16:45 Coffee break

16:45 - 17:45 **Pro-con debate - To treat or not to treat. Food AIT: is it worth it?**
Chairs: *Alberto Alvarez-Perea, Spain / Carmen Riggioni, Spain*

Pro: *Pablo Rodríguez del Río, Spain*
Con: *Margitta Worm, Germany*

17:45 - 19:15 **Oral abstract presentation from participants**
Chairs: Antonella Cianferoni, United States / Susanne Halken, Denmark

17:45 – 18:00 O01 - Intensity Of Pain Associated With Subcutaneous Administration Immunotherapy In Pediatric Age
Cristiana Cancela Ferreira, Portugal

18:00 – 18:15 O02 - Up-Dosing Phase Of A Cooked-Egg Oral Immunotherapy Protocol: Improving Security
Daniella Gereda Martinez, Spain

18:15 – 18:30 O03 - Deep Immunophenotyping Of Early And Late Cellular Events Shows Tolerance Induction By Successful High Dose CpG-Based Immunotherapy In A Murine Asthma Model
Guillem Montamat, Luxembourg

18:30 – 18:45 O04 - Eosinophilic Esophagitis In Paediatric Patients Undergoing Oral Immunotherapy For IgE-Mediated Milk Allergy
Mireia Arnan, Spain

18:45 – 19:00 O05 - Immunological Changes On Maintenance Phase Of Oral Immunotherapy With Cooked Hen´s Egg In Pediatric Patients
Jorge Alejandro Mauledoux, Spain

19:00 – 19:15 O06 - 1,25-Dihydroxy Vitamin D3 Adjuvant Enhances Sublingual Immunotherapy Efficiency In Pediatric Asthma: A Controlled Clinical Trial
Lobna Abdelaziz Abdelazim Abdelaziz El-Korashi, Egypt

20:00 - 24:00 Dinner with guided tour

Saturday, 22 September 2018

08:30 - 10:20 **Practical workshops II**

Sevilla — Topic 4: Oral immunotherapy (OIT) in milk allergy
Chairs: Antonella Muraro, Italy; Giovanni Pajno, Italy

Cordoba — Topic 5: OIT in egg allergy
Chairs: Alberto Alvarez-Perea, Spain; Carmen Riggioni, Spain

Granada — Topic 6: AIT in peanut allergy
Chairs: Pasquale Comberiati, Italy; Marta Vazquez-Ortiz, United Kingdom

10:20 - 10:45 Coffee break

10:45 - 11:45 **Poster discussion Session II**
Chairs: Ozlem Cavkaytar, Turkey / Domingo Barber, Spain

P08 - Evaluation Of IL-10/IL-17 Ratio As A Predictor Of Response To Allergen Immunotherapy In Children With Allergic Rhinitis
Catalina Cojanu, Romania

P09 - Oral Immunotherapy for milk allergy using omalizumab: A Case Report
Yadira Y Gordón Trigueros, Spain

P10 – Pediatric Anaphylaxis Cases Due To Allergen Immunotherapy In Tartu: A Single-Center Experience
Anneli Larionova, Estonia

P11 – The Efficacy Of SLIT With Ambrosia And Artemisia In Children With Allergic Rhinoconjunctivitis
Hanna Kasianenko, Ukraine

P12 – Factors That May Influence The Adherence On Specific Immunotherapy For The Treatment Of Allergic Respiratory Disease: A Pilot Study
Ingrid Johana Gil-Serrano, Spain

P13 - Utility Of Specific Allergen Immunotherapy On Physician's Prescription Of Medication Among Children With Allergic Rhinitis
Prapasri Kulalert, Thailand

P14 - Acceptance Of Sublinguial Immunotherapy By Parents For Their House Dust Mite Sensitive Children With Recurrent Wheeze And Or Nocturnal Cough
Purushotam Dan, India

P15 - Evaluation Of PD-1 Expression On Different Subpopulations Of T-Lymphocytes In Donors And Patients With Allergic Rhinitis
Nadezhda Knauer, Russia

11:45 - 13:15	**Session V - Present and future of food allergy AIT** *Chairs: Giovanni Pajno, Italy / Pablo Rodríguez del Río, Spain*
11:45 – 12:05	The increasing interest of industry in food immunotherapy *Antonella Muraro, Italy*
12:05 - 12:25	Eosinophilic esophagitis as an adverse event after OIT. How to deal with it *Antonella Cianferoni, United States*
12:25 - 12:45	The future of food allergy IT *Marta Vazquez-Ortiz, United Kingdom*
12:45 - 13:15	Open debate with speakers
13:15 - 13:30	Closing remarks *Montserrat Alvaro, Spain*

ABSTRACTS

Friday, 21 September 2018
Poster Discussion Session I
13:45 – 14:45

P01 - Fraction Of Exhaled Nitric Oxide In Children Undergoing Allergen Immunotherapy For IgE-Mediated Food Allergy: Towards Precision Medicine

Stefania Arasi, Lucia Caminiti, Giuseppe Crisafulli, Laura Cannavò, Giulia Cafarella, Giovanni B Pajno
University of Messina, Messina, Italy

Background

The fraction of exhaled nitric oxide (eFeNO) is a non-invasive tool correlating to allergic airways inflammation and has been independently associated with increased food-specific IgE and the outcome of a food challenge. Oral immunotherapy (OIT) is the only active effective treatment for food allergy (FA). However, there are stil many gaps in OIT treatment. Furthermore, asthma is one of the major risk factors for OIT outcome. To our best knowledge this is the first study reporting the longitudinal evaluation of eFeNO in a pediatric cohort undergoing OIT.

Materials and methods

Prospective evaluation of eFeNO and sIgE with/without spirometry in collaborating children suffering from severe persistent IgE-mediated FA: before, during (half of the mantainance dose) and after a consolidate OIT protocol to cow's milk (CM) or hen's egg (HE). Informed written consent was obtained by parents before the treatment.

Results

We have so far enrolled 14 children (n male=10), aged 8 ± 4 (mean±SD) before the beginning of OIT with CM (n=9) and HE (n=5). Ten children have concomitant allergic asthma (A). eFeNO values have been successfully collected before, during and after OIT in each patient who completed the desensitization protocol (n=9). OIT is currently ongoing in the remaining 5 patients. Preliminary data show no significant differences in eFeNO values among the three time points. However, eFeNO values related with OIT outcomes. The highest FeNO values (>35 ppb) have been assessed in the 2 children who interrupted OIT during the build- up phase for concomitant severe A: one at the increasing dose of 17 ml and one at 150 ml of CM.

Conclusion

This preliminary data show the potential role of eFeNO in managing the up-dosing of OIT protocols in patients with bronchial hyperreactivity. This biomarker might be a

step forward in the perspective of a precision OIT, tailored on the single patients. However, this promising data need to be confirmed.

P02 - Macroarray Diagnostic And Sublingual Allergen Specific Immunotherapy Of Polysensitization Children

Olena Viktorivna Sharikadze
Shupyk National Medical academy of postgraduate education, Kiev, Ukraine

Background

The efficacy of allergen- immunotherapy in polysensitization children has not yet been fully resolved. The possibility of evaluating the full patient's sensitivity profile for making a decision about choosing a therapy regimen until recently was limited. The emergence of new diagnostic methods - gives the opportunity to review the old algorithms in the appointment of therapy. This is especially important in children.

Materials and methods

To evaluate the efficacy of the use of macro diagnostics for the appointment of an allergen immunotherapy in children.250 children aged 1-17 years with atopic dermatitis, allergic rhinitis and asthma were measured by MAD ALEX for the determination of the spectrum of sensitization to allergic components and extracts of the inhalation and food allergens to solve the issue of tactics of management and selection of the allergen of immunotherapy.

Results

In 250 examined patients, Ig E dependent reactions were found in 244 (97.6%). 25% of patients had a total IgE more than 1000 (kU/L). Sensitization to food allergens was found in 62% of which the most common were allergens - proteins of milk, eggs, fish, nuts. In 187 children, sensitization to inhalant allergens was detected. Polysensitization occurred in 165 children. Molecules of house dust mites p Der p23, Der p 7, r Der p 11 were found in 30% of patients. 15 % children has polysensitization which was associated with sensitization to minor timothy allergens Phl p7, Phl p 12.

Conclusion

The use of macro-diagnostics makes it possible to take into account the possibility of sensitization to molecules of allergens, which are crucial in the development of allergic symptoms, but are not decisive in extracts used for therapy. Knowledge of the profile of the child's sensitization allows for timely initiation of therapy taking into account the possible risks of developing side-effects and taking into account the reasons for the lack of effectiveness.

P03 - Adherence To Sublingual Immunotherapy In Real-Life

Polina Y. Shahid, Tihomir B. Mustakov
Departement of Clinical Allergy, UMHAT Alexandrovska, Sofia, Bulgaria

Background

Allergen immunotherapy (AIT) modifies the natural course and complications of allergic diseases. Adherence to therapy is important for its effectiveness, however such data is limited. Sublingual immunotherapy (SLIT), as any other long-term treatment, faces the problem of adherence and patient compliance is a major barrier to achieving optimal outcomes. The aim of our real-life study was to retrospectively evaluate adherence to sublingual immunotherapy across children of different ages.

Materials and methods

Our study population consisted of 81 children (50♂, 31♀) aged between 4 and 15 years (mean age 7.5y). AIT was indicated for respiratory allergic disorders. Sensitivity to aeroallergens such as pollens (38 children), mites (32) and molds (11) was confirmed by a positive skin prick test and specific IgE assay. Patients were divided into three groups based on their age: group A (4-6y), group B (7-12y) and group C (13-18y).

Results

Among 81 children who initiated SLIT, 47% completed 3 years of treatment and only 15% - 4 years. The total dropout rate was 53% (3rd year) and 85% (4th year). Group C showed a higher dropout rate (50%) than group A (44%) and group B (27%) did. Optimal adherence with SLIT was reached in children aged six and seven. The most common reasons for discontinuing SLIT were the inability to take the medication as scheduled, cost, concurrent illness, and adverse effects.

Conclusion

Allergen immunotherapy is relatively time-consuming and patients should receive adequate initial education about treatment duration and adherence benefits. Compliance measures such as electronic reminders and more frequent visits may be beneficial. Unsurprisingly, young children demonstrate better adherence probably due to parental involvement.

P04 - Oral Immunotherapy On Children With Cow's Milk Allergy

António Jorge Cabral, **Alexandra Rodrigues**, Carolina Freitas Fernandes, Graça Araújo, Ana Marques
Hospital Central do Funchal, Funchal, Portugal

Background

Cow's milk allergy (CMA) is the most common food allergy in young children and up to 20% maintain it until the second decade of life, representing a heavy burden for patients and their families. No cure is available and strict avoidance of the food allergen is the only therapeutic option to prevent anaphylactic reactions and to resolve chronic associated symptoms. However, the natural history is left unchanged with likely increased sensitization as well as lowering of the threshold of reactivity. Therefore an active treatment is required and oral immunotherapy (OIT) seems to be a promising treatment.

Materials and methods

Thirty nine patients with documented CMA underwent OIT according to a standardized protocol that consists in increasing doses during the day in a hospital setting. A maintenance dosage is then continued at home for roughly two weeks and, at that time, new increase in dosage is made, under medical surveillance. The final desired dosage is 200mL per day that is ideally achieved after a 12 weeks period.

Results

Compliance to treatment was satisfactory, since only 3 patients didn't complete the protocol. One refused continuation after the initiation, 2 showed symptoms during the protocol, at 5mL and 7,5mL, severe enough to prevent dose increase. Two patients are completing procedure at the time of this abstract. The remaining cases completed the program and all are now able to tolerate cow's milk without any untoward effects or need for preventive drugs. Of these, one had suspended the protocol due to allergic symptoms, but was able to finish it one year later. Allergic reactions were common during the treatment, particularly when increasing the dose, with over half of the patients showing side-effects, usually requiring medication.

Conclusion

As shown in other studies, OIT helped these patients overcome their food allergy. The protocol used represents a safe and effective alternative approach in the management of milk allergic patients. Further attempts to standardize these procedures are necessary.

P05 - Sublingual immunotherapy with Pru P 3 –review of 7 cases

Maria João Vasconcelos, Alice Coimbra, Diana Silva
Serviço de Imunoalergologia, Centro Hospitalar de São João, EPE, Porto, Portugal

Background

In the Mediterranean area, lipid transfer protein (LTP) is a pan-allergen often associated with persistent severe systemic reactions. In this region, a large percentage of patients with food-dependent exercise induced anaphylaxis (FDEIA) are sensitized to LTP. The risk of severe reactions and the potential to react to a progressive number of LTP containing food makes this an important target for specific sublingual immunotherapy (SLIT) with the presumed primary culprit sensitizer - Pru p 3.

Aim

Evaluation of the management of patients with confirmed LTP food allergy treated with SLITPru p 3 and assessment of its efficacy and safety.

Materials and methods

A review of all patients treated with SLIT Pru p 3 between 2013 and 2016. The protocol was used according to the manufacturer's recommendations (Bioportugal®, ALK-Abelló). Efficacy was defined as negative peach challenge between 6 and 12 months of treatment and/or by negative oral challenges with previously allergic food. Adverse reactions were classified according to WAO grading system.

Results

Seven patients, 57% female, all with anaphylaxis to fresh fruits (peach, apple, orange) and/or walnuts and with positive LTP skin tests and/or specific IgE, (median of Pru p 3of 8.8 interquartile range [4.2-18.5] ISU) were included. The median age of onset of symptoms was 15 [12-19] years. During the 4-day build-up phase, 86% presented oral pruritis and/or angioedema and one presented a grade 2 systemic reaction. During the maintenance phase, no systemic reactions were reported. One patient completed the treatment successfully (36 months), 3 are currently under SLIT (12, 22 and 27 months of treatment) and 4 patients discontinued treatment (8, 12, 14 and 17 months). Two reported adherence difficulties, 1 emigrated and 1 stopped due to persistent symptoms. Tolerance to other LTP containing foods such as apple, strawberry, walnut, and hazelnut was achieved. Even in those who did not complete the treatment, tolerance to peach and other foods was maintained, even with exercise.

Conclusion

Immunotherapy with peach allergen extract was an effective and safe therapeutic option, even after twelve months of treatment, in this group of patients with Pru p 3 sensitization. Peach and other fresh fruits or walnuts that previously caused symptoms were tolerated. Oral tolerance induction was not confirmed, but desensitization was maintained even after stopping treatment

P06 - Steroid Sparing Effect Of Sublingual Immunotherapy: Real Life Study In Mono/Polisensitized Children With Asthma

Nilufer Galip(1), Arzu Babayigit(2), Nerin Nadir Bahceciler(2)
1. University of Kyrenia, Kyrenia, Cyprus
2. Near East University, Nicosia, Cyprus

Background

Retained modifying effect of AIT is tempting especially for pediatric allergists, as their major goal is to prevent asthma or cure asthma in the long-term. Based on the fact that, one of the major concerns of parents is corticophobia, avoidance or successful discontinuation of ICS for at least one year might be recommended as an objective parameter in evaluating the long-term success of AIT in childhood allergic respiratory diseases. Hereby, in this real life study we aimed to determine the impact of SLIT retrospectively in children with mild-moderate persistent asthma in terms of successful ICS discontinuation.

Materials and methods

All children up to 18 years of age with the diagnosis of allergic asthma with or without allergic rhinitis, followed by the Division of Paediatric Allergy and Immunology of Near East University Hospital and who were initiated allergen-specific (SLIT) between 2010-2014 were included in the study. Data on age, gender, duration of symptoms, diagnosis, number/type of allergens sensitized and mean daily dose of ICSs at initiation of IT were recorded from the Hospital database system, retrospectively. Children with maintained asthma control with no need of ICSs as controller medication for at least 6 months were defined as "ICS avoidance" patients.

Results

Ninety-children (mean±SD age 8,92±4,17yrs) were enrolled, 56,7%(n=60) being poly-sensitized. Mono, 2-simultaneous and multiple-pollen-mix allergen SLIT were prescribed in 84.4%, 17,8%, 7,8%, respectively. ICS was avoided in 70%, with no significant difference in mono/vs/poly-sensitized patients. ICS-avoidance rates in mono-allergen, pollen-mixture and 2-simultaneous-allergen SLIT were 93,6%, 83,3%, 73,7%, respectively. Longer-duration SLIT resulted in significantly more ICS-avoidance(p:0,0001).

Conclusion

SLIT with mono/multiple-mixed/simultaneous allergens in childhood asthma resulted in retained-avoidance of ICS. Steroid-sparing effect of SLIT in polysensitized children warrants further investigation.

Characteristics of the study population.

Table 1.

Age (Mean ±SD)	8,92±4,17
Gender (M/F) (%)	65.3/34.4
DIagnosis (%)	25.6
Asthma	74.4
Asthma/Rhinitis	
Sensitization patterns (%)	28.9
HDM	50
HDM+other	12.2
One pollen	6.7
>1 pollen	2.2
Other	
Sensitization Status (%)	43,3
Monosensitized	56,7
Polisensitized	
Treatment	
ICS Use (%)	64,4
Dose of ICS (mcg) (Mean /range)	426,72 (200-500)
IT regimen (%)	
Multiple	27,8 (2-36)
Indoor+ Outdoor (Simultaneous)	17,8
Mixture pollen	7,8
Mono	74,4
Compliance to the SLIT (%)	
Completed	65
Interrupted by self decision	2.2
Compulsarily interrupted*	32.2

P07 - Sensitization Pattern To Aeroallergens And Food Allergens Among Pediatric Patients With Common Allergic Diseases

Pauline Florence Robles Santos Estrella(1), Marysia Stella Tiongco Recto(2), Madeleine W Sumpaico(2), Mary Ann Roldan Castor(2)
1. St. Luke's Medical Center, Quezon City, Philippines
2. UP-PGH, Quezon City, Philippines

Background

Aeroallergens and Food allergens associated with common allergic diseases may have change through the years.

Materials and methods

Cross sectional study of pediatric patients from January 2006 to December 2011 diagnosed with allergic rhinitis, bronchial asthma, atopic dermatitis and/or urticaria to determine the frequency of aeroallergens and/or food allergens.

Results

Two hundred eighty nine patients were included in the study. There were 180 male (62%) and 109 female (38%). The mean age was 9.07 years + 4.4 SD. Some patients were tested for aeroallergens or food allergens only. The frequency of common aeroallergens were as follows: Indoor – housedustmite 215/289 (74%), cockroach 147/289 (51%) and cat's hair 32/289 (11%). Outdoor allergens were grouped into grasses, weeds and tree pollens. Most common were as follows respectively: Johnson grass (Sorghum jalepense) 33/289 (11%), pigweed (Amaranthus spinosus) and mango tree pollen (Mangifera indica) 15/289 (5%). Food allergens were as follows: crabmeat and bagoong alamang 18/110 (16%), squid 13/110 (12%), shrimp 12/110 (11%), eggwhite 7/110 (6%), mussel 6/110 (5%), peanut and oyster 5/110 (4.5%), chocolate, cow's milk, chicken and rice grain 4/110 (4%).

Conclusion

Compared to previous studies, dustmite remains to be the most common indoor aeroallergen. There were no changes in the frequency of allergens associated with common allergic condition through the years.

O01 - Intensity Of Pain Associated With Subcutaneous Administration Immunotherapy In Pediatric Age

Cristiana Ferreira(1), Isabel Rezende(2), Arminda Guilherme(1), Ines Lopes(1)
1. CHVNG/E, Gaia, Portugal
2. CHPORTO, Porto, Portugal

Background

Allergen immunotherapy is the only treatment that can safely and effectively change the natural history of allergic diseases. In the literature, there are few studies evaluating the perception of pain associated with the administration of subcutaneous immunotherapy with allergens.

Materials and methods

To evaluate the intensity of pain associated with the subcutaneous injection of allergen immunotherapy in a paediatric population with respiratory allergy treated with allergen subcutaneous immunotherapy, followed in an Immunoallergology outpatient clinic. Possible correlations between the intensity of pain with demographic and clinical factors and/or manifested adverse reactions were also analysed.

During 4 consecutive weeks, nurses performed the evaluation of pain associated with subcutaneous injections of allergen immunotherapy in children (7 to 16 years-old), trought an anonymous questionnaire. This questionnaire used 2 different pain evaluation scales, according to the children's age: the selfreporting faces scale (score 0 to 10; 5 to 8 years of age) and the numeric scale (score 0 to 10; >8 year-old) and also identify any relation with demographic data, clinical data and with the occurrence of any adverse reactions.

Results

Of the fourty six patients included most were males, with rhinitis/rhinoconjuntivitis, receiving subcutaneous immunotherapy with mites. Doses varied between 0.25 and 0.5 mL. Seven local adverse reactions were recorded, all of them mild. 22% of patients did not mention any pain. Of the 36 patients that mentioned some pain, 33 indicated mild pain and only 3 rated pain as moderate. The median pain referred was 1 and the mean was 1.5. The maximum pain reported was of 6. No other significant differences in pain scores were noted between different groups of patients even considering patients with and without local reactions or in patient receiving divided injections in both arms.

Conclusion

In this study, subcutaneous allergen immunotherapy was shown to be only a mildly painful procedure, associated with only a few local reactions and therefore being a safe option for most of our allergic pediatrics patients.

O02 - Up-Dosing Phase Of A Cooked-Egg Oral Immunotherapy Protocol: Improving Security

Daniella Gereda, Adrianna Machinena, Jorge Mauledoux, Jaime Lozano, Davinia Vasquez, Mar Folque, Ana Maria Plaza, Montserrat Alvaro
Hospital Sant Joan de Deu, Barcelona, Spain

Background

Our group has previously published data regarding safety in a raw egg-OIT protocol, reporting adverse reactions in 7.6% of doses and many studies reported early discontinuation due to severe adverse events. More information about cooked egg (CE) Oral immunotherapy (OIT) safety is needed.

Aim

To evaluate the safety of the up-dosing phase of a CE-OIT protocol.

Materials and methods

Retrospective study. Children over 5 years with egg-allergy, clinical history, positive skin prick test (SPT ≥ 3 mm) and specific IgE (s-IgE > 0.35 KU/L) with a confirming oral food challenge (OFC) were included. All underwent a 28 step CE-OIT protocol, beginning with a 4-day initial schedule (18 steps) following up-dosing weekly intervals (10 steps) reaching a total dose of one well-done omelette (7.5g of egg protein). Patients did not receive pre medication. Data were collected for demographics, s-IgE, SPT, adverse events at OFC, and all dose-related reactions were registered during the up-dosing phase.

Results

43 children, 70% boys. Median age at OFC: 9 years (7-12). 53.5% had other food allergies, 46.5% atopic dermatitis, 42% asthma, 21% allergic rhinitis. Median at baseline: total IgE 612 KU/L (243-1611), egg-white s-IgE 6.22 (1.87, 24.85), ovomucoid s-IgE 3.8 (1.8- 14.1), egg-white SPT 10.4 mm (7.4-12.6) and ovomucoid SPT 9.6 mm (7.3-11.7). 55.8% were anaphylactic before beginning our protocol. At OFC 51% of patients presented anaphylaxis (39.5% mild, 11.5% moderate), 41.9% urticaria, and 4.7% gastrointestinal symptoms. Only 2 patients did not perform OFC because of recent anaphylaxis. 76.7% of patients managed to finish the up-dosing phase, 23.3% withdrew. 6044 doses were administrated and adverse events occurred

in 3% of the doses. 7.3 % of adverse events/dose occurred within withdrawals while 1.4% occurred in patients who finished up-dosing phase. 28% had 1 anaphylaxis, 11.6% presented 2 or more anaphylaxis. Epinephrine was required in 14% of children. 100% of patients, who needed 2 or more epinephrines, dropped off our protocol. Only 1 patient required 4 epinephrines. From withdrawals 90% were anaphylactic at the initial OFC. 1 patient (4%) dropped off because he moved away. No significant difference was found in total IgE, s-IgE nor SPT between withdrawals and active patients.

Conclusion

We find our protocol a safer procedure than raw egg OIT, given the lower reaction/dose ratio. Discontinuation was associated with frequent mild- moderate reactions and anaphylaxis at OFC. All children who needed two or more epinephrines dropped off our CE-OIT protocol.

O03 - Deep Immunophenotyping Of Early And Late Cellular Events Shows Tolerance Induction By Successful High Dose CpG-Based Immunotherapy In A Murine Asthma Model

Guillem Montamat, Cathy Leonard, Olivia Domingues, Caroline Davril, Justine Heckendorn, Coralie Guerin, Markus Ollert
Luxemboug Institute of Health, Esch-Sur-Alzette, Luxembourg

Background

Allergen-specific immunotherapy (AIT) is the only curative treatment for perennial allergic rhinitis/asthma which can restore allergen immune tolerance with long term effects. CpG oligodeoxynucleotides (CpG-ODN) is a promising adjuvant for AIT shown to induce immune tolerance at high doses. Applying these properties to an AIT model, a successful high dose CpG-based AIT (hCpG-AIT) has been established in a murine allergic asthma model to the major cat allergen Fel d 1. This study aims to deeply phenotype cellular events at two crucial steps of this immunotherapy.

Materials and methods

Mice were sensitized by three i.p. injections containing a mixture of Fel d 1 and alum. Subsequently, the animals received three i.p injections of immunotherapy using a solution of Fel d 1 and CpG-ODN (1.05mg/kg). Finally, an allergen airway challenge was performed through nasal instillation. Twenty-four hours after the first AIT injection, spleen, mediastinal lymph nodes (MLN) and peritoneal cavity cells were isolated. Cells were also extracted from lungs, MLN and spleen after the complete course of hCpG-AIT and subsequent challenge. All the samples were immunophenotyped by mass cytometry. Three groups of animals were analyzed: allergic, hCpG-AIT treated and control.

Results

After the first CpG-AIT injection, the percentage of plasmacytoid dendritic cells (pDCs) was increased by 3-fold in the spleen and by 20-fold in the MLN in the hCpG-AIT group. Upon complete hCpG-AIT, a clear improvement of allergic parameters was found in the lungs, among which the relative numbers of eosinophils and mast cells were reduced by 20- and 10-fold respectively. High CpG-AIT also reduced the IL-13 expression from lung Th2 cells by 2-fold. In MLN, hCpG-AIT diminished the relative number of B cells by 20% and their CD69 expression by 50%. In addition, hCpG-AIT decreased the Gata3 expression in MLN Th2 cells by 50%. In the spleen, hCpG-AIT induced a 25% increase of the Treg ratio and a 15% increase of FoxP3 expression in these cells.

Conclusion

Using mass cytometry, a single cell high throughput immunophenotyping technology, we studied the early and late immune cell events in a high dose CpG-based AIT model. The analyses of the early events showed that hCpG-AIT caused pDCs upregulation in lymphoid organs. The characterization of the late events revealed a reduction of the allergic effector cells and Th2 response as well as the induction of systemic tolerance. These results will help to further understand how high dose CpG AIT modulates the immune system towards tolerance.

O04 - Eosinophilic Esophagitis In Paediatric Patients Undergoing Oral Immunotherapy For IgE-Mediated Milk Allergy

Mireia Arnan, Rosa Jiménez, Carmen Riggioni, Olga Dominguez, Monica Piquer, Yadira Gordon, Ana Maria Plaza, Montserrat Alvaro
Hospital Sant Joan de Déu, Barcelona, Spain

Background

Oral immunotherapy (OIT) has emerged as a promising allergen-specific therapy for patients with IgE-mediated food allergy, however it´s possible adverse events such as eosinophilic esophagitis (EoE) are still under investigation. Our aim was to describe clinical characteristics, evolution and treatment of children diagnosed with EoE during milk-OIT for IgE-mediated milk allergy.

Materials and methods

Retrospective study including IgE-mediated milk allergic patients, under 18 years of age, who underwent milk–OIT from 2007 to 2015. Follow-up was based on hospital protocol (approved by the ethics committee) and endoscopy was performed in all children who showed symptoms compatible with EoE. EoE diagnosis and treatment response was assessed histologically according to EAACI criteria 2011.

Results

178 children that underwent milk-OIT were recruited. EoE was confirmed in 3.37% of patients (n=6 /178), 50% were male. 50% of patients had multiple food allergies, 83% were sensitized to pneumoallergens and 33% had asthma. Median age at milk-OIT onset was 7.3yrs (range 4.4-13.8yrs). Median time between beginning milk-OIT and symptoms suggesting EoE was 6.63yrs (range 1-month to 9.29yrs). Median time between starting milk-OIT and EoE diagnosis was 7.9yrs (range 3.4 months to 9.8yrs). Most common symptoms were abdominal pain (4/6), dysphagia (3/6), impaction (2/6) and vomit (2/6). All patients who presented abdominal pain associated other symptoms.

With regards to treatment:

Three patients were PPI (proton pump inhibitor) responsive and none required withdraw of daily dose of milk to control EoE. Other two patients (also continuing milk doses), have responded to swallowed corticosteroids, and are currently undergoing treatment with PPI and waiting a re-evaluation. Dietary therapy was followed by the last patient (milk exclusion, 6-food and elemental diet) after trying PPI without response, and EoE resolution was only achived with swallowed corticosteroids.

Conclusion

In our population, milk-OIT children were diagnosed with EoE in 3.7% of patients. PPIs were a usefull first line treatment for patients with EoE+OIT. None of these patients required milk exclusion diet to control their esophagitis, being able to continue the treatment with milk in all cases. Our results confirm the need for long-term follow-up of patients undergoing milk-OIT. Whenever gastrointestinal symptoms are present, EoE should be ruled out. The exact role of milk-OIT as a trigger for EoE needs to be further investigated using prospective, longitudinal properly designed trials.

O05 – Immunological Changes On Maintenance Phase Of Oral Immunotherapy With Cooked Hen´s Egg In Pediatric Patients

Jorge Alejandro Mauledoux, Adriana Machinena, Daniella Gereda, Jaime Lozano, Mar Folque, Marcia Dias, Ana Plaza, Montserrat Alvaro
Hospital Sant Joan de Deu, Barcelona, Spain

Background

Strict avoidance diet is the only accepted management for egg allergic children. Oral immunotherapy (OIT) might be an optional treatment, in order to achieve egg desensitization. Immunological positive markers of desensitization development might be measured as a predictor of success in OIT.

OBJETIVES: To describe immunological changes during, at least, a six month period of maintenance phase.

Materials and methods

Retrospective study and follow-up of egg allergic patients included in oral immunotherapy (OIT) with cooked hen´s egg. Allergic children over 5 years with a positive clinical history and skin prick test (SPT ≥ 3 mm) and/or specific IgE (sIgE > 0.35 KU/L) and a positive oral food challenge (OFC) were included. Clinical symptoms at OFC and in maintenance phase were registered. Measurement of s-IgE and SPT for hen´s egg and components: ovalbumin, ovomucoid, egg-white and yolk were obtained before the up-dosing phase (T0) and after 6 months period of maintenance phase (T1), taking 1 whole egg in a well-cooked omelet (7.5 gr of protein) 3 times a week by protocol. Non-parametric wilcoxon test was done for analysis.

Results

22 patients were included, 63.6% male. 54.5% had other food allergies, 50% atopic dermatitis, 31.8% asthma and 13.6% allergic rhinitis. Median age at the beginning of the protocol was 8y (SD 2.71). All patients underwent an OFC and 50% had anaphylaxis; epinephrine was administrated in 11.1% of them. The first control in maintenance phase (T1) was done at a mean time of 10.6 months (SD 2.76). In this period of OIT, 31.8% (n=7) had suffered anaphylaxis (6 mild, 1 moderate), no epinephrine was administrated, 30% had needed oral antihistaminic and 20% inhaled salbutamol. Statistical significance between s-IgE at T0 vs T1 was obtained: egg-white (80.2 vs 6.3 KU/L (p <0.001)); ovomucoid (20.3 vs 14.1 (p <0.001)); ovoalbumin (42.5 vs 2.1 (p <0.001)). Likewise for SPT: egg-white (9.9 vs 6.5 mm (p 0.009)); ovoalbumin (7.5 vs 4.3 mm (p 0.005)); ovomucoid (9.2 vs 6.4 (p 0.003)).

Conclusion

Immunological changes were obtained in both s-IgE and SPT for components of hen's egg with significant differences after, at least, 6 months of maintenance phase cooked egg OIT. By contrast on previous studies with raw egg OIT, no statistically significant results were obtained. It is necessary to continue a prolonged follow-up of these patients to determine the success of OIT.

O06 - 1,25-Dihydroxy Vitamin D3 Adjuvant Enhances Sublingual Immunotherapy Efficiency In Pediatric Asthma: A Controlled Clinical Trial

Lobna Abdelaziz Abdelazim Abdelaziz El-Korashi, Ola Elsayed Nafae, Lamiaa Gaber Zake, Nana Abdelrahman Mohamed
Zagazig University, Zagazig, Egypt

Background

Sublingual immunotherapy (SLIT) is an efficient and safe treatment for bronchial asthma which its immune mechanisms have been well investigated in the last few years. In this approach, gradually cumulated doses of the allergen are required to achieve clinical efficiency. 1,25-dihydroxy vitamin D3 is one of SLIT adjuvants that have been considered in improving the allergen availability to the immune system in order to enhance the SLIT efficiency and decrease the allergen dosing. Some murine models proved the role of 1,25-dihydroxy vitamin D3 in enhancing SLIT efficiency (1), although few clinical studies have been conducted in small cohorts of patients to test it in humans. Therefore, we evaluated the effect of combining 1,25-dihydroxy vitamin D3 with natural allergen extract of mixed grass pollens-specific SLIT in asthmatic children.

Materials and methods

Forty children, aged 5-18 years, with bronchial asthma were included in 6 months, randomized, placebo-controlled trial. The case group (n=20) received mixed grass pollen- specific SLIT adjuvanted with vitamin D while the placebo group (n=20) received natural allergen extract of mixed grass pollens-specific SLIT without any adjuvant. We assessed serum level of IL10 and IL17 before and after SLIT in both groups. Secondary outcomes including lung function, and serum level of Calcifediol were also measured.

Objectives: To compare the clinical efficiency and the serum level of IL10 and IL17 in children with bronchial asthma received mixed grass pollens -specific SLIT adjuvanted with 1,25-dihydroxy vitamin D3 with placebo group.

Results

When compared with the placebo group, SLIT adjuvanted with vitamin D group therapy showed more significant reduction of asthma symptoms and the medication score ($P < 0.001$ We also observed more significant reduction in serum level IL-17 (case group, $P = 0.032$; placebo group, $P = 0.021$) and more significant elevation in serum IL-10 level in the case group (case group, $P < 0.001$; placebo group, $P = 0.001$). We reported a significant improvement of forced expiratory volume in one second in the both groups (case group, $P = 0.012$; placebo group, P =0 .017) and there was a significant increase in serum level of Calcifediol in the case group ($P = 0.046$).

Conclusion

SLIT adjuvanted with vitamin D is an effective and safe modality of immunotherapy in treating pediatric asthma.

P08 - Evaluation Of IL-10/IL-17 Ratio As A Predictor Of Response To Allergen Immunotherapy In Children With Allergic Rhinitis

Catalina Cojanu(1), Liliana Rogozea(2), Ioana Agache(3)
1. Theramed Medical Center, Brasov, Romania
2. Transylvania University, Brasov, Romania
3. Faculty of Medicine, Brasov, Romania

Background

Allergic rhinitis (AR) is efficiently treated using allergen immunotherapy (AIT). No clinical or immunological biomarkers are validated as predictors of successful AIT. Increased serum IL-17 was suggested as a predictor of poor response to AIT in children with AR. IL-10 is described as a biomarker of induction of immune tolerance via AIT. Our hypothesis was that high IL-10/low IL-17 ratio is related to response to AIT.

Materials and methods

We evaluated 16 children with AR (mean age 8.13 ± 3.07 years old) ,13 (81%) boys, undergoing subcutaneous AIT (SCIT) for at least 2 years with house dust mites (14 cases, 87.5%) and grasses (2 cases, 12,5%). SCIT responders were defined as having no symptoms after natural allergen exposure, negative skin prick test and negative nasal provocation test for the SCIT allergen. Serum levels of IL-17 and IL-10 were measured using commercially available quantitative sandwich enzyme immunoassays. High IL-10/low IL-17 ratio at the end of SCIT was evaluated as a predictor of SCIT success in multiple regression analysis together with age at SCIT start, duration of SCIT, sensitization pattern (mono-/polysensitized), lack of asthma association, allergen type (seasonal/perennial), allergen avoidance, compliance to SCIT schedule, level of sensitization (low/high), low levels of serum IL-17.

Results

5 (31.3%) AR children fulfilled the criteria for SCIT responder. Serum IL-10 levels were increased in all patients receiving SCIT but with mean values higher in responders. 4 children had high serum IL-17, and all were non-responders. 12 children had a high IL-10/low IL-17 ratio, 5 of which were responders and 7 non-responders. All 4 cases with high IL-10/high IL-17 were encountered only in non-responders. However in the multiple regression analysis high IL-10/low IL-17 ratio did not reach statistical significance.

Conclusion

High IL-10/low IL-17 ratio did not predict response to SCIT in children with allergic rhinitis

P09 - Oral Immunotherapy for milk allergy using omalizumab: A case report

Yadira Y Gordón Trigueros, Carmen Riggioni Viquez, Olga Domínguez, Monica Piquer, Davinia Vásquez, Rosa Jiménez Feijoo, Ana M Plaza, Montserrat Alvaro Lozano
Hospital Sant Joan De Deu, Barcelona, Spain

Background

Omalizumab (OMZ) is a recombinant humanized monoclonal antibody that binds IgE. Currently it's approved for treating allergic asthma and chronic spontaneous urticaria. OMZ has also been used off-label for other allergic conditions including food allergy. Studies suggest that OMZ used during oral immunotherapy (OIT) for cow's milk allergy (CMA) can decrease the time required to reach maintenance dosing and adverse events, however the length of the OMZ treatment maintenance phase is still under debate.

Case report

A 13 years old female with the diagnosis of CMA at 8 months of age, after a moderate anaphylaxis with milk formula. She followed a strict cow's milk (CM) elimination diet but suffered adverse events with hidden CM allergen resulting in 2 moderate anaphylaxis. She was first seen by our pediatric allergy team at 5 years old, when she was diagnosed with CMA, severe allergic asthma and sensitization to cat dander and house dust mites. At 6 years old, she had persisting symptoms of asthma and exacerbations despite high-dose of long acting beta agonists in combination with corticosteroids, so it was prescribed OMZ showing clinical and spirometrical improvement. Six months after beginning treatment with OMZ, she started CM-OIT following a step-up protocol. The up-dosing phase lasted 5 months, no adverse events were reported and she was able to tolerate 200 ml of CM. During the first 4 years of maintenance phase, our patient had 200 ml CM daily as well as products containing CM protein. She only presented one mild adverse reaction associated with exercise as a cofactor in the first year of maintenance phase. OMZ was finally stopped at fifth year of treatment (11 years old), at that moment she had well controlled asthma without any maintenance treatment. During the first 6 months, she had no reactions with CM. After that, she started frequent mild reactions and 3 moderate anaphylaxis to CM (1 associated with cofactor) during the next 10 months. This required gradual adjustments of the CM-OIT. Finally, the patient was able to tolerate 100 ml CM without serious adverse events for the past 4 months.

Conclusion

OMZ is effective in protecting from adverse events during OIT. This effect disappears after the discontinuation even though having been used for 5 years. Thus, patients need to be carefully monitored after OMZ withdrawal. Large clinical trials are needed with the follow-up of patients who have received combined treatment with OMZ and CM-OIT to determine the effectiveness and length of treatment.

Table 1. Evolution of specific CM-IgE and fractions

Laboratory findings	**Initial (without OMZ)**	**Year 1 (OMZ + CM-OIT)**	**Year 4 (OMZ + CM-OIT)**	**Year 6 (1 year after stopping OMZ)**
Total IgE (KUI/L)	1477,00	1012,00	796,00	367,00
Specific CM-IgE (KU/L)	1022,00	474,00	86,90	>100
α-lactalbumin (KUI/L)	20,20	-	17,00	36,50
β-lactoglobulin (KUI/L)	41,50	-	11,80	25,90
Casein (KUI/L)	1856,00	676,00	>100	>100

P10 - Pediatric Anaphylaxis Cases Due To Allergen Immunotherapy In Tartu: A Single-Center Experience

Anneli Larionova, Mari Kivivare, Maire Vasar, Kaja Julge, Tiia Voor
Children' s Clinic of Tartu University Hospital, Tartu, Estonia

Background

Allergen immunotherapy is considered an effective treatment method that has been used on rhinitis, asthma and venom anaphylaxis, but its' use is limited due to potential

of producing systemic reactions (SRs). The estimated frequency of subcutaneous immunotherapy (SCIT) related SRs is 0.1-4 % of all injections. Our aim was to assess anaphylaxis cases due to allergen immunotherapy (AIT) in our center.

Materials and methods

A retrospective review of anaphylaxis cases (ICD-10 codes T78.0 – T78.2) consulted and admitted in Children' s Clinic of Tartu University Hospital between 2010 – 2014.

Results

During the study period, there were 3 patients diagnosed AIT-associated anaphylaxis. Interestingly all three cases occurred in December 2014, which was the third month of treatment (out of pollen season) and they all had reached the same phase of treatment. All patients were male, treated with standardized depot alum – adsorbed pollen (2 tree pollen, 1 grass pollen) extracts. Injections were applied subcutaneously by the same experienced nurse. We had a total of 63 anaphylaxis patients (68% male, M:F ratio 2:1). Main anaphylaxis triggers were food (65%), insect stings (17.5%) and idiopathic anaphylaxis (6.3%), followed by less frequent cause SCIT (4.8%). According to WAO subcutaneous immunotherapy systemic reaction grading system all reactions were classified as Grade 2, involving upper and lower respiratory symptoms and cutaneous symptoms in all and gastrointestinal symptoms in one patient. All patients stopped AIT because of systemic reactions. The total number of injections of SCIT during year 2014 was 527, according to this the frequency of SCIT related systemic reactions was 0.5%. No SRs have been reported on subcutaneous immunotherapy after this period.

Conclusion

The incidence of severe systemic reactions due to SCIT is rare in our center. Although the risk factors for severe systemic reactions were absent, three anaphylactic reactions arose in a certain particular time period, which might have been caused by the properties of the allergen extract.

P11 - The Efficacy Of SLIT With Ambrosia And Artemisia In Children With Allergic Rhinoconjunctivitis

Hanna Kasianenko, Serhii Goncharuk, Yurii Bazhora
Odessa National Medical University, Odessa, Ukraine

Background

The aim of the study was to investigate the efficacy of the initial course of sublingual immunotherapy (SLIT) with ambrosia and artemisia in children with allergic rhinoconjunctivitis (ARC).

Materials and methods

We examined 330 children aged 5 to 18 years living in the southern regions of Ukraine, with ARC. Sensitization to major and minor components of weed allergens (ambrosia, artemisia) was determined using ImmunoCAP (Phadia) technology. Sensitization to the major component of ambrosia (w230 - nAmb a 1) was detected in 188 patients (58.93%), to the major component of artemisia (w231 - nArt v 1) in 48 (15.04%) patients. Combined sensitization was noted in 83 (26.01%) patients. Only 5 patients (1.52%) have sensitization to the major component of grass (g213-rPhlp1, rPhlp 5b), and 6 (1.82%) have sensitization to the minor component of grass (g214-rPhlp7, rPhlp 12). All patients with sensitization to the major components of ambrosia and artemisia (319 children) received the initial course of SLIT (Diater, Spain) after the flowering season. Criteria for exclusion from the group were: the presence of adenoid vegetations, complicated rhinosinusitis and conjunctivitis, wheezing.

Results

The efficacy of the treatment was assessed by the laboratory data after the completion of the SLIT course (sIgE, sIgG4, IgE total, ECP) in 186 patients. A decrease in sIgE was noted in 82.8%, a decrease in total IgE in 89.4%, ECP in 90.3% of patients. The increase was observed in sIgG4 in 74.7% of the subjects.
The dynamics of clinical symptoms was evaluated after one year of treatment according to the criteria: has not changed; episodic symptoms; decrease in the duration of seasonal symptoms; absence of symptoms. The initial treatment significantly reduced the symptoms of ARC and their duration in 254 children (79.6%); 12 (3.76%) episodes were occasional and 37 (11.6%) had no symptoms completely. Only in 16 (5.02%) clinical symptoms remained of the same intensity.
The amount of drug therapy (dosage of the drugs used during the flowering season) was evaluated according to the criteria: it did not change; decreased; drugs were not used. The amount of therapy did not change in 53 children (16.6%), decreased in 223 (69.9%). 41 children (12.6%) did not use medications.

Conclusion

The initial SLIT course is an effective method of treating children with seasonal ARC, which reduces the clinical symptoms, accompanied by the positive dynamics of laboratory indices, and contributes to a significant reduction in the amount of drug therapy in patients.

P12 - Factors That May Influence The Adherence On Specific Immunotherapy For The Treatment Of Allergic Respiratory Disease: A Pilot Study

Ingrid Johana Gil-Serrano, Cristina Blasco Valero, Blanca Vila-Indurain, Teresa Garriga Baraut
Pediatric allergy unit. Pediatric Pneumology section. Hospital Universitari Vall d'Hebron, Barcelona, Spain

Background

The allergic respiratory disease represents one of the most prevalent chronic disease in children; although allergen immunotherapy (AIT) has been demonstrated to be an effective treatment for the disease, there is not always a good adherence to this treatment. The aim of this study is to determine which factors may influence the adherence to AIT for allergic respiratory disease in our patients.

Materials and methods

Retrospective evaluation of 110 patients diagnosed of allergic rhinitis (AR) and/or allergic asthma (AA) on which subcutaneous AIT was first prescribed, with an inclusion period of one year. Demographical characteristics, allergological evaluation, and factors by which AIT was not initiated or not continued were evaluated.

Results

Mean age was 10 years (range=3-17), 60% (n=66) patients were males. Thirty-two percent (n=35) of the patients had AR, and 66.3% (n=73) had AA and AR. From the total patients, 9% (n=10) did not initiated AIT due to economic issues, and 6.3% (n=7) of patients did not initiated because of improvement of symptoms with conventional treatment (n=3) or parents didn't want to start this specific treatment (some of them had doubts on the efficacy of the treatment, n=4). On the other hand, 10% (n=11) of the patients who initiated the AIT did not continued the treatment, from which 1.8% (n=2) were due to economic issues, 1.8% (n=2) because of adverse events (both of them had bronchospasm), 4.5% (n=5) due to personal problems (most frequent was to have an unstable family for example divorced parents who were not able to go to each appointments), and 1.8% (n=2) for lack of response. One of the patients suspended AIT for improvement of symptoms after 8 months of treatment. As secondary findings: From all the patients, the most common composition of the AIT was House Dust Mite in 84.5% (n=93) children. Fifty-eight percent (n=64) of the patients had a complete response to AIT after a year (asymptomatic and/or needed promptly rescue medication), 13.6% (n=15) had partial response to AIT (still had some symptoms or need some rescue medication) and 5.4% (n=6) children had not responded (still had all symptoms and need all rescue medication).

Conclusion

The most influential factor for not starting AIT in our patients is due to economic problems. For patients who started AIT, the most influential factor for not continuing, was personal problems as not having a supportive family, economic issues and the presence of adverse reaction.

P13 - Utility Of Specific Allergen Immunotherapy On Physician's Prescription Of Medication Among Children With Allergic Rhinitis

Prapasri Kulalert
Division of Allergy and Immunology, Department of Pediatrics, Faculty of medicine, Thammasat University, Pathumthani, Thailand

Background

Allergic rhinitis is the common allergic disease in children. Intranasal corticosteroid, oral H1 antihistamine and antileukotirene are commonly prescribe in these children. Subcutaneous immunotherapy (SCIT) has been widely used for the treatment of allergic rhinitis in children. In daily practice, physicians usually step down medications in children who underwent immunotherapy if their clinical symptoms have well controlled. Physician's prescription patterns for allergic rhinitis medication is the appropriate parameter to show efficacy of immunotherapy. The aim of this study was to compare physician's prescription of medication before and after treatment with immunotherapy in children with allergic rhinitis.

Materials and methods

This study was a one-group, before-after design (self-controlled design) in children under 15 years old who was diagnosed allergic rhinitis and underwent allergen specific immunotherapy at the Pediatric Allergy Clinic of Thammasat Hospital, Pathumthani, Thailand. Total amount of allergic rhinitis medication 1 year before and 1 year after underwent immunotherapy were collected. The primary outcome was to compare amount of medication before and after immunotherapy. Outcome measures were analyzed using paired t-tests for normally distributed data and Wilcoxon signed-rank test for skewed data.

Results

A total chart of 10 children were reviewed, of which 7 (70%) were male. The mean age was 12.7 ± 1.6 years. 6 (60%) children were treated with mite immunotherapy, 3 (30%) children were treated with mite and cockroach immunotherapy, and 1 (10%) were treated with cockroach immunotherapy, respectively. Intranasal steroid was prescribed 8.4 ± 3.9 bottles before initiation immunotherapy and 4 ± 3.7 bottles after initiation immunotherapy, p-value < 0.01. Oral H1-antihistamine was prescribed

265.5 ± 92.9 tablets before initiation immunotherapy and 171.5 ± 94.2 tablets after initiation immunotherapy, respectively, p-value = 0.02. Oral antileukotrienes was prescribed 257.5 ± 105.8 tablets before initiation immunotherapy and 99.4 ± 90.3 tablets after initiation immunotherapy, respectively, p-value =0.01.

Conclusion

Immunotherapy is effectiveness in children with allergic rhinitis. Our studies showed pattern of physician's prescription of medication was significant decrease after treatment with immunotherapy.

P14 - Acceptance Of Sublinguial Immunotherapy By Parents For Their House Dust Mite Sensitive Children With Recurrent Wheeze And Or Nocturnal Cough

Purushotam Dan
Mandore sattelite hospital, Jodhpur, India

Background

Allergen immunotherapy is known for more than 100 years and it is only treatment strategy having disease modifying capability .But traditional subcutaneous immunotherapy is less popular in paediatric patients because of potential side effects and painful injections.We did a survey at our out patient clinic to know acceptibility of sublingual immunotherapy in parents for their symptomatic mite sensitive children.

Materials and methods

Between january 2017 to december 2017 children between age of 6 to 10 years attending our clinic with history of recurrent wheeze and nocturnal cough were tested for selected indoor allergens.Parents of house dust mite sensitive children were counselled about specific avoidance measures.They were told about potential disease modifying capability of sublingual immunotherapy,its potential benifits and short comings and then they were given option to enroll for sublingual immunotherapy for their symptomatic children.In sublingual immunotherapy we used here glycerinated extract of house dust mite.Parents were demonstrated how drop should be held under the tongue for a specific period of time,and then residual swallowed.

Results

Total 30 children tested positive for house dust mite.Out of 30 symptomatic children who were tested positive for house dust mite, 12 had parentral history of asthma or allergic rhinitis,among these parents when asked to enroll for sublingual immunotherapty, 10 out of 12 parents[>80%] enrolled for subligual immunotherapy for their children.Rest 18 parents of mite sensitive symptomatic children without parentral history of allergic disease when asked to enroll for sublingual immunothwerapy,7[>35%]chose for sublingual immunothjerapy. Overall more than

50%,17 out of 30 parents were ready to be enrolled for sublingual immunopthjerapy for their children.

Conclusion

Sublingual immunotherapy is well accepted by parents for their house dust mite sensitive symptomatic children specially more with positive parentral history.

Symptomatic house dust mite children with negative parentral history of allergic disease.	Symptomatic house dust mite children with negative parentral history of allergic disease.

P15 - Evaluation Of PD-1 Expression On Different Subpopulations Of T-Lymphocytes In Donors And Patients With Allergic Rhinitis

Nadezhda Knauer, Ekaterina Pashkina, Yulia Konyakhina, Daria Demina, Vera Nepomnyaschikh, Marina Leonova, Vladimir Kozlov
Research institute of fundamental and clinical immunology, Novosibirsk, Russia

Background

The pathogenesis of allergy includes different mechanisms, such as increasing of number of activated effector cells or decreasing of number of cells with suppressive activity. Thus, the evaluation of markers of activation and suppression such as PD-1 and CD25 on T-lymphocytes in healthy donors and patients with allergy before and after the allergen-specific immunotherapy (ASIT) can be interesting.

Materials and methods

There were 5 groups 6 persons each included in the study: healthy volunteers (group I, age 21,5 (20;28)); naïve patients with allergic rhinitis (AR) before and after the first course of ASIT (groups II and III respectively, age 32 (19;46)); patients who had previous courses of ASIT before and after the new course (groups IV and V respectively; age 36 (20;52)). All patients had sensitization to birch pollen allergens of dust mite allergens confirmed by skin prick tests. Peripheral blood mononuclear cells were extracted from heparinized blood, then they were stained for flow cytometry. Statistical analysis was made by using Mann-Whitney and Wilcoxon criteria, the result was considered as significant in the case $p<0,05$.

Results

We found the significant decrease of CD4+CD25+cells after the therapy in patients with several courses of ASIT in the past. Donors had higher amount of CD4+CD25hiPD-1+cells than patients before the first course of ASIT and patients with ASIT in the past before and after the new course. There was the significant increasing of CD4+PD-1+ cells after therapy in both groups (groups III and V). Donors had the lower amount of CD8+CD25+cells than patients. The level of CD8+CD25+PD-1+cells is less in the donors group than in patients after therapy, the amount of these cells increases significantly after therapy.

Conclusion

We found the decreasing of CD4+lymphocytes expressing CD25, which can be considered as the marker of activation, after the therapy, however the number of CD8+CD25+ cells increases in patient groups. In the same time, the number of CD4+CD25hi cells associated with the population of T-regulatory cells had higher level of PD-1-expression in donor group than in patient groups. The number of cells expressing PD-1, which can regulate negatively the immune response, increases after therapy. These results can confirm the hypothesis that allergic diseases can be associated not only with increasing the number of activated effector cells, but with reduction of subpopulations with suppressive activity. The data also demonstrate the changing of balance between activating and suppressing of immune response after the immunotherapy.

SPEAKERS' DOCUMENTS

Only to be used for individual study purposes

EAACI Guidelines on Allergen Immunotherapy: Allergic Rhinoconjunctivitis

Alberto Alvarez, Spain

Graham Roberts, United Kingdom

Accepted: 20 September 2017

DOI: 10.1111/all.13317

POSITION PAPER

WILEY Allergy

EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis

G. Roberts[1,2,3*] | O. Pfaar[4,5*] | C. A. Akdis[6,7] | I. J. Ansotegui[8] | S. R. Durham[9] | R. Gerth van Wijk[10] | S. Halken[11] | D. Larenas-Linnemann[12] | R. Pawankar[13] | C. Pitsios[14] | A. Sheikh[15] | M. Worm[16] | S. Arasi[17,18] | M. A. Calderon[9] | C. Cingi[19] | S. Dhami[20] | J. L. Fauquert[21] | E. Hamelmann[22] | P. Hellings[23,24] | L. Jacobsen[25] | E. F. Knol[26] | S. Y. Lin[27] | P. Maggina[28] | R. Mösges[29] | J. N. G. Oude Elberink[30,31] | G. B. Pajno[17] | E. A. Pastorello[32] | M. Penagos[9] | G. Rotiroti[33] | C. B. Schmidt-Weber[34] | F. Timmermans[35] | O. Tsilochristou[36] | E.-M. Varga[37] | J. N. Wilkinson[38] | A. Williams[39] | L. Zhang[40] | I. Agache[41] | E. Angier[42] | M. Fernandez-Rivas[43] | M. Jutel[44,45] | S. Lau[46] | R. van Ree[47] | D. Ryan[48] | G. J. Sturm[49,50] | A. Muraro[51]

[1]The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK

[2]NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[3]Clinical and Experimental Sciences and Human Development in Health Academic Units, Faculty of Medicine, University of Southampton, Southampton, UK

[4]Department of Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[5]Center for Rhinology and Allergology, Wiesbaden, Germany

[6]Swiss Institute of Allergy and Asthma Research (SIAF), University Zurich, Davos, Switzerland

[7]Christine Kühne Center for Allergy Research and Education, Davos, Switzerland

[8]Department of Allergy and Immunology, Hospital Quironsalud Bizkaia, Erandio, Bilbao, Spain

[9]Allergy and Clinical Immunology, National Heart and Lung Institute, Imperial College London, London, UK

[10]Section of Allergology, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

[11]Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

[12]Center of Excellence in Asthma and Allergy, Hospital Médica Sur, Mexico City, Mexico

[13]Department of Pediatrics, Nippon Medical School, Tokyo, Japan

[14]Medical School, University of Cyprus, Nicosia, Cyprus

[15]Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK

[16]Department of Dermatology and Allergy, Charité Campus Mitte, Universitätsmedizin Berlin, Berlin, Germany

[17]Department of Pediatrics, Allergy Unit, University of Messina, Messina, Italy

[18]Molecular Allergo'logy and Immunomodulation – Department of Pediatric Pneumology and Immunology, Charite Medical University, Berlin, Germany

[19]Department of Otorhinolaryngology, Medical Faculty, Eskisehir Osmangazi University, Eskisehir, Turkey

[20]Evidence Based Health Care Ltd, Edinburgh, UK

[21]CHU Clermont-Ferrand University Hospital (CHU Estaing), Unité d'allergologie de l'enfant, Clermont-Ferrand, France

[22]Children's Hospital Bethel, EvKB, Bielefeld University, Bielefeld, Germany

[23]Department of Otorhinolaryngology, University Hospitals Leuven, Leuven, Belgium

Abbreviations: AGREE II, Appraisal of Guidelines for Research & Evaluation; AIT, allergen immunotherapy; AR, allergic rhinoconjunctivitis; ARIA, Allergic Rhinitis and its Impact on Asthma; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; EPIT, epicutaneous immunotherapy; HDM, house dust mite; ICER, incremental cost-effectiveness ratio; NARES, nonallergic rhinitis with eosinophilia syndrome; QALY, quality-adjusted life years; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SMD, standardized mean difference; SmPC, summary or product characteristics; SPT, skin prick test.

*Denotes equal contribution.

[24]Department of Otorhinolaryngology, Academic Medical Center Amsterdam, Amsterdam, The Netherlands
[25]Allergy Learning and Consulting, Copenhagen, Denmark
[26]Departments of Immunology and Dermatology/Allergology, University Medical Center Utrecht, Utrecht, The Netherlands
[27]Johns Hopkins Department of Otolaryngology – Head and Neck Surgery, Baltimore, MD, USA
[28]Allergy and Clinical Immunology Unit, 2nd Department of Pediatrics, NKUA Athens University, Athens, Greece
[29]Clinical Research International Ltd, Hamburg, Germany
[30]Department of Allergology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[31]GRIAC Research Institute, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[32]Department of Allergy and Immunology, Asst Grande Ospedale Metropolitano Niguarda, University of Milano, Milano, Italy
[33]Department of Allergy and Medical Rhinology, The Royal National Throat Nose and Ear Hospital, University College Hospital, London, UK
[34]Center of Allergy and Environment (ZAUM) & Institute of Allergy Research, Helmholtz Center Munich, Munich, Germany
[35]European Anaphylaxis Taskforce – Nederlands Anafylaxis Netwerk, Dordrecht, The Netherlands
[36]Division of Asthma, Allergy and Lung Biology, Department of Paediatric Allergy, Children's Allergy Service, King's College London, Guy's and St. Thomas' National Health Service Foundation Trust, London, UK
[37]Department of Paediatric and Adolescent Medicine, Respiratory and Allergic Disease Division, Medical University of Graz, Graz, Austria
[38]Pharmaceutical Group of the European Union, Brussels, Belgium
[39]Allergy Department, Guys and St Thomas' NHS Foundation Trust, London, UK
[40]Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, Beijing, China
[41]Faculty of Medicine, Department of Allergy and Clinical Immunology, Transylvania University Brasov, Brasov, Romania
[42]Department of Clinical Immunology and Allergy, Northern General Hospital, Sheffield, UK
[43]Allergy Department, Hospital Clinico San Carlos, IdISSC, Madrid, Spain
[44]ALL-MED Medical Research Institute, Wroclaw, Poland
[45]Wroclaw Medical University, Wroclaw, Poland
[46]Department of Pediatric Pneumology and Immunology, Charité Universitätsmedizin, Berlin, Germany
[47]Departments of Experimental Immunology and of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[48]Usher Institute of Population Health Sciences and Informatics, University of Edinburgh Medical School, Edinburgh, UK
[49]Department of Dermatology and Venerology, Medical University of Graz, Graz, Austria
[50]Outpatient Allergy Clinic Reumannplatz, Vienna, Austria
[51]Department of Women and Child Health, Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region, University of Padua, Padua, Italy

Correspondence
Antonella Muraro, Department of Women and Child Health, Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region, University of Padua, Padua, Italy.
Email: muraro@centroallergiealimentari.eu

Funding information
European Academy of Allergy & Clinical Immunology; BM4SIT project, Grant/Award Number: 601763

This Guideline published by the European Academy of Allergy and Clinical Immunology (EAACI) has drawn on data from a systematic review of the literature, more recent published studies and multi-stakeholder expert clinical opinion. This Guideline is aimed at healthcare professionals who are encouraged to take the recommendations into account in the context of delivering clinical care. This Guideline is not a substitute for professional clinical judgment, which professionals need to exercise in the context of delivering personalised healthcare.

Abstract

Allergic rhinoconjunctivitis (AR) is an allergic disorder of the nose and eyes affecting about a fifth of the general population. Symptoms of AR can be controlled with allergen avoidance measures and pharmacotherapy. However, many patients continue to have ongoing symptoms and an impaired quality of life; pharmacotherapy may also induce some side-effects. Allergen immunotherapy (AIT) represents the only currently available treatment that targets the underlying pathophysiology, and it may have a disease-modifying effect. Either the subcutaneous (SCIT) or sublingual (SLIT) routes may be used. This Guideline has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on AIT for AR and is part of the EAACI presidential project "EAACI Guidelines on Allergen Immunotherapy." It aims to provide evidence-based clinical recommendations and has been informed by a formal systematic review and meta-analysis. Its generation has followed the Appraisal of Guidelines for Research and Evaluation (AGREE II) approach. The process included involvement of the full range of stakeholders. In general, broad evidence for the clinical efficacy of AIT for AR exists but a product-specific evaluation of evidence is recommended. In general, SCIT and SLIT are recommended for both seasonal and perennial AR for its short-term benefit. The strongest evidence for long-term benefit is documented for grass AIT (especially for the grass

tablets) where long-term benefit is seen. To achieve long-term efficacy, it is recommended that a minimum of 3 years of therapy is used. Many gaps in the evidence base exist, particularly around long-term benefit and use in children.

KEYWORDS
allergen immunotherapy, allergic conjunctivitis, allergic rhinitis, allergy, rhinoconjunctivitis

1 | INTRODUCTION

Allergic rhinoconjunctivitis (AR) is an allergic disorder of the nose and eyes, resulting in a chronic, mostly eosinophilic, inflammation of the nasal mucosa and conjunctiva.[1,2] Allergic rhinitis, with or without conjunctivitis, is one of the most prevalent allergic diseases affecting around a fifth of the general population.[3-5] It is associated with considerable loss of productivity and impaired school performance.[6]

Allergic rhinoconjunctivitis can usually be diagnosed from its typical presentation (Figure 1). Symptoms include itching, sneezing, watery nasal discharge, and nasal congestion.[2] Commonly, there are associated ocular symptoms (watery, red and/or itchy eyes). Symptoms may be described as seasonal and/or perennial; as intermittent or persistent; or mild, moderate or severe according to their impact on the quality of life.[8] Symptoms are related to exposure to the offending allergen as well as to nonspecific triggers such as smoke, dust, viral infections, strong odors, and cold air.[2] Symptoms on exposure to 1 or more aeroallergens supported by evidence of allergen-specific IgE sensitization to the relevant allergens confirm the diagnosis. AR may co-exist with other forms of rhinitis (Figure 1). Additionally, AR may be associated with symptoms of sinusitis, hearing problems, and asthma.[2]

The aims of AR management are to control symptoms and reduce inflammation. Where possible, allergen avoidance can be recommended. Effective allergen avoidance is, however, often not feasible.[9,10] Many patients rely on pharmacotherapy with, for example, oral or topical antihistamines, intranasal corticosteroids, topical cromoglycate, or leukotriene receptor antagonists.[2] However, these therapies do not alter the natural history of AR and may also induce side-effects. Additionally, despite medication, a significant number of patients continue to experience symptoms that impair their quality of life. Allergen immunotherapy (AIT) with the subcutaneous (SCIT) or sublingual (SLIT) administration of the culprit allergen(s) may not only desensitize a patient, thereby ameliorating symptoms, but also deliver long-term clinical benefits that may persist for years after discontinuation of treatment.[11-13]

This Guideline has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Guideline on Allergen Immunotherapy: Allergic Rhinoconjunctivitis Taskforce and is part of the EAACI Guidelines on Allergen Immunotherapy. This Guideline aims to provide evidence-based recommendations for the use of AIT

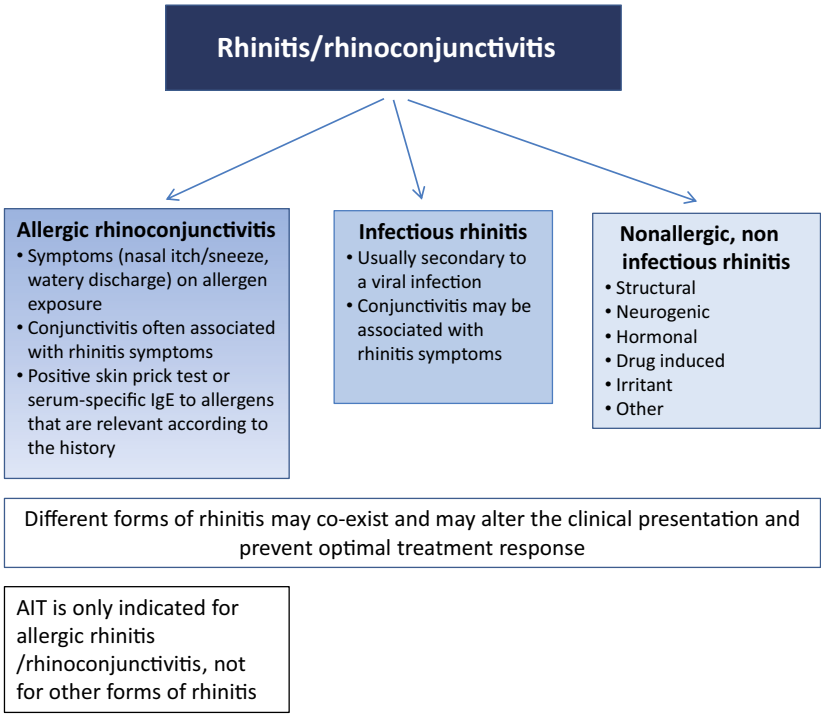


FIGURE 1 Differential diagnosis of allergic rhinoconjunctivitis. Adapted from Roberts *et al* 2013.[7] Local allergic rhinitis may be seen where there is only evidence of local nasal allergic sensitization.[15,16,26] There are numerous other causes of nonallergic, noninfectious rhinitis, an example is nonallergic rhinitis with eosinophilia syndrome (NARES). In individual patients, symptoms may be driven by more than one trigger. Rhinosinusitis is not included in the scope of this Guideline

BOX 1 Key terms

Allergen immunotherapy (AIT)	Repeated allergen administration at regular intervals to modulate immune response in order to reduce symptoms and the need of medication for clinical allergies and to prevent the development of new allergies and asthma. This is also sometimes known as allergen-specific immunotherapy, desensitization, hyposensitization, or allergy vaccination.
Conjunctivitis	Inflammation of the conjunctiva characterized by watery, itchy, red eyes.
Efficacy	*Short-term treatment efficacy*: clinical benefit to the patient while they are receiving AIT. *Long-term treatment efficacy*: clinical benefit to the patient for at least 1 y after cessation of the AIT course.[14]
Rhinitis	Inflammation of the nasal mucosa resulting in at least 2 nasal symptoms: rhinorrhea, blockage, sneezing, or itching.
Sensitization	Detectable allergen-specific IgE antibodies, either by means of skin prick test (SPT) and/or specific-IgE antibodies in a serum sample.
Subcutaneous immunotherapy (SCIT)	Form of AIT where the allergen is administered as subcutaneous injections.
Sublingual immunotherapy (SLIT)	Form of AIT where the allergen is administered under the tongue with formulation as drops or fast-dissolving tablets which are administered through the sublingual route.

for patients of all ages with allergic rhinitis with or without conjunctivitis. The term AR will henceforth be used to denote either allergic rhinitis or Allergic rhinoconjunctivitis (see Box 1 for definitions of key terms). The primary audience are clinical allergists (specialist and subspecialists); the document may also provide guidance to other healthcare professionals (e.g, physicians from other disciplines, nurses, and pharmacists working across a range of primary, secondary, and tertiary care settings) dealing with AR. The development of the Guideline has been informed by a formal systematic review (SR) and meta-analysis of AIT for AR,[14] with systematic review principles being used to identify additional evidence, where necessary.

2 | METHODOLOGY

This Guideline was produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach,[17,18] a structured approach to guideline production (see Table S1). This is designed to ensure appropriate representation of the full range of stakeholders, a careful search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations and steps to ensure that the risk of bias is minimized at each step of the process. The process started on April 2015 beginning with detailed face-to-face discussions agreeing on the process and the key clinical areas to address, followed by face-to-face meetings, and regular web conferences in which professional and lay representatives participated.

2.1 | Clarifying the scope and purpose of the guidelines

The scope of this EAACI Guideline is multifaceted, providing statements that assist clinicians in the optimal use of AIT in the management of patients with AR and identifying gaps for further research.

2.2 | Ensuring appropriate stakeholder involvement

Members of the EAACI Taskforce on AIT for AR represented a range of 18 countries and disciplinary and clinical backgrounds, including allergists (specialist and subspecialists), pediatricians, primary care specialists, ophthalmologists, otolaryngologists, pharmacists, immunologists, nurses, and patient representatives. Methodologists took the lead in undertaking the underpinning SR, while clinical academics took the lead in formulating recommendations for clinical care. Representatives of immunotherapy product manufactures were given the opportunity to review and comment on the draft guidelines as part of the peer review and public comment process at the final stage. These comments were considered by Taskforce members, and, where appropriate, revisions were made.

2.3 | Systematic reviews of the evidence

The initial full range of clinical questions that were considered important was rationalized through several rounds of iteration to agree on 1 key question: What are the effectiveness, cost-effectiveness, and safety of AIT in patients with AR? This was then pursued through a formal SR of the evidence by independent methodologists as previously published[14,19]; only double-blind RCTs were included in the effectiveness analyses. We continued to track evidence published after our SR cutoff date of October 31, 2015, and, where relevant, studies were considered by the Taskforce chairs. This evidence will formally be considered in the systematic review update that will precede the update of this Guideline (discussed below).

2.4 | Formulating recommendations

We graded the strength and consistency of key findings from the SR and performed meta-analyses, using a random-effects model to take into account the heterogeneity of findings.[14] These were used to formulate evidence-based recommendations for clinical care[20] (Box 2). This involved formulating clear recommendations with the strength of evidence underpinning each recommendation. Where the

BOX 2 Assigning levels of evidence and strength of recommendations

Level of evidence	
Level I	Systematic reviews, meta-analysis, randomized controlled trials
Level II	Two groups, non-randomized studies (e.g., cohort, case–control)
Level III	One group, non-randomized (e.g., before and after, pretest, and post-test)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case series)
Level V	Case reports and expert opinion that include narrative literature, reviews, and consensus statements
Grades of recommendation	
Grade A	Consistent level I studies
Grade B	Consistent level II or III studies or extrapolations from level I studies
Grade C	Level IV studies or extrapolations from level II or III studies
Grade D	Level V evidence or troublingly inconsistent or inconclusive studies at any level
Strength of recommendations	
Strong	Evidence from studies at low risk of bias
Moderate	Evidence from studies at moderate risk of bias
Weak	Evidence from studies at high risk of bias

Recommendations are phrased according to the strength of recommendation: strong: "is recommended"; moderate: "can be recommended"; weak: "may be recommended in specific circumstances"; negative: "cannot be recommended".

Approach adapted from Oxford Centre for Evidence-based Medicine—Levels of Evidence and Grades of Recommendations.[20] The adaptation involved providing an assessment of the risk of bias, based on the Cochrane risk of bias tool, of the underpinning evidence and highlighting other potentially relevant contextual information.

systematic review did not cover the clinical area, we took a hierarchical approach reviewing other evidence until we could formulate a recommendation, that is: (i) other systematic reviews on the subject to see whether these provided any clarity on the topic; (ii) RCTs within these systematic reviews; (iii) other RCTs known to Taskforce members; and (iv) a consensus-based approach within the Taskforce. This evidence was graded as described in Box 2 using the SR results[14] and clearly labeled in the recommendation tables. Recommendations apply to all ages unless otherwise indicated in the tables. When there were insufficient pediatric data, we extrapolated from the adult recommendation where it was biologically likely that the intervention would also be effective in children, but downgraded the recommendation by at least 1 level. Taskforce members identified the resource implications of implementing the recommendations, barriers, and facilitators to the implementation of each recommendation, advised on approaches to implementing the recommendations, and suggested audit criteria that can help with assessing organizational compliance with each recommendation.

2.5 | Peer review and public comment

A draft of these guidelines was externally peer-reviewed by invited experts from a range of organizations, countries, and professional backgrounds. Additionally, the draft guideline was made available on public domain on the EAACI Web site for a 3-week period in May 2017 to allow a broader array of stakeholders to comment. All feedback was considered by the Taskforce members and, where appropriate, final revisions were made in light of the feedback received. We will be pleased to continue to receive feedback on this guideline, which should be addressed to the corresponding author.

2.6 | Identification of evidence gaps

The process of developing this Guideline has identified a number of evidence gaps which are prioritized (Table 10).

2.7 | Editorial independence and managing conflict of interests

This Guideline was funded and supported by EAACI. The funder did not have any influence on the guideline production process, on its contents or on the decision to publish. Taskforce members' conflicts of interest were declared at the start of the process and taken into account by the taskforce chairs as recommendations were formulated. Final decisions about strength of evidence for recommendations were checked by the methodologists who had no conflict of interests in this area.

2.8 | Updating the guidelines

European Academy of Allergy and Clinical Immunology plans to update this guideline in 2022 unless there are important advances before then.

3 | GENERAL CONSIDERATIONS BEFORE INITIATING AIT FOR AR

3.1 | General considerations

Allergen immunotherapy is only indicated in the presence of symptoms strongly suggestive of AR, with or without conjunctivitis (Table 1).[8,14,21] Many patients will also have co-existing asthma. There should be symptoms on aeroallergen exposure with evidence of allergen-specific IgE sensitization (positive SPT or serum-specific IgE).[14] Identification of the allergen(s) driving symptoms is the first level of patient stratification ensuring that the correct allergen solution is used for AIT. Occasionally, SPT or specific IgE results may

TABLE 1 General considerations for allergen immunotherapy (AIT) for allergic rhinoconjunctivitis

General indications	Key references	Contextual considerations
AIT should be considered when all of these criteria are met: • Symptoms strongly suggestive of AR, with or without conjunctivitis • There is evidence of IgE sensitization (positive SPT and/or serum-specific IgE) to one or more clinically relevant allergen • Experience moderate-to-severe symptoms which interfere with usual daily activities or sleep despite regular and appropriate pharmacotherapy and/or avoidance strategies	Dhami[14]	A diagnosis of AR and evidence of IgE sensitization were entry criteria for RCTs in the systematic review.
AIT may also be considered in less severe AR where a patient wishes to take advantage of its long-term effect on AR and potential to prevent asthma with grass pollen AIT	Kristiansen[25] Halken[23]	AIT has the potential to alter the natural history of disease reducing AR symptoms after completing an adequate period of immunotherapy and preventing the development of asthma in the short term, up to 2 y post-AIT.
Standardized AIT products with evidence of efficacy in the clinical documentation should be used	Dhami[14]	These products have consistent formulations, and so different batches are likely to have similar effects. The meta-analysis[14] reveals a considerable heterogeneity in effectiveness between products, and therefore, a product-specific evaluation of efficacy is recommended.

The Summary of Product Characteristics (SmPC) should be checked for licensed indications which may differ between preparations.

not clearly identify the key allergen(s) causing the AR symptoms in polysensitized patients. Component resolved diagnostics may have a role in deciding which aeroallergen(s) should be chosen but definitive trials are awaited. An alternative approach is to use nasal or conjunctival provocation testing to prove the clinical relevance of the allergic sensitization in the relevant (target) organs before initiation of AIT but again definitive evidence is awaited.

Allergen immunotherapy is indicated in those patients with moderate-to-severe symptoms (e.g, Allergic Rhinitis and its Impact on Asthma (ARIA) categories moderate-to-severe intermittent or persistent[22]), despite avoidance measures and pharmacotherapy, that interfere with their usual daily activities or sleep. AIT may also be considered in cases with less severe AR where the patient wishes to have the benefit of its long-term effect on rhinitis and a potential disease-modifying effect to prevent asthma.[23] AIT products with evidence of efficacy for AR should be used when available.[11,24]

3.2 | Absolute and relative contraindications

Even when AIT is suitable for a patient with AR, clinicians must consider whether there are any specific patient-related absolute or relative contraindications (Table 2), where the risk from AIT may outweigh the expected benefits. The summary of product characteristics (SmPC) should be reviewed for specific contraindications for individual preparations.

4 | AIT FOR AR: EVIDENCE-BASED, CLINICAL RECOMMENDATIONS

To underpin this guideline, a SR of the AIT literature was undertaken.[14] In general, the meta-analysis suggested that both SCIT and SLIT are effective for AR. They were associated with reductions in symptoms and with medication use. There were insufficient data to determine which of SCIT and SLIT are most effective.

Moderate to substantial heterogeneity was observed in some outcomes evaluated in the meta-analysis.[14] This heterogeneity can be explained by the study design (particularly the different outcomes used), study population and the products evaluated. There are data to indicate which preparations are most likely to be effective, so an individual product-based evaluation of the evidence for efficacy is strongly recommended before treatment with a specific product is initiated. Not all AIT products provide sufficient data to support their efficacy in clinical practice.[14] As a result of this, the recent German, Austrian and Swiss guideline has followed a product-specific approach.[11] This approach is more difficult across Europe with differing local regulations[47] and availability of products.[48] The specific recommendations in this guideline need to be seen in this context; only standardized AIT products with evidence of efficacy in the clinical documentation should be prescribed. The only exception should be orphan allergens where only a few patients are affected; these are discussed below in the specific allergen section.

Subcutaneous immunotherapy is in general recommended for the treatment of AR in children and adults with moderate-to-severe disease that is suboptimally controlled despite pharmacotherapy[14] (Table 3). The evidence for short-term benefit for continuous SCIT is stronger for seasonal rhinitis (Grade A for adults) than for perennial rhinitis (Grade B for adults), where fewer studies have been performed and results are more heterogeneous (Table 3). SCIT is recommended for seasonal disease whether pre- or pre/coseasonally (Table 3, Grade A for adults). Pre/coseasonal therapy benefits from a shorter course of treatment but the 1 head-to-head trial suggests that continuous therapy may be more effective.[49]

Subcutaneous immunotherapy may be administered in aqueous formulation (rarely in Europe) or as a depot adsorbed on aluminum hydroxide or tyrosine. SCIT using either unmodified or modified

TABLE 2 General contraindications for allergen immunotherapy (AIT) for allergic rhinoconjunctivitis

	Key references	Contextual considerations
The following are considered to be contraindications:		
Uncontrolled or severe asthma	Bernstein[31], Bousquet[29], Calderon[34], Cox[28], CSM 1986[32], Lockey[30], Normansell[33], Pfaar[11]; Pitsios[27]	Weak evidence of risk with uncontrolled asthma, active systemic autoimmune disease, and malignancy from case reports or case series of adverse events with AIT. Taskforce considered that these were contraindications to AIT. Though initiation of AIT is contraindicated during pregnancy, an ongoing AIT is permissible when having been well tolerated by the patient in the past
Active, systemic autoimmune disorders (unresponsive to treatment)	Cabrera[35], Fiorillo[37], Pfaar[11], Sánchez-Morillas[36]; Pitsios[27]	
Active malignant neoplasia	Larenas-Linnemann[39], Pfaar[11]; Wöhrl[38]	
AIT initiation during pregnancy	Metzger[40], Pfaar[11]	
With the following, AIT should only be used with caution when benefits outweigh potential risks in an individual patient:		
Partially controlled asthma	Virchow[41]	One trial with SLIT tablet[41] included some subjects with partially controlled asthma without compromising safety; it is important that confirmatory evidence is acquired.
Beta-blocker therapy (local or systemic)	Cleaveland[44], Hiatt[42], Lang[45]; Pfaar[11]	Weak evidence of risk. May compromise a patient's ability to tolerate an episode of anaphylaxis. This must be considered when deciding whether AIT is appropriate.
Severe cardiovascular diseases, for example, coronary artery disease	Larenas-Linnemann[39]; Linneberg[46]	
Systemic autoimmune disorders in remission or organ specific	Larenas-Linnemann[39], Pitsios[27]	Weak evidence of risk from case reports, case series of adverse events with AIT or expert opinion based on clinical experience. Taskforce considered that careful consideration on a case-by-case basis with discussion between patient and the treating physician is required before deciding whether or not to commence AIT.
Severe psychiatric disorders	Pitsios[27]	
Poor adherence	Pitsios[27]; Pfaar[11]	
Primary and secondary Immunodeficiencies	Larenas-Linnemann[39]; Pitsios[27]	
History of serious systemic reactions to AIT	Calderon[34]; Pfaar 2014[11]	

The Summary of Product Characteristics (SmPC) should also be checked for product-specific contraindications which may differ between preparations.

allergen extracts is recommended for treatment of AR and provides short-term benefit (Table 3, Grade A for adults). This is based on evidence from the meta-analysis[14] that showed both unmodified allergen extracts (SMD [95% CI] −0.65 [−0.93, −0.36]) and allergoids/polymerized extracts (−0.60 [−0.89, −0.31]) to be effective in reducing symptoms compared to placebo, with additional support from reduced medication requirements and combined symptom-medication scores. Although clinical trials of modified allergens involved shorter courses of treatment, there have been no head-to-head comparisons with unmodified preparations evaluating efficacy or adverse events using a placebo-controlled, randomized design.

In general, SLIT can be recommended for the treatment of seasonal AR in adults and children. SLIT has been shown to provide short-term benefit during therapy with moderate-to-severe disease that is suboptimally controlled despite pharmacotherapy (Table 3).[14] SLIT is recommended to be taken either continuously or pre-/coseasonally commencing a minimum of 2 months and ideally 4 months prior to the start of the pollen season (Grade A for adults).

Sublingual immunotherapy may be taken daily either as fast tablets or drops that are retained under the tongue for at least 1 minute and then swallowed (the summary of the SmPC should also be checked for product specific recommendations). Both are recommended (grades A and B, respectively, for adults) based on short-term reductions in symptoms and rescue medication for sublingual tablets for seasonal AR (Table 3). There are only convincing evidence for effectiveness of SLIT tablets in perennial AR (Grade A) (Table 3).

Sublingual grass pollen tablet immunotherapy for at least 3 years is recommended (Grade A) for the short-term treatment of grass pollen-driven AR in adults.[86,87,108,109] Sublingual house dust mite (HDM) tablet immunotherapy for at least 1 year is recommended (Grade A) for the short-term treatment of perennial HDM AR in adults.[50-55]

While higher doses and/or increased cumulative doses may be more effective, they may be associated with more side-effects[56-58]; decisions on dose in AIT must be made balancing efficacy and side-effects.[59]

4.1 | Other approaches of AIT for AR

Other approaches aim to improve patient convenience and adherence with shorter courses, while improving or maintaining efficacy and reducing the risk of systemic side-effects (Table 4). As such, adjuvants to AIT extracts are possible candidates.[112] For example, TLR-4 agonists (Th1-inducing adjuvant monophosphoryl lipid A) in combination with a grass allergoid have demonstrated effectiveness,[113] although in a phase 3 trial, efficacy was modest[114] (Grade A

TABLE 3 Recommendations: allergen immunotherapy (AIT) for treatment of allergic rhinoconjunctivitis: schedules, products, formulations

For each recommendation, an individual product-based evaluation of the evidence for efficacy is recommended before treatment with a specific product is initiated given the heterogeneity in the meta-analysis results. The SmPC should also be checked for for product specific recommendations.

Recommendation	Adults		Children and adolescents		Strength of recommendation	Other considerations	Key references
	Evidence level	Grade of recommendation	Evidence level	Grade of recommendation			
SCIT							
Seasonal allergic rhinitis							
Continuous SCIT is recommended for seasonal AR for short-term benefit in those with moderate-to severe disease	I	A	I	B	Strong recommendations for adults based on low risk of bias studies.[60-62] Moderate recommendation for children as just one open RCT with risk of bias reporting solely pediatric data.[63]	Consistent results, low risk of severe systemic allergic side-effects. Most studies reported pediatric and adult data together.	Dhami[14] for example, Adult: Dolz[64], Charpin[61], Ferrer[62], Jutel[75], Scadding[65], Walker[60] Paediatric: Jacobsen[63]
Pre- and pre-/coseasonal SCIT is recommended for seasonal AR for short-term benefit	I	A	I	B	Strong recommendation for adults based on low risk of bias studies.[69-72] Moderate recommendation for children as only combined adult/pediatric data, one study with low risk of bias[73] and with one with unclear risk of bias RCTs[74] available.	Consistent results in adult studies; low risk of severe systemic allergic side-effects.	Dhami[14] SR, for example, Adult: Balda[69], Bodtger[70], Bousquet[74], Frew[58], Varney[71], Zenner[72] Adult/pediatric: Bousquet[74], Weyer[73]
Continuous grass pollen SCIT is recommended for seasonal AR for short- and long-term benefit	I	A	I	B	Strong recommendation for adults based on above evidence plus 2 low risk of bias long-term studies.[83,84] Moderate recommendation for children as one long-term open RCT with risk of bias.[63]	A few adult studies and one pediatric study (designed to assess whether SCIT prevents asthma) demonstrating long-term effectiveness.	Dhami[14] SR, for example, Adult: Durham[83], James[84] Pediatric: Jacobsen[63]
Perennial allergic rhinitis							
Continuous SCIT is recommended for perennial AR due to HDM for short-term benefit	I	B	I	C*	Strong recommendation for adults based on one study with low risk of bias[67] plus one with high risk of bias.[68] No exclusive pediatric data. Moderate recommendation for children, based on extrapolation from adult studies.	Few small adult studies, considerable heterogeneity[66] and risk of systemic allergic side-effects. *Recommendation for children downgraded from B to C due to lack of exclusive pediatric data.	Dhami[14] SR, for example, Adult: Dokic[67], Ewan[68], Varney[66]
All							

(Continues)

TABLE 3 (Continued)

For each recommendation, an individual product-based evaluation of the evidence for efficacy is recommended before treatment with a specific product is initiated given the heterogeneity in the meta-analysis results. The SmPC should also be checked for for product specific recommendations.							
	Adults		Children and adolescents				
Recommendation	Evidence level	Grade of recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
Modified (allergoids) and unmodified allergen extracts for pollens and HDM SCIT are recommended for AR for short-term benefit	I	A	I	B	Strong recommendation for adults based on high-quality studies for both modified[61,67,76-78] and nonmodified[60,61,69-73,76,79,80] allergen extracts. Weak recommendation for children as no exclusive pediatric randomized, placebo-controlled data.	Consistent results, low risk of severe systemic allergic side-effects. No exclusive pediatric randomized, placebo-controlled data.	Dhami[14] SR, for example, Modified: Ceuppens[81], Corrigan[77], Dokic[67], Klimek[78], Riechelmann[82] Nonmodified: Balda[69], Bodtger[70], Brunet[76], Charpin[61], Frew[58], Ortolani[79], Scadding[65], Varney[71], Walker[60], Weyer[73], Zenner[72] Modified and nonmodified: Bousquet[74]
SLIT							
Seasonal allergic rhinitis							
Pre-/coseasonal SLIT is recommended for seasonal ARs for short-term benefit	I	A	I	A	Strong recommendation based on high-quality adult[86-89] and pediatric[90-92,155,156] studies.	Consistent results, low risk of severe systemic allergic side-effects.	Dhami 2017[14] SR, for example, Adult: Dahl[85], Dahl[86], Didier[56], Durham[87], Palma-Carlos[96], Worm[89] Pediatric: Blaiss[99], Bufe[98], Caffarelli[90], Halken[97], Pajno[91], Wahn[156]
Continuous SLIT can be recommended for seasonal AR for short-term benefit	I	A	I	A	Moderate-to-strong recommendation based on low[100] and high[101,102] risk of bias adult studies plus low,[111] moderate[103] and unclear[57] risk of bias pediatric studies.	Some heterogeneity between studies particularly pediatric ones, low risk of severe systemic allergic side-effects.	Dhami[14] SR, for example, Adult: Amar[100], Ariano[101], Creticos[93], Panzner[102] Pediatric: Bufe[103], Valovirta[57], Valovirta[111].
SLIT with aqueous solutions can be recommended for seasonal AR for short-term benefit.	I	B	I	A	Moderate recommendation for adults based on a mixture of low[104] and high[101,105,106] risk of bias studies. Strong recommendation for pediatrics based on low risk of bias studies.[91,92]	Some heterogeneity between adult studies, low risk of severe systemic allergic side-effects.	Dhami[14] SR, for example, Adult: Ariano[101], Bowen[105], Feliziani[104] Pediatric: Pajno[91], Stelmach[92]

(Continues)

TABLE 3 (Continued)

For each recommendation, an individual product-based evaluation of the evidence for efficacy is recommended before treatment with a specific product is initiated given the heterogeneity in the meta-analysis results. The SmPC should also be checked for for product specific recommendations.							
	Adults		Children and adolescents				
Recommendation	Evidence level	Grade of recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
SLIT with grass pollen tablets is recommended for AR for short-term benefit.	I	A	I	A	Strong recommendation based on low risk of bias adult[86,87,108,109] and pediatric[97-99,111] studies.	Nonimportant heterogeneity between studies, low risk of severe systemic allergic side-effects.	Dhami[14], SR, e.g Adult: Dahl[86], Didier[56], Didier[108], Durham[87], Durham[109] Pediatric: Blaiss[99], Bufe[98], Halken[97], Valovirta[111]
Grass pollen SLIT tablets or solution with continuous therapy is recommended for AR for long-term benefit.	I	A	I	A	Strong recommendation for adults based on low risk of bias studies.[108,109] One low risk of bias pediatric study[110,111]	Effective up to 2 y after cessation in adults.[108,109] One pediatric study was designed to look at prevention of asthma.	Dhami[14] SR, e.g Adult: Didier[94], Durham[109] Pediatric: Valovirta 2011[110] and 2017[111] Adult and pediatric: Ott[145]
Perennial allergic rhinitis							
SLIT with aqueous solutions may not be recommended for perennial AR for short-term benefit.	I	C*	I	A	*Weak recommendation against use for adults based on just one high risk of bias RCT so only a grade C recommendation.[107] Cannot be recommended in children based on 4 negative RCTs and 1 positive RCT.	Low risk of severe systemic allergic side-effects. Studies of low[106,139,140,146] and high[144] risk of bias suggest that it is not effective in children.	Dhami[14] SR, for example, Adult: Guez[107] Pediatric: Bahçeciler[139], de Bot[146], Hirsch[140], Marcucci[144], Tari[106]
SLIT with HDM tablets is recommended for AR for short-term benefit.	I	A	I	A	Strong recommendation based on low risk of bias adult[50-54] and mixed adult/pediatric[51,55] studies.	Nonimportant heterogeneity between studies, low risk of severe systemic allergic side-effects.	Dhami[14] SR, e.g Adult: Bergmann[53], Demoly[52], Mosbech[54], Passalacqua[50], Passalacqua[147] Adult and pediatric: Nolte[51], Okubo[55]
HDM SLIT tablet with continuous therapy can be recommended for AR for long-term benefit.	I	B	-	C*	Moderate recommendation based on one large, low risk of bias study.[53] No pediatric data.	One study demonstrates effectiveness for a year post-treatment[53]; data require replication especially as 3 y therapy required for grass pollen. *No pediatric data, extrapolated from adult data.	Adult: Bergmann[53]

Continuous: year-round therapy. Preseasonal: before a pollen season. Coseasonal: during a pollen season. Not all AIT preparations are licensed for children and adolescents. Long-term is defined as at least 1 y after cessation of the AIT course. See allergen factors section for other specific allergens.

TABLE 4 Recommendations: other approaches for allergen immunotherapy (AIT) for treatment of allergic rhinoconjunctivitis

For each recommendation, an individual product-based evaluation of the evidence for efficacy is recommended before treatment with a specific product is initiated given the heterogeneity in the meta-analysis results. Where available, the SmPC should also be checked for for product specific recommendations.							
	Adults		Children and adolescents				
Recommendation	Evidence level	Grade of recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
A combination of the TLR-4 agonist monophosphoryl lipid A with pollen allergoid is recommended for AR	I	A	III	B	Strong recommendation for adults based on 3 low risk of bias studies.[113,114,172] Weak recommendation for children.[130]	Consistent randomized controlled data; only one ragweed pollen study, others are grass and tree pollen. Only one uncontrolled before and after study pediatric study.[130]	Adult: Drachenberg[113], DuBuske[114], Drachenberg[95], Patel[172] Pediatric: Drachenberg[130]
Combining anti-IgE injections with AIT for AR is recommended for reducing side-effects	I	A	I	A	Strong recommendation based on one low risk of bias adult[117] and one low risk of bias pediatric[116] study.	Consistent evidence but the required length of cotherapy unclear.	Adult: Casale[117] Pediatric: Rolinck-Werninghaus[116]
Recombinant AIT can be recommended for birch and grass pollen allergy	I	A	-	B	Moderate recommendation based on 2 double-blind placebo-controlled RCTs of unclear risk of bias.[75,119]	Some evidence of benefit for adults, no pediatric data.	Adult: Jutel[75], Pauli[119]

for adults, B for children) and there are no head-to-head comparisons with conventional preparations. There is also 1 trial demonstrating efficacy for this approach with ragweed pollen[172] and one with tree pollen.[95] The TLR-9 agonist (Bacterial DNA oligonucleotides containing a CpG motif) fused to Amb a 1, the major allergen of ragweed showed efficacy in a phase 2 trial[115] although this was not observed in a subsequent phase 3 trial. The combination of anti-IgE injections with conventional and rush AIT with nonmodified extracts has been proven to be effective with a marked reduction in systemic side-effects in studies of children[116] and adults[117] (Grade A recommendation). This is an expensive approach, and there is concern as to when and how to discontinue the anti-IgE when AIT maintenance therapy is achieved.[118]

Recombinant AIT is attractive as it allows accurate standardization of allergen products, has potential for personalized therapy based on individual allergen sensitivities and a hypothetical lower risk of inducing new sensitizations. Subcutaneous recombinant birch (Bet v 1)[119] and a five-recombinant grass allergen mix[75] have been shown to be efficacious with no safety concerns (Grade A for adults, B for children). However, there are no commercially products available at present. A recombinant B-cell epitope-based vaccine, comprising a recombinant hybrid grass allergen mix combined with a hepatitis B domain surface Pre-S protein as an immunologic carrier has shown efficacy in a phase 2 trial.[120] T-cell peptide immunotherapy for cat allergy using mixtures of short T-cell epitopes via the intradermal route had promising results in environmental chamber phase 2 studies[121]; however, it has been reported that a subsequent phase 3 study did not demonstrate effectiveness.[122] Studies with other allergen peptide approaches are in progress.[124]

There has been recent interest in the use of alternative modalities of delivery including the epicutaneous, intradermal and intralymphatic routes. In RCTs, epicutaneous grass pollen immunotherapy (EPIT) has shown modest benefit[125] although accompanied by local eczematous reactions at the patch application site. Intradermal grass pollen immunotherapy inhibited allergen-induced cutaneous late responses although in a subsequent RCT, it was ineffective and there was evidence of exacerbation of seasonal outcomes and Th2 inflammation in the skin.[126] The intralymphatic route, using a grass pollen extract and a modified cat allergen extract, showed efficacy in some trials[127,128] but not in others.[129]

5 | ALLERGEN FACTORS THAT MAY AFFECT THE EFFICACY OF AIT FOR AR

5.1 | Standardization of allergen extracts

For the common allergens, many companies now provide characterized, standardized, stable preparation for AIT as recommended by EMA.[47,132] For others, such as molds, there are problems with the complexity, variability, and stability of the allergens.[133] The lack of standardized extracts may hamper the diagnosis of eligible patients for AIT and may impede the effectiveness of AIT.[133,134] Additionally, nonstandardized preparations may vary between batches increasing

the potential for side-effects. Further purification and characterization of such allergens[134-136] may result in better extracts for the future. Where possible, standardized allergen products should be used for AIT. Further discussion is available in a position paper on regulatory aspects of AIT.[47]

5.2 | Formulation of SLIT preparations

In deciding on the appropriate preparation to use for AIT, the formulation should be taken into account. For example, 3 large studies have shown efficacy for HDM SLIT tablets,[52,53,54] whereas 3 HDM SLIT studies with sublingual drops were negative,[107,140,146] and another only demonstrated efficacy in the first and not the second year.[50] However, many factors such as differences in allergen content,[141] administered volume, number of participants, and statistical power of the study may explain the differences between tablets and drop trials. We recommend that AIT products with evidence of efficacy in the clinical documentation should be used when they are available.

5.3 | Allergen mixtures

Both mixtures of grass pollen and mixtures of tree pollen are frequently used in AIT and such an approach is effective.[14] The use of different, nontaxonomically related allergens mixed in 1 AIT product has been evaluated in a very limited number of studies. One SCIT study showed that a depigmented-polymerized mixed grass/birch pollen extract was effective over placebo.[142] A small study in children demonstrated efficacy using a mixture of grass pollen and HDM SLIT.[143] SLIT drops that employed a monomeric *Phleum pratense* grass pollen extract was more effective when given alone compared to when given in an equivalent dose as part of a combination with a 9-pollen, multi-allergen, sublingual extract.[100]

There are a number of potential drawbacks of mixing allergens including a dilutional effect, potential allergen degradation due to enzymatic activity of some allergens and the difficulties of adequately demonstrating efficacy of a high number of allergen combinations and/or different products. The EMA has recommended that only homologous allergens (usually ones that are taxonomically related[132], for example, a mixture of grass pollen extracts[56]) should be mixed and that allergens with enzymatic activity (e.g, HDM) should be never used in a mixture. We therefore recommend only homologous allergens to be mixed in AIT preparations until further evidence is available substantiating the efficacy of other mixtures (Grade A) (Table 5) (Table S1). Alternatively, extracts should be given separately.

5.4 | Specific allergens

In the recent meta-analysis, there were sufficient SCIT and SLIT studies for subgroup analyses by specific allergens.[14] Short-term effectiveness was demonstrated for HDM (symptoms score SMD −0.73; 95% CI −1.37, −0.10), grass pollen (−0.45; −0.54, −0.36), tree pollen (−0.57; −0.92, −0.21), and weed pollen (−0.68; −1.06, −0.30). However, there was substantial heterogeneity for all allergens, particularly molds (−0.56; −2.29, 1.18), suggesting that different preparations may be more or less effective. Before a product is used, an individual product-based evaluation of the evidence for efficacy is recommended.

There are some orphan allergens where robust data from RCTs are sparse or nonexistent. Where there is a clinical need, the available evidence of efficacy and safety needs to be weighed against the needs of the individual patient. Where therapy is considered in the patient's best interest, an early evaluation of its impact on the patient's clinical symptoms is required to determine whether or not therapy should be continued. The generation of controlled clinical trial data to assess efficacy and safety of these orphan products should be encouraged. There will always be orphan allergens where such studies are uneconomic and have to be regulated as named patient products.[47]

6 | PATIENT FACTORS THAT MAY IMPACT ON THE EFFICACY OF AIT FOR AR

The approach to immunotherapy is a good example of patient stratification. Immunotherapy will only work when directed to the specific allergen(s) driving symptoms. So identifying the driving allergen(s) with a thorough history and assessment of allergic sensitization is an essential example of patient stratification. Not all patients benefit from AIT[14] and further stratification approaches to identify the responders would be useful.

6.1 | Polysensitized patients

Epidemiological data indicate that most patients with AR are polysensitized.[148] Consequently, consideration needs to be given as to whether patients are (i) clinically monoallergic (where only 1 allergen is driving symptoms) and polysensitized or (ii) poly-allergic (symptoms with overlapping exposure to multiple different allergens) and polysensitized. Immunotherapy with a single allergen extract is effective in the first,[149] while immunotherapy has been shown to be ineffective[150] or less effective in the last situation.[151] This may be apparent from the history or may need investigation with component-resolved diagnostics or assessment with nasal or conjunctival provocation challenges where the clinician is experienced in these diagnostic procedures.[137] Polysensitized patients who are monoallergic are recommended to receive AIT for the specific allergen that is driving their AR symptoms (Grade A).

For a polysensitized patient who is poly-allergic for homologous (biologically related) allergens (e.g, 2 grass pollens), a single allergen preparation or a mixture of 2 homologous allergens is recommended (Grade B).[137] For poly-allergic patients where allergens are not homologous, separate AIT preparations for 1 or 2 of the clinically most important allergens might be recommended with doses given 30-60 minutes apart at separate locations when 2 are selected (Grade C).[32,137] This represents a trade-off between efficacy and

TABLE 5 Recommendations: allergen factors that affect the efficacy of AIT for allergic rhinoconjunctivitis

	Adults		Children and Adolescents				
Recommendation	Evidence level	Grade of recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
Either a single allergen species or a mixture of well-documented homologous allergens from the same biological family are recommended for patients with AR who are allergic to grass pollens, tree pollens, or HDM	I	A	I	A	Strong recommendations on basis of low risk of bias grass pollen (single grass, e.g,[85,98,99]); mixture of grasses, e.g,[56,145]), tree pollen (single tree, e.g,[61,70]; mixture of trees, e.g,[69]) and house dust mite (single, e.g,[66]; mixture, e.g,[147]) studies.	Strong RCT evidence that these are effective approaches. Supported by regulators.	Demoly[137], Dhami[14], EMA[132] Adult: Balda[69], Bodtger[70], Charpin[61], Dahl[85], Didier[56], Ott[145], Passalacqua[147], Varney[66], Varney[71] Pediatric: Bufe[98]
Mixtures of allergens from nonrelated biological families are not recommended for AIT.	I	B	—	C*	Strong recommendation against use of allergen mixtures is based on the little available evidence.	No evidence of effectiveness for almost all mixtures. Exception is one positive low risk of bias study in adults (grass and tree pollen mix),[142] and this product would therefore be indicated for use for AIT. *No pediatric data, extrapolated from adult data.	Bonertz[47], EMA[132] Adult: Amar[100], Nelson[151], Pfaar[142]

Examples of homologous, taxonomically related allergens from the same biological family are the grasses or tree pollens. Also see Table 3.

safety as both seem to be dose-dependent. More studies are needed to further address this important clinical challenge.

6.2 | Co-existing asthma

Co-existing asthma is seen in many participants in the published AR AIT studies.[14] Co-existing asthma has no impact on the efficacy of AIT for AR[103] and may also lead to improvement in asthma.[43] When controlled, mild-to-moderate asthma does not seem to be a safety issue with AIT (Grade A recommendation).[41,43] In 1 large recent asthma SLIT trial, participants with not well-controlled asthma based on an Asthma Control Questionnaire (ACQ-6) were included safely in the study.[41] We await confirmatory evidence and emphasize that efforts should be taken to control asthma before commencing AIT. Uncontrolled or severe asthma are definitely considered to be an absolute contraindication to AIT.[25-31]

6.3 | Specific pediatric issues

Similar to adults, AIT should be considered in pediatric patients with AR with evidence of IgE sensitization to clinically relevant allergens (Grade A) (Tables 1 and 3).

The evidence for the efficacy of AIT for AR is limited in children younger than 5 years of age. Some clinical studies have shown the efficacy and safety of both SCIT and SLIT in preschool children,[88,152-155] and children were included from 5 years onward in several of the well-powered SLIT tablet trials.[98,156] Experience suggests that repeated injections of SCIT may be stressful in preschool children. It is recommended that the decision to start the treatment has to be taken on a case-by-case basis together with the patients and their family (Grade D). The decision should depend on several factors, such as the severity of the allergic disease, the clear exposure-symptoms pattern supported by allergic sensitization testing, the impairment of the health-related quality of life and the expected acceptance and adherence to the AIT.

There are more data to drive recommendations for school age children and adolescents although major gaps still exist (Table 3). Many of the SCIT trials are now relatively old, many enrolled only a few children and/or did not present pediatric only analyses. Continuous and pre- and pre/coseasonal SCIT can be recommended (Grade B) for children with seasonal AR (Table 3). Continuous SCIT is also recommended for perennial AR but with a weaker grade due to the lack of exclusive pediatric data (Grade C) (Table 3). There are no exclusive pediatric, placebo-controlled data for allergoid preparations, but 1 controlled trial with a preseasonal treatment regimen has indicated long-term efficacy of preseasonal grass pollen immunotherapy in this age group.[157] Two further open RCTs also suggest that SCIT for grass pollen-driven AR does have a long-term benefit.[63,158]

For SLIT, there are more recent pediatric trial data to support this approach. In general, pre-/coseasonal and continuous SLIT is recommended for seasonal AR (Grade A) (Table 3). Both tablet and aqueous formulations are recommended (Grade A) (Table 3). There is now one recently published trial supporting the long-term effectiveness for a grass pollen tablet and reduction in asthma symptoms[110,111] (Grade A). For perennial allergic rhinitis, the evidence is not as good. There are no consistent data to recommend SLIT with aqueous solutions for perennial allergic rhinitis, but the SLIT tablet approach has been demonstrated to be effective in the short term in mixed adult/adolescent studies[51,55] (grade A).

6.4 | Elderly

A detailed allergy history is especially important when evaluating older adults suffering with rhinitis as other types of rhinitis may mimic AR symptoms. There are very few studies specifically evaluating the use of AIT in the elderly (defined here as >65 years as this is usually exclusion criteria in AIT trials) but SLIT with grass pollen and HDM has been demonstrated to be effective and safe in 2 studies.[159,175] AIT elicits clinical responses comparable to studies with younger patients. Another important consideration in this age group, when contemplating treatment with AIT, is the higher prevalence of comorbidities. Examples are hypertension, coronary artery disease, cerebrovascular disease, malignancy and/or cardiac arrhythmias. Also, treatment with medication such as beta-blockers may impair the treatment of anaphylaxis with adrenaline (epinephrine) (see Table 2). AIT can be recommended in otherwise healthy elderly patients with AR whose symptoms cannot be adequately controlled by pharmacotherapy (Grade A for SLIT, B for SCIT).

6.5 | Pregnancy

There is 1 prospective study investigating the safety of AIT in pregnancy[161] and several retrospective studies that suggest that there is no greater risk of prematurity, fetal abnormality, or other adverse pregnancy outcome in women who receive AIT during pregnancy.[39] Observations about anaphylaxis in pregnant and breastfeeding women are largely derived from case reports and are generally reassuring.[162] However, the balance between benefits and potential risks in pregnant patients needs to be discussed with the patient. Systemic reactions and their resultant treatment can potentially harm the baby and/or mother. It is therefore recommended that AIT is not initiated during pregnancy (Grade D) but, if already initiated, AIT may be continued during pregnancy or breastfeeding in agreement with the patient's general practitioner (GP) and obstetrician if former AIT treatment has previously been tolerated well (Grade C).

6.6 | Adherence

There is a great variance between studies (both real-life studies and clinical trials) in the criteria used for evaluating adherence and in the rates of adherence.[163-169] The range of reported adherence varied from 18% to over 90%, higher in clinical studies than real-life surveys with overlapping ranges for SCIT and SLIT. The main causes for poor adherence are reported to be side-effects, inconvenience, lack of efficacy or forgetting to use.[163-165,167,168,170] A few other factors

TABLE 6 Recommendations: patient factors that affect the efficacy of allergen immunotherapy (AIT) for allergic rhinoconjunctivitis

Recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
Polysensitized patients					
Polysensitized patients who are monoallergic are recommended to receive AIT for the specific allergen that is driving their AR symptoms	I	A	Strong recommendation, based on RCTs with low risk of bias[56,109]	Expert review of RCTs[137,149]	Didier[56], Demoly[137], Durham[109], Nelson[149]
Polysensitized patients who are poly-allergic for taxonomically related homologous allergens can be recommended to receive either a single allergen or a mixture of homologous allergens from that biological family that covers all the major allergens	II	B		Expert review of RCT data	Demoly[137], EMA advice[132]
Patients who are poly-allergic for nonhomologous allergens may be recommended to start AIT with either the allergen responsible for most of their allergic rhinoconjunctivitis symptoms or separate treatment with the 2 clinically most important allergens	II	C		Expert review of RCT data	Demoly[137], EMA advice[132], Pfaar[142]
Co-existing asthma					
Controlled asthma is not a contraindication to AIT	I	A	Strong recommendation based on low risk of bias studies[43]	Evidence described in asthma AIT systematic review.[43]	Dhami[14], Virchow[41], Dhami[43]
Specific pediatric issues					
Consideration of AIT is recommended in pediatric patients with AR with evidence of IgE sensitization to clinically relevant allergens	I	A	Strong recommendations from low risk of bias studies [e.g 90,91,92,98]	See Table 3 for detailed review.	Bufe[98], Caffarelli[90], Pajno[91], Stelmach[92]
In children aged 2-5 y of age, it may be recommended that consideration should be given to likely benefits and risks associated with AIT for AR	IV	D	Weak recommendation based on little available evidence	May be more difficult to make a definitive diagnosis of AR in preschool children. Safety seems to be similar in this age group as per older patients.	Rienzo[173], Rodriguez-Santos[174]
Elderly					
AIT can be recommended in otherwise healthy elderly patients (>65 y) with AR	I	A (SLIT), B (SCIT)	Moderate recommendation for SLIT based on 2 consistent RCT studies of unclear risk of bias.[159,175] Moderate recommendation for SCIT based on only one relatively small, low risk of bias study.[160]	Detailed clinical assessment is recommended to exclude other types of rhinitis in elderly patients.	Bozek 2012[175], 2014[159], 2016[160]
Pregnancy					
Immunotherapy is not recommended to be initiated during pregnancy	V	D		Based on balance of additional risk vs benefits.	Expert opinion

(Continues)

TABLE 6 (Continued)

Recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
Maintenance immunotherapy may be recommended to be continued (at the achieved dose) during pregnancy	III	C	Weak recommendation based one cohort study[161] and one case series[40]		Shaikh[161], Metzger[40]
Adherence					
It is recommended that patients should be informed about how immunotherapy works and the need to take regular doses and complete the course of treatment.	IV	C	Based on a survey of allergists.	Based on observational data	Scurati[164]
Reminders are recommended for patients on immunotherapy to improve treatment adherence.	III	C	One interventional study (educational session, phone calls, emails)	Consider mobile phone texts, social media, and applications (apps)	Savi[169]
Patients receiving SLIT can be recommended to be followed up every 3 mo to improve treatment adherence	II	B	Moderate recommendation based on one quasi-randomized study.[171]	Method of randomization unclear.	Vita[171]

have been associated with poor adherence, for example, age and patient's educational level. Potential ways to improve adherence are the use of reminder mechanisms (e.g, alarm on mobile phone, Internet-based tools, short message service (SMS) electronic reminders, social networks, mobile applications (apps), and monitoring systems —this approach should be tailored to the patient (Grade C). Patient education and good communication between physician and patient are key (Grade C).[169] One randomized study suggests that adherence is much better with 3-monthly follow-up appointments compared to 6 or 12-monthly follow-up (Grade B).[171] Recommendations are summarized in Table 6.

7 | HOW LONG AIT SHOULD BE CONTINUED FOR IN AR?

Most clinical studies evaluating the efficacy of AIT follow participants for 1 or 2 years on therapy. The EMA currently recommends an experimental, randomized, controlled design involving 3 years of therapy with a 2-year follow-up period off treatment. These studies demonstrate a sustained benefit for 3 years of SLIT-tablet grass pollen therapy for 2 years off therapy.[94,109,111,176] There are some data to suggest that HDM SLIT tablets give sustained benefit for at least 1 year after 1 year of therapy in 1 RCT[53] and also after 3 years of therapy in a SLIT drop RCT.[177] More data are required for HDM, and evidence is required on the optimal duration of therapy. Grass pollen SCIT for 3-4 years has been shown to result in long-term efficacy for 3 years after discontinuation.[83] In a recent study, either SCIT or SLIT tablets were effective compared to placebo over 2 years, but 2 years were insufficient for long-term efficacy as measured 1 year off treatment.[65] In another adult study, participants randomized to 3 years of ragweed continued to benefit after 2 years post-SCIT.[178] Similarly, children randomized to 3 or 5 years HDM SCIT had similar outcomes at 5 years.[179] So, in summary, for patients with AR, a minimum of 3 years of AIT is recommended to achieve long-term efficacy after treatment discontinuation (Grade A) (Table 7).

8 | ADVERSE EVENTS WITH AIT FOR AR

8.1 | SCIT

Subcutaneous immunotherapy is a safe and well-tolerated treatment when the injections are given in a medical setting by experienced personnel trained in the early recognition of systemic reactions and how to manage them (Table 8).[11,180-182] There must be immediate access to resuscitation equipment and a physician trained in the management of anaphylaxis (Grade C).

Systemic allergic adverse reactions to SCIT can range between mild-to-severe adverse reactions of the skin, upper and lower airways, gastrointestinal tract, or the cardiovascular system (see Table S2 in online supplement for details of classification).[123] In a 3-year real-life US survey study that included over 20 million injection

TABLE 7 Recommendations: how long should AIT for allergic rhinoconjunctivitis be continued?

Recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Contextual comments	Key references
AIT is recommended as benefit is seen from the first year of therapy	I	A	Strong recommendation based on low risk of bias studies (e.g[53,56,58,69,72,74,85,94])	Generally consistent data	Dhami[14], Bergmann[53], Bousquet[74], Didier[94], Dahl[85], Frew[58]
It is recommended that to achieve long-term benefits, immunotherapy should be continued for a minimum of 3 y	I	A	Strong recommendation based on low risk of bias long-term adult studies,[56,56,83,84,94,108,109,145] one high risk of bias pediatric study (due to its open design although it was randomized)[63] plus one recently published low risk of bias pediatric study.[111]	Consistent data	Adult: Arroabarren[179], Didier[56], Didier[108], Didier[94], Durham[83], Durham[109], James[84], Lin[177], Naclerio[178], Ott[145], Scadding[65] Pediatric: Jacobsen[63], Stelmach[223], Valovirta[111]

visits, systemic reactions were reported in 0.1% of injections; there were no fatalities[182] although 4 were reported in a follow-up survey by the same group.[183] Fatal allergic adverse reactions have though been reported in earlier surveys.[30,31] Over 80% of reactions occurred within 30 minutes after injection; very few of the delayed ones were severe. It is therefore recommended that patients stay in clinic for at least 30 minutes after an injection (Grade C).

A European real-life, prospective, survey performed by members of the Immunotherapy Interest Group of EAACI on 4316 patients in France, Germany, and Spain was published after our SR was completed.[184,185] It demonstrated that SCIT and SLIT for respiratory allergy are safe in general in the pediatric and adult population and found only a low number of systematic reactions (SRs). For SCIT, SRs were found in 2.1% of all SCIT-treated patients. Independent risk factors for SRs during SCIT were the use of natural extracts, the absence of symptomatic allergy medications, asthma diagnosis, sensitization to animal dander or pollen, cluster regimens (vs rush), and a previous episode of anaphylaxis. Further possible risk factors for systemic adverse reactions have been described (Box 3[11]). When 1 or more severe adverse reactions occur, the allergist (specialist and subspecialists) should re-evaluate the benefits and risks of SCIT therapy with the patient and decide whether or not treatment should be continued (Grade D). In any case, cessation of treatment or adaptation of the dosing schemes for the next injection should follow the summary of product characteristics (SmPC).

Redness, itching, or swelling represents local reactions at the injection site and occurs frequently after around half of injections.[14] Local measures (e.g, cooling or topical glucocorticoids) or oral antihistamines may be helpful for these reactions. Increased local adverse reactions do not predict an increased individual risk of a systemic adverse reaction.[186] In case of enlarged local adverse reactions (redness and/or swelling >10 cm in diameter) occur at the injection site, the SmPC provides adaptation of the dosing schemes for the next injection. When local adverse effects occur, premedication with an H1-antihistamine can be used to reduce the frequency and severity of adverse reactions (Grade A recommendation), but this prophylactic treatment does not prevent the onset of SRs or anaphylaxis.[187,188] Also, studies indicate that modified allergen extracts are associated with less adverse effects.[189-192] For aluminum hydroxide containing SCIT products, granulomas have been described from a foreign body reaction mainly caused by incorrect intradermal administration as well as contact allergic reactions, new onset of protein contact dermatitis, or a vasculitis inflammatory reactions have been reported.[193-195] If these reactions to SCIT occur, treatment with another aluminum hydroxide-free product is preferred (Grade D).[11]

8.2 | SLIT

Sublingual immunotherapy is regarded to be a safe and well-tolerated treatment (Table 8).[11,14,196,197,198]

Severe SRs with SLIT appear to be much less likely than with SCIT although the overall rate of any adverse reactions is similar in both SCIT and SLIT[14,184] (see Tables S2 and S3 in online supplement for details of classification[123,199]). In a review of 66 SLIT studies (over 4000 patients who received over a million doses), there was 1 SR for approximately every 4 years of treatment and only 1 severe SR per 384 treatment years.[198] There are no new safety concerns in more recent studies.[14] Several severe reactions—in some cases with anaphylaxis—are described in the literature occurring within 30 minutes of sublingual administration of allergens in droplet or tablet form.[34] In these cases, SLIT was not administered according to the standards (nonstandardized extracts, rush protocols, excessive allergen dose, patients in whom SCIT had previously been interrupted due to severe reactions). Patients should be observed for at least 30 minutes after the first dose (Grade C) and supervised by staff able to manage anaphylaxis (Grade C). As in SCIT, concomitant, uncontrolled asthma has been reported to be associated with severe systemic reactions after SLIT.[34] In the recently published European Survey, the rate of SRs under SLIT was also reported to be low (1.1% of all SLIT-treated patients).[184,185]

The majority of adverse events in SLIT develop at home without any medical observations. Patients should therefore be thoroughly informed about how to recognize and manage reactions, particularly severe ones (Grade D). Patients also need education on what to do if a dose is forgotten and when SLIT should be temporarily interrupted (e.g, oropharyngeal lesions) (Grade D).[11] When 1 or more

severe adverse reactions occur, the allergist (specialist and subspecialists) should rediscuss the benefits and risks of SLIT with the patient and decide whether or not treatment should be continued (Grade D). As for SCIT, cessation of treatment or adaptation of the dosage should follow the summary of product characteristics (SmPC).

The frequency of local adverse events during SLIT correlates with the dosage and has been reported to be 40-75%, for example, temporary local mucosal reactions (oral pruritus or dysesthesia, swelling of the oral mucosa, throat irritation) or abdominal pain.[34,197-199] Most of these reactions occur during the initial phase of the treatment course (commonly in the first 3 weeks). They are commonly considered to be of mild intensity and self-limiting.[34,97] Nevertheless, these reactions may lead to cessation of treatment, as observed in 4-8% of cases reported in recent trials of SLIT tablets.[56,85,99,138] (see section "adherence"). As in SCIT, local adverse reactions may be diminished by the intake of oral antihistamines (Grade A).

For SLIT, temporary cessation of therapy may be advised in a number of situations to reduce the potential for adverse effects. For example, for 7 days following dental extraction or oral surgery or following shedding of a deciduous tooth; while an oral ulcer or open wound in the mouth heals; or during an upper respiratory tract infection in patients with asthma. Individual product SmPCs may list additional advice.

9 | PREVENTIVE EFFECTS OF AIT FOR AR

A 3-year course of AIT reduces the likelihood that children and adolescents with allergic rhinitis driven by pollen allergy go on to develop asthma up to 2 years post-AIT.[23] There is currently no convincing evidence for a preventive effect of HDM AIT or for prevention of new sensitivities.[23] This is further discussed in the EAACI AIT Prevention Guidelines.[23]

10 | PHARMACOECONOMIC ASPECTS OF AIT VERSUS PHARMACOTHERAPY FOR AR

Pharmacoeconomic studies that only analyze costs in monetary units have reported beneficial healthcare expenditure of AIT in the long-run although savings are not expected in the first year. The majority of pharmacoeconomic studies support the viewpoint that AIT gives value for money, with cost-effectiveness within 6 years of treatment initiation.[201] Retrospective and prospective observational studies have shown that SCIT and SLIT positively affect healthcare expenditure in pharmacotherapy with a reduction in expenditure of 12% to 80%.[202-206] A reduction in medical costs in the AIT vs placebo groups has been repeatedly reported, but these savings did not compensate the costs of AIT.[202,207,208]

In contrast to cost-only studies, cost-effectiveness and cost-utility analysis evaluate the effects of treatment in terms of clinical benefits or health-related quality of life (i.e, quality-adjusted life years [QALYs]). An incremental cost-effectiveness ratio (ICER), which is defined as costs divided by benefits, can be calculated to estimate the costs of a certain gain. Several health economics studies that include cost-effectiveness and cost-utility calculations have demonstrated that SCIT and SLIT are economically advantageous to pharmacotherapy.[209-212]

Seven studies based on RCT data conducted from a health system perspective and using QALYS as their outcome measure suggests that SLIT and SCIT would be considered cost-effective in this patient population in United Kingdom at the standard National Institute for Health and Care Excellence (NICE) cost-effectiveness threshold of £20 000 (€24 616) per QALY.[213-219] The studies comparing SCIT and SLIT have given mixed results and do not allow us to conclude whether either treatment is more cost-effective.[220] ICERs for cost evaluations of AIT seem to vary substantially between different health systems suggesting that straightforward conclusions may not be generalizable even across seemingly similar countries.[215] Finally, the quality of the studies and the general lack of attention to characterizing uncertainty and handling missing data should be taken into account when interpreting these results.

11 | SUMMARY, GAPS IN THE EVIDENCE AND FUTURE PERSPECTIVES

The EAACI Taskforce on AIT for AR has developed this guideline as part of the EAACI AIT Guidelines Project. This guideline has been informed by a formal SR and meta-analysis of AIT for AR.[14] The guidelines provide evidence-based recommendations for the use of AIT for patients with AR with or without allergic conjunctivitis. A comparison of SCIT and SLIT is provided in Figure 2. Practical guidance is provided in Box 4 and a summary of the guidelines is provided in Box 5. An approach to the use of AIT for AR across the healthcare system is summarized in Figure 3. The recommendations should be of value to all healthcare professionals involved in the management of patients with AR. There are barriers to the wider use of AIT but equally there are facilitators that could be put into place to widen access to AIT (Table 9).

The key limitation of this guideline is the considerable heterogeneity seen in elements of the underpinning meta-analysis. For newer products, such as the SLIT grass pollen and house dust mite tablets, we have consistent low risk of bias data and very secure recommendations. For older products, such as house dust mite SCIT products, there is considerable heterogeneity in the meta-analysis weakening the strength of recommendations around those products. Many of these older studies were poorly designed and reported; for example, it is often not clear whether intention-to-treat or per-protocol analyses were being reported making it impossible to combine similar analyses in the meta-analysis. Indirect comparisons within the meta-analysis strongly suggest that some products are more effective than others. A network analysis approach, which allows indirect comparisons across trials based on a common comparator (usually

TABLE 8 Recommendations: adverse events with allergen immunotherapy (AIT) for allergic rhinoconjunctivitis

Recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Contextual comments	Key references
SCIT or SLIT					
For correctly selected patients, SCIT or SLIT is recommended as, appropriately administered, it is safe and well tolerated	I	A	Strong recommendation based on low risk of bias RCT studies and observational studies[14]	Consistent evidence	Dhami[14]
It is recommended that asthma should be controlled before commencing AIT as insufficiently controlled asthma is a risk factor for both SCIT and SLIT	III	C		Expert opinion from observational studies	Bernstein[31], Amin[200], Calderon[34]
Premedication with an antihistamine is recommended as it reduces the frequency and severity of local and systemic cutaneous reactions but does not eliminate the risk of other systemic adverse reactions including anaphylaxis	I	A	Strong recommendation based on low risk of bias RCTs.[187,188]	Consistent strong evidence from RCT studies	Nielsen[187], Reimers[188]
When one or more severe adverse reactions occur, it may be recommended that the allergist (specialist and subspecialists) should rediscuss the benefits and risks of AIT therapy with the patient and decide whether or not treatment should be continued. This decision and continuation of treatment should be in line with the Summary of Product Characteristics (SmPC).	V	D		Expert opinion from clinical experience	Expert opinion
SCIT					
It is recommended that patients should remain under observation for at least 30 min after a SCIT injection	III	C		Consistent observational data	Epstein[182]
If subcutaneous granulomas develop with aluminum hydroxide containing SCIT products, it may be recommended that a replacement allergen extract that does not contain aluminum hydroxide should be used.	V	D		Expert opinion	Pfaar[11]
It is recommended that SCIT should be administered by competent staff with immediate access to resuscitation equipment and a doctor trained in managing anaphylaxis.	III	C		Consistent observational data on adverse effects reported in SR	Dhami[14]
SLIT					
It is recommended that patients should remain under observation for at least 30 min after an initial SLIT dosage	III	C		Expert opinion based on consistent observational data	Calderon[34]
It is recommended that initial SLIT dosage should be administered by competent staff with immediate access to resuscitation equipment and a doctor trained in managing anaphylaxis.	IV	C		Consistent observational data on adverse effects reported in SR	Dhami[14]
It is recommended that patients receiving SLIT should be informed about how to recognize and manage reactions, particularly severe ones. Patients also need to know what to do if a SLIT preparation is forgotten and when SLIT should be temporarily interrupted (e.g, oropharyngeal lesions).	V	D		Expert opinion from clinical experience	Expert opinion

BOX 3 Risk factors for systemic reactions during AIT

Current allergy symptoms and potential allergen exposure
Current infections
Mast cell disease
Previous systemic reaction to SCIT or SLIT
Uncontrolled or severe asthma
A high degree of sensitization
Excess dose escalation during initiation
Beta-blockers use
Poor injection technique
Overdose of allergen extract
Failure to follow manufacturer's recommendation for dose reduction when change to new production batch
High-intensity physical exercise

Adapted from Pfaar et al.[11].

the placebo group), would allow us to improve our comparative estimates between products.[221] This would allow product-specific recommendations to be made. The different local regulations[47] and availability of products[48] makes this difficult at a European level. So before treatment with a specific product is initiated, clinicians need to undertake an individual product-based evaluation of the evidence for efficacy, focusing on low risk of bias studies which are generally the larger, more recent ones.[11]

There are a number of areas in this guideline where there is no low risk of bias evidence, and these signify the gaps in the current evidence base. The key ones are highlighted here and in Table 10. There is a major gap in the evidence base for the clinical effectiveness of AIT in children and adolescents with recommendations at least 1 grade lower than for adults in most areas. As AR usually starts in childhood and AIT has the potential to change the natural course of the disease and prevent the development of asthma, this age group has most to benefit. Once safety is established in adult studies, pediatric studies need to be commenced using validated, common outcome measures.[11] There are also little data in the

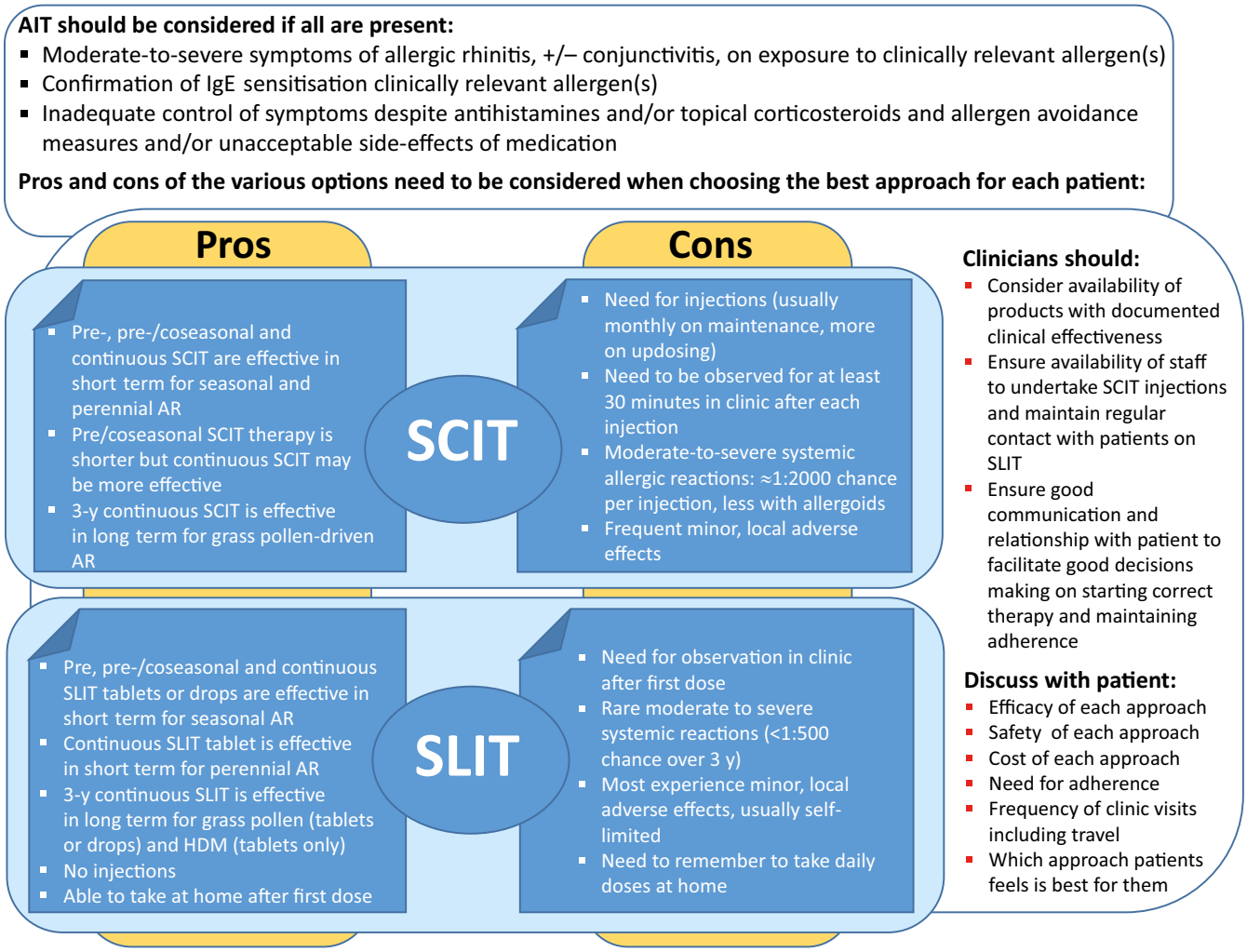


FIGURE 2 Schematic approach to deciding which approach to allergen immunotherapy (AIT) is best to use in individual patients. For details to specific recommendations, see table 3. For details about local and systematic adverse reactions, see adverse event section above

BOX 4 Practical considerations for healthcare professionals delivering AIT

- Training and facilities
  - Expertise in the diagnosis and differential diagnosis of AR by history and supporting SPT or specific IgE testing.
  - Training in recognition and management of severe allergic reactions including anaphylaxis.
  - Availability of equipment and trained personal to manage severe allergic reactions.
  - Training in administration of specific AIT products.
  - Facilities to observe patient for at least 30 minutes with SCIT injections and initial dose of SLIT.
- Assessing patient and deciding on best approach
  - Effective communication with patients and/or family about practicalities of AIT, expected benefits and potential adverse effects.
  - Identification of clinical contraindications to AIT.
  - Select an AIT product with documented evidence for efficacy and safety, for the patient's specific presentation, wherever possible.
- Undertaking AIT
  - Start AIT for seasonal AR at least 4, and preferably 2, months before the pollen season.
  - Preferably start AIT for perennial AR when allergen exposure is lowest and avoidance measures are in place.
  - Dose reductions (usually 50%) or split doses for adverse effects, intercurrent illness, or delayed dosing as recommended by SmPC for SCIT.
  - Dose interruption with oral lesions and other issues as recommended by SmPC for SLIT.
  - Facilities to regularly follow up patient promoting adherences to therapy and watching for adverse effects.

elderly particularly for patients with multimorbidity. Additionally, more RCTs need to follow participants postcessation of therapy to establish long-term clinically effectiveness, especially for HDM respiratory allergy. Dose-finding studies are needed. Agreement about the clinically meaningful effect size of AIT treatment would assist in the interpretation of clinical trial data and help facilitate stratification studies to help predict which patients will respond best to which forms of AIT. The collection of patent-reported outcomes in studies would ensure the patient experience is captured. Additionally, we need data from randomized cost-effectiveness and cost-utility studies to use in discussions with healthcare funders. We need biomarkers to predict and quantify the effectiveness of AIT to assist in patient selection.[222] Suboptimal adherence with AIT is likely to impact on its effectiveness; novel approaches to improve effectiveness should be developed in partnership with patients. Also, to allow better comparison of safety between approaches, studies need to use a unified approach to classifying side-effects is required. A common and international recognized language should be used when reporting severe adverse reactions, such as the MedDRA classification and AIT-related local and systemic reactions should be reported in line with internationally standardized classification such as the WAO-grading system.[123,199] Filling these gaps would allow the generation of much clearer guidelines for clinicians allowing them to stratify patients to the best therapy. It may not be possible to achieve this with only randomized, controlled prospective data; large, real-life, controlled data need to be examined although the potential for bias and confounding needs to be acknowledged.

Despite all these gaps, we have clear evidence for the clinical effectiveness of AIT, for SCIT, SLIT tablets, and SLIT drops, for adults and children with moderate-to-severe AR that is otherwise uncontrolled despite pharmacotherapy. We have evidence-based recommendations for specific patient groups and specific approaches. There is now a need to ensure that primary care healthcare professionals know which patients might benefit from AIT (Box 6), that national healthcare providers understand that AIT is cost-effective and that patients and patient support groups are aware of this approach. This will be supported by the implementation strategy for this guideline with efforts being put into disseminating the guideline. This will be supported with materials such as schedules and country-specific product evaluations as exemplified by the German, Austrian, and Swiss guideline.[11] Finally, as new evidence is published, these guidelines will need to be updated with revision of specific recommendations to reflect the new data.

ACKNOWLEDGMENTS

The EAACI Guideline: AIT for rhinoconjunctivitis Taskforce would like to thank Kate Crowley and Lynn Reeve for their administrative assistance; Stefan Vieths and Andreas Bonertz for their advice; Claus Bachert, G. Walter Canonica, Gabriele Di Lorenzo, Peter Eng, Hans Joergen Malling, and Harold Nelson for their constructive, expert review of the draft guidelines; all the EAACI members who commented on the draft guideline via the public Web site; and to funding from EAACI and the BM4SIT project (grant number 601763) in the European Union's Seventh Framework Programme FP7.

AUTHOR CONTRIBUTIONS

G Roberts and O Pfaar jointly chaired the EAACI Guideline: AIT for rhinoconjunctivitis Taskforce; together with A Muraro and A Sheikh, they conceptualized the manuscript. CA Akdis, IJ Ansotegui, SR Durham, R Gerth van Wijk, S Halken, D Larenas-Linnemann, R Pawankar, C Pitsios, A Sheikh, and M Worm all initially drafted sections of the guideline. S Arasi, M Calderon, C Cingi, S Dhami, JL

BOX 5 Summary of the EAACI Rhinoconjunctivitis AIT Guidelines

- AIT should be considered with symptoms strongly suggestive of allergic rhinitis, with or without conjunctivitis; evidence of IgE sensitization to 1 or more clinically relevant allergens; and moderate-to-severe symptoms despite regular and/or avoidance strategies.
- AIT may also be considered in less severe AR where a patient wishes to take advantage of its long-term effect on rhinitis and potential to prevent asthma with grass pollen AIT.
- More standardized products with documented evidence for efficacy in clinical trials are needed.
- Standardized AIT products with evidence of efficacy in the clinical documentation should be used when they are available.
- An individual product-based evaluation of the evidence for efficacy is recommended before treatment with a specific product is initiated.
- Key contraindications are severe or uncontrolled asthma; active, systemic autoimmune disorders; active malignant neoplasia. Careful review of benefits and risks is required with history of severe reactions, beta-blocker therapy, severe cardiovascular disease, other autoimmune disorders, severe psychiatric disease, poor adherence, and immunodeficiency. The individual patient's conditions should be considered when deciding whether to prescribe AIT and the summary of product characteristics (SmPC) should be reviewed for specific contraindications for individual preparations.
- For each recommendation, an individual product-based evaluation of the evidence for efficacy is recommended before treatment with a specific product is initiated given the heterogeneity in meta-analysis results:
    - Continuous SCIT is recommended for seasonal (Grade A for adults, B for children) or perennial (Grade B for adults, C for children) AR for short-term benefit in those with moderate-to severe disease.
    - Pre- and pre-/coseasonal SCIT is recommended for seasonal AR for short-term benefit (Grade A for adults, B for children).
    - Both modified (allergoids) and unmodified allergen SCIT extracts are recommended for AR for short-term benefit (Grade A for adults, B for children).
    - Continuous grass pollen SCIT is recommended for AR for short- and long-term benefit (Grade A for adults, B for children).
    - Pre-/coseasonal or continuous SLIT is recommended for seasonal ARs for short-term benefit (Grade A).
    - SLIT with tablets for pollens or HDM can be recommended for AR for short-term benefit (Grade A).
    - SLIT aqueous solutions for pollens can be recommended for AR for short-term benefit (Grade B for adults, A in children).
    - SLIT aqueous solutions for HDM cannot be recommended for AR for short-term benefit.
    - Continuous grass pollen SLIT tablets or SLIT solution is recommended for AR for long-term benefit (Grade A).
    - HDM SLIT tablet can be recommended for AR for long-term benefit (Grade B for adults, C for children).
- Polysensitized patients who are poly-allergic for taxonomically related homologous allergens can be recommended to receive either a single allergen or a mixture of homologous allergens from that biological family that covers all the major allergens (Grade A).
- Patients who are poly-allergic for nonhomologous allergens may be recommended to start AIT with either the allergen responsible for most of their allergic rhinoconjunctivitis symptoms or separate treatment with the 2 clinically most important allergens (Grade C).
- In children aged 2-5 y of age, it is recommended that consideration should be given to likely benefits and risks associated with AIT for AR (Grade D).
- AIT can be recommended in otherwise healthy elderly patients with AR whose symptoms cannot be adequately controlled by pharmacotherapy (Grade A for SLIT, B for SCIT).
- If patients have not started AIT and are pregnant, it is recommended to wait until after pregnancy to initiate therapy (Grade D).
- It can be recommended that patients on SLIT are followed up every 3 mo to maximize adherence (Grade B).
- To achieve long-term efficacy, it is recommended that a minimum of 3 y of therapy is used (Grade A).
- Premedication with an antihistamine is recommended as it reduces the frequency and severity of local and systemic cutaneous reactions but does not eliminate the risk of other systemic adverse reactions including anaphylaxis (Grade A).
- It is recommended that patients should wait in the clinic for at least 30 minutes after a SCIT injection (Grade C).
- It is recommended that SCIT should be administered by competent staff, trained to diagnosed symptoms of early systemic reactions or anaphylaxis, with immediate access to resuscitation equipment and a doctor trained in managing anaphylaxis. (Grade C).
- It is recommended that patients should wait in clinic for at least 30 minutes after an initial SLIT dosage and staff and equipment should be available to manage any severe local or systemic reaction or anaphylaxis (Grade C).
- It is recommended that patients receiving SLIT should be informed about how to recognize and manage adverse reactions, particularly severe ones (Grade D).

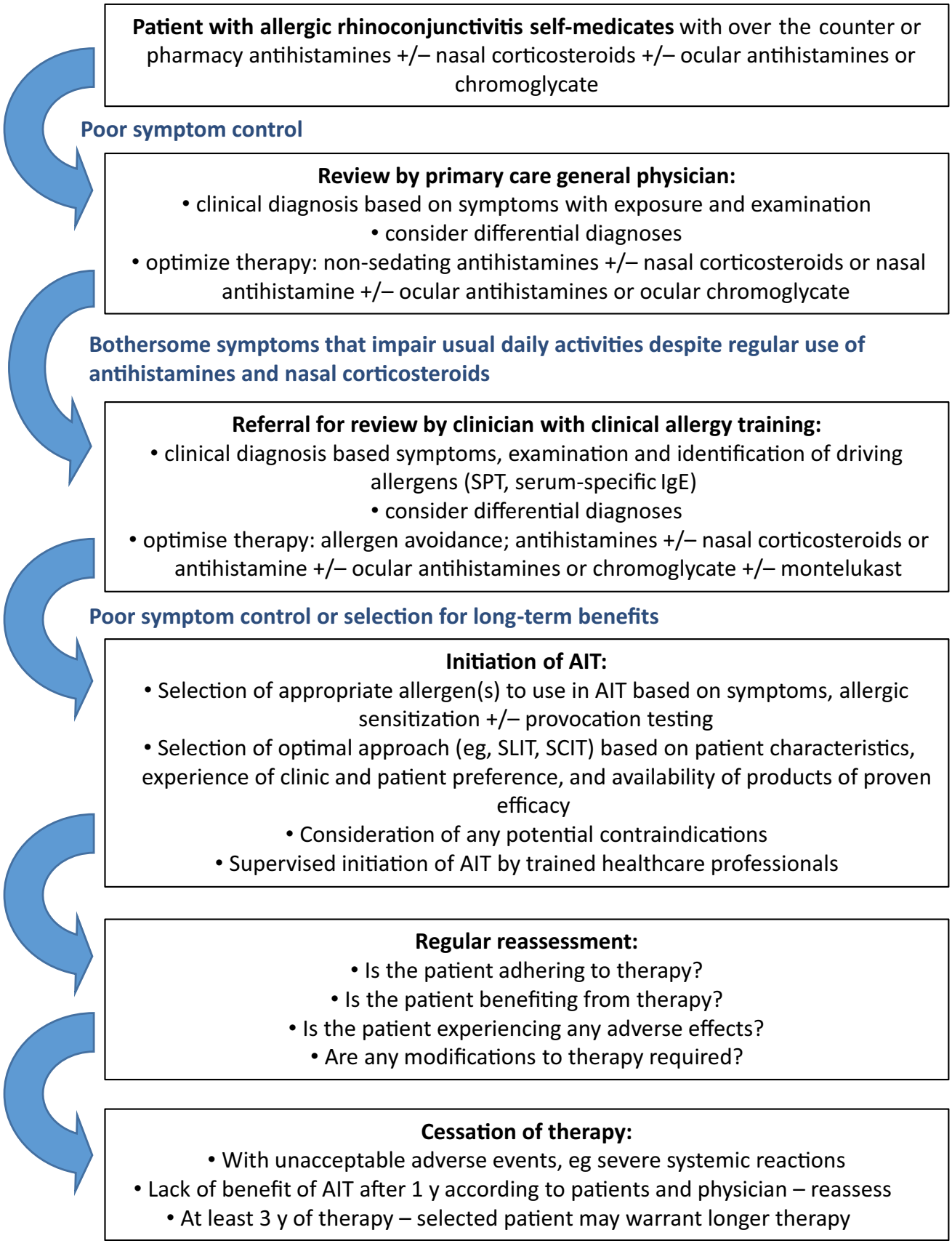


FIGURE 3 Approach to using allergen immunotherapy (AIT) for allergic rhinoconjunctivitis. Schematic illustration of the approach to using AIT for AR starting with self-medication and management in primary care moving to assessment by a clinician trained in clinical allergy for consideration and initiation of AIT in suitable patients. Structure of healthcare systems differs between countries

TABLE 9 Implementation considerations: AIT for treatment of allergic rhinoconjunctivitis

Recommendation areas	Barriers to implementation	Facilitators to implementation	Audit criteria	Resource implications
SCIT or SLIT therapy	Lack of awareness of how to assess severity of AR Appreciation of SCIT and SLIT as treatment options Access to providers offering SCIT and/or SLIT at convenient locations and/or affordable cost Lack of knowledge about the relative efficacies and safety of different products	Development of integrated care pathways for AR incorporating primary and secondary care Increase in number of specialists able and willing to provide SCIT and/or SLIT Subsidized provision of SCIT and SLIT Document detailing and training about the efficacy and safety of individual products	Proportion of patients with moderate-to-severe seasonal AR who are offered and use SCIT or SLIT	The resource implications include professional time to develop and agree integrated care pathways The costs of training and upskilling allergist (specialist and subspecialists) to deliver SCIT and/or SLIT Training of primary care nurses and doctors to deliver immunotherapy as shared care agreements where appropriate Financial costs of subsidizing access to SCIT and SLIT
Selecting the appropriate AIT in patients with polysensitization +/− polyallergy	Lack of documentation for individual AIT products Effective identification of the key allergen(s) driving symptoms	Information to clinicians and patients about the better efficacy of single allergen or a mixture of well-documented homologous allergens Use of component-resolved diagnosis and provocation testing	Proportion of patients receiving either a single allergen or a mixture of well-documented homologous allergens Proportion of patients where additional measures are taken to identify the driving allergen(s)	Training for clinicians Availability of appropriate AIT products Access to component-resolved diagnostics and provocation testing
Using AIT in patients with controlled, co-existing asthma	Lack of education of clinicians and patients	Information to clinicians and patients about safety of AIT with co-existing asthma Control asthma before commencing AIT	Proportion of patients with co-existing asthma receiving AIT	Available AIT service
Consideration of AIT in pediatric patients with AR	Available AIT clinical service for children	Information about the place of AIT in managing AR in children for health purchases, primary care clinicians and patients	Proportion of pediatric patients with moderate-to-severe seasonal AR who use continuous SCIT	Availability of a clinical service for children able to deliver AIT for AR.
Consideration of AIT in otherwise healthy elderly patients with AR	Lack of access to AIT for AR in general or specific products	Information about the place of AIT in managing AR in the elderly for health purchases, primary care clinicians and patients	Proportion of elderly patients with moderate-to-severe seasonal AR who use AIT	Availability of a clinical service able to deliver AIT for AR
Adherence to AIT	Lack of patient education about AIT	Information for patients and use of simple reminders Three-monthly follow-up for SLIT patients Good physician–patient relationship and communication regarding side-effects and time course of treatments	Assessment of understanding of patients on AIT Assessment of adherence and use of reminders by patients on AIT	Resources to educate patients Investment in written communication and regular follow-up with access to advice regarding side-effects if necessary
Use of premedication with an antihistamine to reduce adverse effects	Lack of knowledge by clinicians and patients	Training of clinicians using AIT	Proportion of patients who receive premedication with antihistamine	Resources for training clinical staff Availability of medication

(Continues)

TABLE 9 (Continued)

Recommendation areas	Barriers to implementation	Facilitators to implementation	Audit criteria	Resource implications
Observation for at least 30 min after a SCIT injection or initial SLIT dosage by trained staff	Lack of understanding by clinicians of delayed effects Lack of trained staff and workforce time pressures	Training of clinicians using SCIT and SLIT Staff availability and rotas for administration and observations	Proportion of patients who wait 30 min after receiving SCIT or initial SLIT dosage Proportion of staff trained in management of severe adverse reactions	Resources for training clinical staff Time set aside for observation
Information for patients receiving SLIT about how to recognize and manage reactions and when therapy should be temporarily interrupted	Lack of understanding by patients receiving SLIT and clinicians administering	Training of patients and clinicians	Proportion of patients receiving SLIT trained in the self-management of severe adverse reactions	Resources for training patients and clinicians

Fauquert, E Hamelmann, P Hellings, L Jacobsen, EF Knol, SY Lin, P Maggina, R Mösges, H Oude Elberink, G Pajno, EA Pastorello, M Penagos, G Rotiroti, CB Schmidt-Weber, F Timmermans, O Tsilochristou, E-M Varga, J Wilkinson, A Williams and L Zhang as members of the Taskforce plus I Agache, E Angier, M Fernandez-Rivas, M Jutel, S Lau, R van Ree, D Ryan, and GJ Sturm as chairs of the other AIT Guidelines were all involved in conceptualizing the guidelines and critically reviewed guideline drafts. S Dhami and S Arasi also provided methodological support to the Taskforce. F Timmermans was the patient group representative. All the authors satisfied the international authorship criteria (further details in Table S2). This guideline is part of the EAACI Guidelines on AIT, chaired by Antonella Muraro, and coordinated by Graham Roberts.

CONFLICT OF INTEREST

G. Roberts has a patent issued: "Use of sublingual immunotherapy to prevent the development of allergy in at risk infants"; and his university has received payments for the activities he has undertaken giving expert advice to ALK, and presenting at company symposia for ALK, Allergen Therapeutics, and Meda, and serving as a member of an Independent Data Monitoring Committee for Merck outside of this work. O. Pfaar reports grants and personal fees from ALK-Abelló, Allergopharma, Stallergenes Greer, HAL-Allergy Holding B.V./HAL-Allergie GmbH, Bencard Allergie GmbH/Allergy Therapeutics, Lofarma, Biotech Tools S.A., Laboratorios LETI/LETI Pharma, and Anergis S.A.; grants from Biomay, Nuvo, and Circassia; and personal fees from MEDA Pharma, Sanofi US Services, Mobile Chamber Experts (a GA^{2}LEN Partner), Novartis Pharma and Pohl-Boskamp, outside this work. CA Akdis has nothing to disclose. IJ. Ansotegui reports personal fees from SANOFI, Bayer, Pfizer, FAES FARMA, MIT FARMA, HIKMA, Menarini, and Bial Aristegui, outside this work. S. Durham reports grants from Regeneron (USA), Biotech Tools, ALK (Denmark), Food Standards Agency (UK), and National Institute of Health Research (UK) and personal fees from Anergis (Switzerland), Circassia (UK), Biomay (Austria), Merck, Allergy Therapeutics (UK), ALK (Hørsholm, Denmark), med update GmbH (Germany), and Allergy Therapeutics, outside of this work. R. Gerth van Wijk reports personal fees from ALK-Abello, Circassia, and Allergopharma, during the conduct of this work. S. Halken reports personal fees from ALK-Abello and from different companies, for example, Meda, Stallergenes, Allergopharma, and ALK-Abello, outside of this work. D. Larenas-Linnemann reports grants and personal fees from Astrazeneca, Boehringer-Ingelheim, MEDA, Novartis, grants and personal fees from Sanofi, UCB, GSK, Pfizer, MSD, grants from Chiesi, TEVA, personal fees from Grunenthal, Amstrong, Stallergenes, ALK-Abelló, personal fees from DBV, outside the submitted work; and Chair immunotherapy committee CMICA, Member immunotherapy committee or interest group EAACI, WAO, SLAAI, Board of Directors and Program Chair CMICA 2018-2019. R. Pawankar has nothing to disclose. C. Pitsios has nothing to disclose. A. Sheikh reports grants from the EAACI during the conduct of this work. M. Worm reports grants from Allergopharma, Novartis, Stallergenes, Medic Pharma,

TABLE 10 Gaps in the evidence for allergen immunotherapy (AIT) for allergic rhinoconjunctivitis

Gaps	Plan to address	Priority
Lack of biomarkers to predict and quantify the effectiveness of AIT	Prospective observational studies to validate potential predictive biomarkers	High
Agreement about the clinically meaningful effect size of AIT treatment (active vs placebo treated patients)	Consensus discussion	High
Low risk of bias randomized controlled data for children and adolescents	More prospective controlled trials using standardized products	High
Evidence for long-term clinical effectiveness after treatment cessation	More prospective controlled trials with follow-up post-treatment cessation in adults and children	High
Standardization of grading of adverse effects of AIT	Future clinical trials should use the WAO local and systemic reaction grading system	High
Approaches to improve adherence with AIT	Working with patients to develop novel approaches that can be tested in prospective controlled trials and real-life settings	High
Randomized cost-effectiveness and cost-utility studies adjusted to socioeconomic differences within and between countries	Additional multinational studies with a health economics focus	High
For some AIT products, there is little or no evidence for clinical effectiveness	Dose ranging studies to optimize dose for efficacy and safety; prospective controlled trials; use of patient reported outcomes; use of products with proven effectiveness	High
Approaches to minimize adverse effects	More prospective observation and controlled trials. A subanalysis of different phenotypes populations in current RCTs and real-life settings	Moderate
Effectiveness of mixtures of homologous allergens from the same, related or different biological families	More prospective controlled trials using the commonest allergens	Moderate
Good evidence base for contraindications to AIT	Registries recording patient details, AIT, outcome and adverse effects	Moderate
Value of provocation tests in identifying the most appropriate allergen to use in AIT	Prospective controlled studies to assess benefit of provocation testing	Moderate
Management of AIT in patients who become pregnant on therapy	More prospective observational studies	Low
Lack of standardized AIT preparations for orphan allergens	Multicentre studies	Low

BOX 6 Key messages for primary care

- Diagnosis of AR is by history
- Where severe, treat with nonsedating, long-acting antihistamine and topical nasal corticosteroid (with appropriate nasal spray training) and/or topical ocular cromoglycate or antihistamine.
- Check for any co-existing asthma; this should be properly controlled when using AIT.
- AIT is effective for AR driven by pollens, house dust mite, and animal dander.
- AIT is indicated for AR with moderate-to-severe symptoms that are not controlled by pharmacotherapy or avoidance strategies (where appropriate).
- AIT may be given by subcutaneous (SCIT) or sublingual route (SLIT) as either SLIT tablets or SLIT drops.
- AIT therapy needs to be continued for at least 3 y for postcessation effectiveness.
- Local adverse effects, which are mild in severity and self-limited without the use of rescue medication, are common with SLIT when starting therapy.
- More severe systemic allergic adverse events are infrequently seen and more commonly with SCIT than SLIT.
- SCIT injections and the initial SLIT dose should be given by healthcare personal who are trained in AIT and the management of any adverse events.
- At least a 30-minute observation period is required for all SCIT injections and the initial dose of SLIT.

and ALK-Abello. S. Arasi reports payment from Evidence-Based Health Care Ltd during the conduct of this work. M. Calderon has received honorarium in advisory boards for ALK and Hal-Allergy and served as a speaker for ALK, Merck, and Stallergenes Greer. C. Cingi has nothing to disclose. S. Dhami reports grants from EAACI to carry out the review, during the conduct of this work. JL Fauquert has nothing to disclose. E. Hamelmannhas served on scientific advisory boards and received honorarium for lectures on scientific meetings for ALK, AllergoPharma, Bencard, HAL, Leti, Stallergenes. P. Hellings has nothing to disclose. L. Jacobsen reports personal fees from EAMG, outside this work. E.F. Knol has nothing to disclose. S.Y. Lin has nothing to disclose. P. Maggina has nothing to disclose. R. Mosges reports personal fees from ALK, Allergopharma, Allergy Therapeutics, Friulchem, Hexal, Servier, Klosterfrau, Bayer, FAES, GSK, MSD, Johnson& Johnson, Meda, Stada, UCB, and Nuvo; grants from ASIT biotech, Leti, Optima, bitop AG, Hulka, and Ursapharm; grants and personal fees from Bencard and Stallergenes; grants, personal fees, and nonfinancial support from Lofarma; nonfinancial support from Roxall, Atmos, Bionorica, Otonomy, and Ferrero; and personal fees and nonfinancial support from Novartis, outside this work. H. Oude Elberlink reports grants from ALK-Abello during the conduct of this work. G.B. Pajno reports grants from Stallergenes during the conduct of this work. E.A. Pastorello has nothing to disclose. M. Penagos reports personal fees from Stallergenes and ALK, outside this work. G. Rotiroti reports personal fees from ALK-Abello, outside this work. C. Schmidt-Weber reports grants from Allergopharma and Leti and honorarium from PLS-Design, Allergopharma, and Leti; is a member of scientific advisory board for Leti; holds shares in PLS-Design; and hopes to develop a patent. F. Timmermans has nothing to disclose. O. Tsilochristou has nothing to disclose. E-M Varga reports lecture fees from ALK-Abello, Stallergenes Greer, Allergopharma, Bencard, MEDA, and Nutricia outside the submitted work. J. Wilkinson has nothing to disclose. A. Williams reports other grants from ALK-Abello (UK) and Diagenics Ltd (UK), outside this work; and travel expenses for education meetings from the EAACI and BSACI. L. Zhang has nothing to disclose. I. Agache has nothing to disclose. E. Angier reports previous advisory board membership for Stallergenes, Meda, and Schering Plough plus a sponsored lecture by Meda and attendance at a ALK SOSA meeting. M. Fernandez-Rivas reports personal fees from ALK, Merck, and GSK. M. Jutel reports personal fees from Allergopharma, Anergis, Stallergenes, ALK, LETI outside the submitted work. S. Lau reports a grant from Allergopharma plus personal fees for data monitoring committee activities for Merck. R. van Ree reports personal fees from HAL-Allergy BV and Citeq BV outside of the submitted work. D. Ryan reports personal fees from Stallergenes, Thermo Fisher, MEDA outside of the submitted work. G. Sturm reports grants and personal fees from ALK-Abello, Novartis, Stallergenes, Bencard Allergy, and Leti outside of the submitted work. A. Muraro reports speaker's honoraria for Novartis, Meda, Nestle, Stallergenes, ALK outside the submitted work.

ORCID

G. Roberts http://orcid.org/0000-0003-2252-1248
O. Pfaar http://orcid.org/0000-0003-4374-9639

REFERENCES

1. Eifan WO, Durham SR. Pathogenesis of rhinitis. *Clin Exp Allergy*. 2016;46:1139-1151.
2. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. *Lancet*. 2011;378:2112-2122.
3. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. *J Allergy Clin Immunol*. 2010;126:778.
4. Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: results from the pediatric allergies in America survey. *J Allergy Clin Immunol*. 2009;124:S43-S70.
5. Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy*. 2009;64:123-148.
6. Walker S, Khan W, Fletcher M, Cullinan P, Harris J, Sheikh A. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. *J Allergy Clin Immunol*. 2007;120:381-387.

7. Roberts G, Xatzipsalti M, Borrego LM, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy*. 2013;68:1102-1116.
8. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma ARIA 2008 update in collaboration with the World Health Organization, GA2LEN and Aller Gen. *Allergy*. 2008;63:8-160.
9. Terreehorst I, Hak E, Oosting AJ, et al. Evaluation of impermeable covers for bedding in patients with allergic rhinitis. *New Engl J Med*. 2003;349:237-246.
10. Sheikh A, Hurwitz B, Nurmatov U, van Schayck CP. House dust mite avoidance measures for perennial allergic rhinitis. Cochrane Database of Systematic Reviews. 2010, Issue 7. Art. No.: CD001563. https://doi.org/10.1002/14651858.CD001563.pub3.
11. Pfaar O, Bachert C, Bufe A, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). *Allergo J Int*. 2014;23:282-319.
12. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol*. 2015;136:556-568.
13. Jutel M, Agache I, Bonini S, et al. International consensus on allergen immunotherapy II: mechanisms, standardization, and pharmacoeconomics. *J Allergy Clin Immunol*. 2016;137:358-368.
14. Dhami S, Nurmatov U, Arasi S, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. *Allergy*. 2017;72:1597-1631.
15. Rondón C, Canto G, Blanca M. Local allergic rhinitis: a new entity, characterization and further studies. *Curr Opin Allergy Clin Immunol*. 2010;10:1-7.
16. Rondon C, Campo P, Herrera R, et al. Nasal allergen provocation test with multiple aeroallergens detects polysensitization in local allergic rhinitis. *J Allergy Clin Immunol*. 2011;128:1192-1197.
17. Agree Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care*. 2003;12:18-23.
18. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *Can Med Assoc J*. 2010;182:E839-E842.
19. Dhami S, Nurmatov U, Roberts G, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: protocol for a systematic review Clinical and Translational. *Allergy*. 2016;6:12.
20. Oxford Centre for Evidence-based Medicine. Levels of evidence and grades of recommendation. 2013. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/ (last accessed 27 July 2017).
21. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases A WHO position paper. *J Allergy Clin Immunol*. 1998;102:558-562.
22. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126:466-476.
23. Halken S, Larenas-Linnemann D, Roberts G, et al. EAACI Guidelines on Allergen Immunotherapy: prevention of allergy. *Pediatr Allergy Immunol*. 2017;28:728-745.
24. Bachert C, Larche M, Bonini S, et al. Allergen immunotherapy on the way to product-based evaluation – a WAO statement. *World Allergy Organ J*. 2015;8:29.
25. Kristiansen M, Dhami S, Netuveli G, et al. Allergen immunotherapy for the prevention of allergy: a systematic review and meta-analysis. *Pediatr Allergy Immunol*. 2017;28:18-29.
26. Campo P, Rondón C, Gould HJ, Barrionuevo E, Gevaert P, Blanca M. Local IgE in non-allergic rhinitis. *Clin Exp Allergy*. 2015;45:872-881.
27. Pitsios C, Demoly P, Bilò MB, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. *Allergy*. 2015;70:897-909.
28. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127:S1-S55.
29. Bousquet J, Hejjaoui A, Dhivert H, Clauzel AM, Michel FB. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract: systemic reactions during the rush protocol in patients suffering from asthma. *J Allergy Clin Immunol*. 1989;83:797-802.
30. Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. *Ann Allergy Asthma Immunol*. 2001;87:47-55.
31. Bernstein DI, Wanner M, Borish L, Liss GM. Immunotherapy Committee AaoAA, and immunology: twelve-year survey of fatal reactions to allergen injections and skin testing: 1990–2001. *J Allergy Clin Immunol*. 2004;113:1129-1136.
32. CSM. Update: desensitising vaccines. *Br Med J*. 1986;293:948.
33. Normansell R, Kew KM, Bridgman AL. Sublingual immunotherapy for asthma. Cochrane Database of Systematic Reviews. 2015, Issue 8. Art. No.: CD011293. https://doi.org/10.1002/14651858.CD011293.pub2.
34. Calderon MA, Simons FE, Malling HJ, Lockey RF, Moingeon P, Demoly P. Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. *Allergy*. 2012;67:302-311.
35. Cabrera GE, Citera G, Gutiérrez M, Scopelitis E, Espinoza LR. Digital vasculitis following allergic desensitization treatment. *J Rheumatol*. 1993;20:1970-1972.
36. Sánchez-Morillas L, Reaño Martos M, Iglesias Cadarso A, Pérez Pimiento A, Rodríguez Mosquera M, Domínguez Lázaro AR. Vasculitis during immunotherapy treatment in a patient with allergy to *Cupressus arizonica*. *Allergol Immunopathol*. 2005;33:333-334.
37. Fiorillo A, Fonacier L, Diola C. Safety of allergenic immunotherapy in systemic lupus erythematosus. *J Allergy Clin Immunol*. 2006;117(2 Suppl):S264.
38. Wöhrl S, Kinaciyan T, Jalili A, Stingl G, Moritz KB. Malignancy and specific allergen immunotherapy: the results of a Case Series. *Int Arch Allergy Immunol*. 2011;156:313-319.
39. Larenas-Linnemann DES, Hauswirth DW, Calabria CW, Sher LD, Rank MA. American Academy of Allergy, Asthma & Immunology membership experience with allergen immunotherapy safety in patients with specific medical conditions. *Allergy Asthma Proc*. 2016;37:e112-e122.
40. Metzger WJ, Turner E, Patterson R. The safety of immunotherapy during pregnancy. *J Allergy Clin Immunol*. 1978;61:268-272.
41. Virchow JC, Backer V, Kuna P, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. *JAMA*. 2016;315:1715-1725.
42. Hiatt WR, Wolfel EE, Stoll S, et al. beta-2 Adrenergic blockade evaluated with epinephrine after placebo, atenolol, and nadolol. *Clin Pharmacol Ther*. 1985;37:2-6.
43. Dhami S, Kakourou A, Asamoah F, et al. Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. *Allergy* 2017;72:1825-1848.

44. Cleaveland CR, Rangno RE, Shand DG. A standardized isoproterenol sensitivity test. The effects of sinus arrhythmia, atropine, and propranolol. *Arch Intern Med*. 1972;130:47-52.
45. Lang DM. Anaphylactoid and anaphylactic reactions. Hazards of beta-blockers. *Drug Saf*. 1995;12:299-304.
46. Linneberg A, Jacobsen RK, Jespersen L, Abildstrom SJ. Association of subcutaneous allergen-specific immunotherapy with incidence of autoimmune disease, ischemic heart disease, and mortality. *J Allergy Clin Immunol*. 2012;129:413-419.
47. Bonertz A, Roberts G, Hoefnagel M, et al. Challenges in the implementation of EAACI Guidelines on Allergen Immunotherapy: a global perspective on the regulation of allergen products. *Allergy* 2018;73:64-76.
48. Ryan D, Gerth van Wijk R, Angier E, et al. Challenges in the implementation of the EAACI AIT guidelines: a situational analysis of current provision of allergen immunotherapy. *Allergy* 2018;73:827-836.
49. Tworek D, Bochenska-Marciniak M, Kuprys-Lipinska I, Kupczyk M, Kuna P. Perennial is more effective than preseasonal subcutaneous immunotherapy in the treatment of seasonal allergic rhinoconjunctivitis. *Am J Rhinol Allergy*. 2013;27:304-308.
50. Passalacqua G, Pasquali M, Ariano R, et al. Randomized double blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. *Allergy*. 2006;61:849-854.
51. Nolte H, Bernstein DI, Nelson HS, et al. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2016;138:1631-1638.
52. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol*. 2016;137:444-451.
53. Bergmann KC, Demoly P, Worm M, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol*. 2014;133:1608-1614.
54. Mosbech H, Canonica GW, Backer V, et al. SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms. *Ann Allergy Asthma Immunol*. 2015;114:134-140.
55. Okubo K, Masuyama K, Imai T, et al. Efficacy and safety of the SQ house dust mite sublingual immunotherapy tablet in Japanese adults and adolescents with house dust mite–induced allergic rhinitis. *J Allergy Clin Immunol*. 2017;139:1840-1848.
56. Didier A, Malling HJ, Worm M, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2007;120:1338-1345.
57. Valovirta E, Jacobsen L, Ljørring C, Koivikko A, Savolainen J. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. *Allergy*. 2006;61:1177-1183.
58. Frew AJ, Powell RJ, Corrigan CJ, Durham SR; UK Immunotherapy Study Group. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2006;117:319-325.
59. Demoly P, Calderon MA. Dosing and efficacy in specific immunotherapy. *Allergy*. 2011;66(Suppl. 95):38-40.
60. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol*. 2001;107:87-93.
61. Charpin D, Gouitaa M, Dron-Gonzalvez M, et al. Immunotherapy with an aluminum hydroxide-adsorbed *Juniperus ashei* foreign pollen extract in seasonal indigenous cypress pollen rhinoconjunctivitis. A double-blind, placebo-controlled study. *Int Arch Allergy Immunol*. 2007;143:83-91.
62. Ferrer M, Burches E, Peláez A, et al. Double-blind, placebo-controlled study of immunotherapy with Parietaria judaica: clinical efficacy and tolerance. *J Investig Allergol Clin Immunol*. 2005;15:283-292.
63. Jacobsen L, Niggemann B, Dreborg S, et al.; The PAT Investigator Group. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. 2007;62:943-948.
64. Dolz I, Martinez-Cocera C, Bartolome JM, Cimarra M. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. *Allergy*. 1996;51:489-500.
65. Scadding GW, Calderon MA, Shamji MH, et al.; Immune Tolerance Network GRASS Study Team. Effect of 2 years of treatment with sublingual grass pollen immunotherapy on nasal response to allergen challenge at 3 years among patients with moderate to severe seasonal allergic rhinitis: the GRASS randomized clinical trial. *JAMA*. 2017;14:615-625.
66. Varney VA, Tabbah K, Mavroleon G, Frew AJ. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. *Clin Exp Allergy*. 2003;33:1076-1082.
67. Dokic D, Schnitker J, Narkus A, Cromwell O, Frank E. Clinical effects of specific immunotherapy: a two-year double-blind, placebo-controlled study with a one year follow-up. *Makedon Akad Na Nauk Umet Oddelenie Za Bioloshki Meditsinski Nauki Pril*. 2005;26:113-129.
68. Ewan PW, Alexander MM, Snape C, Ind PW, Agrell B, Dreborg S. Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite. *Clin Exp Allergy*. 1988;18:501-508.
69. Balda BR, Wolf H, Baumgarten C, et al. Tree-pollen allergy is efficiently treated by short-term immunotherapy (STI) with seven preseasonal injections of molecular standardized allergens. *Allergy*. 1998;53:740-748.
70. Bodtger U, Poulsen LK, Jacobi HH, Malling HJ. The safety and efficacy of subcutaneous birch pollen immunotherapy - a one-year, randomised, double-blind, placebo-controlled study. *Allergy*. 2002;57:297-305.
71. Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *BMJ*. 1991;302:265-269.
72. Zenner HP, Baumgarten C, Rasp G, et al. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. *J Allergy Clin Immunol*. 1997;100:23-29.
73. Weyer A, Donat N, L'Heritier C, et al. Grass pollen hyposensitization versus placebo therapy. I. Clinical effectiveness and methodological aspects of a pre-seasonal course of desensitization with a four-grass pollen extract. *Allergy*. 1981;36:309-317.
74. Bousquet J, Hejjaoui A, Skassa-Brociek W, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. I. Rush immunotherapy with allergoids and standardized orchard grass-pollen extract. *J Allergy Clin Immunol*. 1990;80:591-598.
75. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol*. 2005;116:608-613.
76. Brunet C, Bédard PM, Lavole A, Jobin M, Hébert J. Allergic rhinitis to ragweed pollen: I. Reassessment of the effects of immunotherapy on cellular and humoral responses. *J Allergy Clinical Immunol*. 1992;89:76-86.
77. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A; for the Study Group. Efficacy and safety of preseasonal-specific

immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy*. 2005;60:801-807.
78. Klimek L, Uhlig J, Mosges R, Rettig K, Pfaar O. A high polymerized grass pollen extract is efficacious and safe in a randomized double-blind, placebo-controlled study using a novel up-dosing cluster-protocol. *Allergy*. 2014;69:1629-1638.
79. Ortolani C, Pastorello EA, Incorvaia C, et al. A double-blind, placebo-controlled study of immunotherapy with an alginate-conjugated extract of Parietaria judaica in patients with Parietaria hay fever. *Allergy*. 1994;49:13-21.
80. Tabar AI, Lizaso MT, García BE, et al. Double-blind, placebo-controlled study of Alternaria immunotherapy: clinical efficacy and safety. *Pediatr Allergy Immunol*. 2008;19:67-75.
81. Ceuppens JL, Bullens D, Kleinjans H, van der Werf J, Purethal Birch Efficacy Study Group. Immunotherapy with a modified birch pollen extract in allergic rhinoconjunctivitis: clinical and immunological effects. *Clin Exp Allergy*. 2009;39:1903-1909.
82. Riechelmann H, Schmutzhard J, van der Werf JF, Distler A, Kleinjans HA. Efficacy and safety of a glutaraldehyde-modified house dust mite extract in allergic rhinitis. *Am J Rhinol Allergy*. 2010;24:104-109.
83. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med*. 1999;341:468-475.
84. James LK, Shamji MH, Walker SM, et al. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. *J Allergy Clin Immunol*. 2011;127:509-516.
85. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy*. 2006;61:185-190.
86. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2006;118:434-440.
87. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2006;117:802-809.
88. Pajno GB, Caminiti L, Crisafulli G, et al. Adherence to sublingual immunotherapy in preschool children. *Pediatr Allergy Immunol*. 2012;23:688-689.
89. Worm M, Rak S, de Blay F, et al. Sustained efficacy and safety of a 300IR daily dose of a sublingual solution of birch pollen allergen extract in adults with allergic rhinoconjunctivitis: results of a double-blind, placebo-controlled study. *Clin Transl Allergy*. 2014;11:7.
90. Caffarelli C, Sensi LG, Marcucci F, Cavagni G. Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial. *Allergy*. 2000;55:1142-1147.
91. Pajno GB, Vita D, Parmiani S, Caminiti L, La Grutta S, Barberio G. Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with inhaled fluticasone propionate. *Clin Exp Allergy*. 2003;33:1641-1647.
92. Stelmach I, Kaluzińska-Parzyszek I, Jerzynska J, Stelmach P, Stelmach W, Majak P. Comparative effect of pre-coseasonal and continuous grass sublingual immunotherapy in children. *Allergy*. 2012;67:312-320.
93. Creticos PS, Maloney J, Bernstein DI, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. *J Allergy Clin Immunol*. 2013;131:1342-1349.
94. Didier A, Malling HJ, Worm M, Horak F, Sussman GL. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score. *Clinical Translational Allergy*. 2015;5:12.
95. Drachenberg K, Heinzkill M, Urban E. Short-term immunotherapy with tree pollen allergoids and the adjuvant monophosphoryl lipid-A - Results from a multicentre, placebo-controlled, randomised, double-blind study..[Kurzzeit-Immuntherapie mit Baumpollen-Allergoiden und dem Adjuvans Monophosphoryl Lipid-A]. *Allergologie*. 2002 Jahrgang, Nr. 9;S. 466-474.
96. Palma-Carlos AG, Santos AS, Branco-Ferreira M, et al. Clinical efficacy and safety of preseasonal sublingual immunotherapy with grass pollen carbamylated allergoid in rhinitic patients. A doubleblind, placebo-controlled study. *Allergol Immunopathol (Madr)*. 2006;34:194-198.
97. Halken S, Agertoft L, Seidenberg J, et al. Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. *Pediatr Allergy Immunol*. 2010;21:970-976.
98. Bufe A, Eberle P, Franke-Beckmann E, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol*. 2009;123:167-173.
99. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol*. 2011;127:64-71.
100. Amar SM, Harbeck RJ, Sills M, Silveira LJ, O'Brien H, Nelson HS. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. *J Allergy Clin Immunol*. 2009;124:150-156.
101. Ariano R, Spadolini I, Panzani RC. Efficacy of sublingual specific immunotherapy in Cupressaceae allergy using an extract of *Cupressus arizonica*. A double blind study. *Allergol Immunopathol (Madr)*. 2001;29:238-244.
102. Panzner P, Petras M, Sykora T, Lesna I. Double-blind, placebo-controlled evaluation of grass pollen specific immunotherapy with oral drops administered sublingually or supralingually. *Respir Med*. 2008;102:1296-1304.
103. Bufe A, Ziegler-Kirbach E, Stoeckmann E, et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy*. 2004;59:498-504.
104. Feliziani V, Lattuada G, Parmiani S, Dall'Aglio PP. Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts. A double blind study. *Allergol Immunopathol*. 1995;23:224-230.
105. Bowen T, Greenbaum J, Charbonneau Y, et al. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol*. 2004;93:425-430.
106. Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. *Allergol Immunopathol (Madr)*. 1990;18:277-284.
107. Guez S, Vatrinet C, Fadel R, Andre C. House-dust-mite sublingual swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. *Allergy*. 2000;55:369-375.
108. Didier A, Malling HJ, Worm M, et al. Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. *Clin Exp Allergy*. 2013;43:568-577.
109. Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol*. 2012;129:717-725.
110. Valovirta E, Berstad AK, de Blic J, et al. Design and recruitment for the GAP trial, investigating the preventive effect on asthma development of an SQ-standardized grass allergy immunotherapy tablet in children with grass Pollen-Induced allergic rhinoconjunctivitis. *Clin Ther*. 2011;33:1537-1546.
111. Valovirta E, Petersen TH, Piotrowska T, et al., GAP Investigators. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. *J Allergy Clin Immunol*. 2018;141:529-538.
112. Pfaar O, Cazan D, Klimek L, Larenas-Linnemann D, Calderon MA. Adjuvants for immunotherapy. *Curr Opin Allergy Clin Immunol*. 2012;12:648-657.

113. Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. A well-tolerated grass pollen specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. *Allergy*. 2001;56:498-505.
114. DuBuske L, Frew A, Horak F, Keith P, Corrigan C, Aberer W. Ultra-short-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy Asthma Proc*. 2011;32:239-247.
115. Creticos PS, Schroeder JT, Hamilton RG, et al.; Immune Tolerance Network Group. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med*. 2006;355:1445-1455.
116. Rolinck-Werninghaus C, Hamelmann E, Keil T, et al. The co-seasonal application of anti-IgE after preseasonal specific immunotherapy decreases ocular and nasal symptom scores and rescue medication use in grass pollen allergic children. Omalizumab Rhinitis Study Group. *Allergy*. 2004;59:973-979.
117. Casale TB, Busse WW, Kline JN, et al.; Immune Tolerance Network Group. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2006;117:134-140.
118. Larenas-Linnemann D, Wahn U, Kopp M. Use of omalizumab to improve desensitization safety in allergen immunotherapy. *J Allergy Clin Immunol*. 2014;133:937.
119. Pauli G, Larsen TH, Rak S, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2008;122:951-960.
120. Zieglmayer P, Focke-Tejkl M, Schmutz R, et al. Mechanisms, safety and efficacy of a B cell epitope-based vaccine for immunotherapy of grass pollen allergy. *EBioMedicine*. 2016;11:43-57.
121. Patel D, Couroux P, Hickey P, et al. Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study. *J Allergy Clin Immunol*. 2013;131:103-109.
122. http://www.circassia.com/media/press-releases/circassia-announces-top-line-results-from-cat-allergy-phase-iii-study/. (accessed 31 July 2017)
123. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. *J Allergy Clin Immunol*. 2010;125:569-574.
124. Spertini F, DellaCorte G, Kettner A, et al. Efficacy of 2 months of allergen-specific immunotherapy with Bet v 1-derived contiguous overlapping peptides in patients with allergic rhinoconjunctivitis: results of a phase IIb study. *J Allergy Clin Immunol*. 2016;138:162-168.
125. Senti G, von Moos S, Tay F, et al. Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: a double-blind, placebo-controlled dose escalation study. *J Allergy Clin Immunol*. 2012;129:128-135.
126. Slovick A, Douiri A, Muir R, et al. Intradermal grass pollen immunotherapy increases TH2 and IgE responses and worsens respiratory allergic symptoms. *J Allergy Clin Immunol*. 2017;139:1830-1839.
127. Senti G, Crameri R, Kuster D, et al. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. *J Allergy Clin Immunol*. 2012;129:1290-1296.
128. Patterson AM, Bonny AE, Shiels WE, Erwin EA. Three-injection intralymphatic immunotherapy in adolescents and young adults with grass pollen rhinoconjunctivitis. *Ann Allergy Asthma Immunol*. 2016;116:168-170.
129. Witten M, Malling HJ, Blom L, Poulsen BC, Poulsen LK. Is intralymphatic immunotherapy ready for clinical use in patients with grass pollen allergy? *J Allergy Clin Immunol*. 2013;132:1248-1252.
130. Drachenberg KJ, Heinzkill M, Urban E, Woroniecki SR. Efficacy and tolerability of short-term specific immunotherapy with pollen allergoids adjuvanted by monophosphoryl lipid A (MPL) for children and adolescents. *Allergol Immunopathol (Madr)*. 2003;31:270-277.
131. Patel P, Holdich T, von Weikersthal-Drachenberg KJ, Huber B. Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen. *J Allergy Clin Immunol*. 2014;133:121-129.
132. European Medicines Agency. *Guideline on Allergen Products: Production and Quality Issues*. London: Published by European Medicines Agency; 2008. EMEA/CHMP/BWP/304831/2007. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003333.pdf (accessed 13th August 2017)
133. Coop CA. Immunotherapy for mold allergy. *Clin Rev Allergy Immunol*. 2014;47:289-298.
134. Twaroch TE, Curin M, Valenta R, Swoboda I. Mold allergens in respiratory allergy: from structure to therapy. *Allergy Asthma Immunol Res*. 2015;7:205-220.
135. Lizaso MT, Martínez A, Asturias JA, et al. Biological standardization and maximum tolerated dose estimation of an Alternaria alternata allergenic extract. *J Invest Allergol Clin Immunol*.. 2006;16:94-103.
136. Slater JE, Zoch A, Newman-Gerhardt S, Khurana T. Comparison of total protein profile of alternaria extract obtained from various U.S. Allergenic extract manufacturers. *J Allergy Clin Immunol*. 2014;133:AB100.
137. Demoly P, Passalacqua G, Pfaar O, Sastre J, Wahn U. Management of the polyallergic patient with allergy immunotherapy: a practice-based approach. *Allergy Asthma Clin Immunol*. 2016;12:2.
138. Mosbech H, Deckelmann R, de Blay F, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol*. 2014;134:568-575.
139. Bahceciler NN, Işik UI, Barlan IB, Basaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. *Pediatr Pulmonol*. 2001;32:49-55.
140. Hirsch T, Sahn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. *Paediatr Allergy Immunol*. 1997;8:21-27.
141. Larenas-Linnemann D, et al. Maintenance dosing for sublingual immunotherapy by prominent European allergen manufacturers expressed in bioequivalent allergy units. *Ann Allergy Asthma Immunol*. 2011;107:448-458.
142. Pfaar O, Biedermann T, Klimek L, Sager A, Robinson DS. Depigmented–polymerized mixed grass/birch pollen extract immunotherapy is effective in polysensitized patients. *Allergy*. 2013;68:1306-1313.
143. Swamy RS, Reshamwala N, Hunter T, et al. Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy. *J Allergy Clin Immunol*. 2012;130:215-224.
144. Marcucci F, Sensi L, Frati F, et al. Effects on inflammation parameters of a double-blind, placebo controlled one-year course of SLIT in children monosensitized to mites. *Allergy*. 2003;58:657-662.
145. Ott H, Sieber J, Brehler R, et al. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. *Allergy*. 2009;64:1394-1401.
146. de Bot CMA, Moed H, Berger MY, et al. Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. *Pediatr Allergy Immunol*. 2012;23:151-159.
147. Passalacqua G, Albano M, Fregonese L, et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet*. 1998;351:629632.
148. Migueres M, Dávila I, Frati F, et al. Types of sensitization to aeroallergens: definitions, prevalences and impact on the diagnosis and treatment of allergic respiratory disease. *Clin Transl Allergy*. 2014;4:16.

149. Nelson H, Blaiss M, Nolte H, Würtz SØ, Andersen JS, Durham SR. Efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet in mono- and polysensitized subjects. *Allergy*. 2013;68:252-255.
150. Adkinson NF Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med*. 1997;336:324-332.
151. Nelson HS. Multiallergen immunotherapy for allergic rhinitis and asthma. *J Allergy Clin Immunol*. 2009;123:763-769.
152. Shao J, Cui YX, Zheng YF, et al. Efficacy and safety of sublingual immunotherapy in children aged 3-13 years with allergic rhinitis. *Am J Rhinol Allergy*. 2014;28:131-139.
153. Fiocchi A, Pajno G, La Grutta S, et al. Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. *Ann Allergy Asthma Immunol*. 2005;95:254-258.
154. Agostinis F, Tellarini L, Canonica GW, Falagiani P, Passalacqua G. Safety of sublingual immunotherapy with a monomeric allergoid in very young children. *Allergy*. 2005;60:133-134.
155. Roberts G, Hurley C, Turcanu V, Lack G. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. *J Allergy Clin Immunol*. 2006;117:263-268.
156. Wahn U, Tabar A, Kuna P, et al.; SLIT Study Group. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2009;123:160-166.
157. Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy*. 2006;61:198-201.
158. Keskin O, Tuncer A, Adalioglu G, Sekerel BE, Sackesen C, Kalayci O. The effects of grass pollen allergoid immunotherapy on clinical and immunological parameters in children with allergic rhinitis. *Pediatr Allergy Immunol*. 2006;17:396-407.
159. Bozek A, Kolodziejczyk K, Warkocka-Szoltysek B, Jarzab J. Grass pollen sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with seasonal allergic rhinitis. *Am J Rhinol Allergy*. 2014;28:423-427.
160. Bozek A, Kolodziejczyk K, Krajewska-Wojtys A, Jarzab J. Pre-seasonal, subcutaneous immunotherapy: a double-blinded, placebo-controlled study in elderly patients with an allergy to grass. *Ann Allergy Asthma Immunol*. 2016;116:156-161.
161. Shaikh WA, Shaikh SW. A prospective study on the safety of sublingual immunotherapy in pregnancy. *Allergy*. 2012;67:741-743.
162. Oykhman P, Kim HL, Ellis AK. Allergen immunotherapy in pregnancy. *Allergy Asthma Clin Immunol*. 2015;11:31.
163. Incorvaia C, Masieri S, Berto P, Scurati S, Frati F. Specific immunotherapy by the sublingual route for respiratory allergy. *Allergy Asthma Clin Immunol*. 2010;6:29.
164. Scurati S, Frati F, Passalacqua G, Puccinelli P, Hilaire C, Incorvaia C; Italian Study Group on SLIT Compliance. Adherence issues related to sublingual immunotherapy as perceived by allergists. *Patient Prefer Adherence*. 2010;4:141-145.
165. Egert-Schmidt AM, Kolbe JM, Mussler S, Thum-Oltmer S. Patients' compliance with different administration routes for allergen immunotherapy in Germany. *Patient Prefer Adherence*. 2014;8:1475-1481.
166. Kiel MA, Röder E, van Wijk RG, Al MJ, Hop WC, Rutten-van Mölken MP. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. *J Allergy Clin Immunol*. 2013;132:353-360.
167. Vaswani R, Garg A, Parikh L, Vaswani S. Non-adherence to subcutaneous allergen immunotherapy: inadequate health insurance coverage is the leading cause. *Ann Allergy Asthma Immunol*. 2015;115:241-243.
168. Leader BA, Rotella M, Stillman L, DelGaudio JM, Patel ZM, Wise SK. Immunotherapy compliance: comparison of subcutaneous versus sublingual immunotherapy. *Int Forum Allergy Rhinol*. 2016;6:460-464.
169. Savi E, Peveri S, Senna G, Passalacqua G. Causes of SLIT discontinuation and strategies to improve the adherence: a pragmatic approach. *Allergy*. 2013;68:1193-1195.
170. Makatsori M, Scadding GW, Lombardo C, et al. Dropouts in sublingual allergen immunotherapy trials – a systematic review. *Allergy*. 2014;69:571-580.
171. Vita D, Caminiti L, Ruggeri P, Pajno GB. Sublingual immunotherapy: adherence based on timing and monitoring control visits. *Allergy*. 2010;65:668-669.
172. Patel P, Holdich T, von Weikersthal-Drachenberg KJ, Huber B. Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen. *J Allergy Clin Immunol*. 2014;133:121-129.
173. Rienzo VD, Minelli M, Musarra A, et al. Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. *Clin Exp Allergy*. 2005;35:560-564.
174. Rodriguez-Santos O. Sublingual immunotherapy in allergic rhinitis and asthma in 2-5-year-old children sensitized to mites. *Rev Alerg Mex*. 2008;55:71-75.
175. Bozek A, Ignasiak B, Filipowska B, Jarzab J. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. *Clin Exp Allergy*. 2012;43:242-248.
176. Durham SR, Emminger W, Kapp A, et al. Long-term clinical efficacy in grass pollen–induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol*. 2010;125:131-138.
177. Lin Z, Liu Q, Li T, Chen D, Chen D, Xu R. The effects of house dust mite sublingual immunotherapy in patients with allergic rhinitis according to duration. *Int Forum Allergy Rhinol*. 2016;6:82-87.
178. Naclerio RM, Proud D, Moylan B, et al. A double-blind study of the discontinuation of ragweed immunotherapy. *J Allergy Clin Immunol*. 1997;100:293-300.
179. Arroabarren E, Tabar AI, Echechipía S, Cambra K, García BE, Alvarez-Puebla MJ. Optimal duration of allergen immunotherapy in children with dust mite respiratory allergy. *Pediatr Allergy Immunol*. 2015;26:34-41.
180. Cox L, Calderon M, Pfaar O. Subcutaneous allergen immunotherapy for allergic disease: examining efficacy, safety and cost-effectiveness of current and novel formulations. *Immunotherapy*. 2012;4:601-616.
181. Malling HJ. Minimising the risks of allergen-specific injection immunotherapy. *Drug Saf*. 2000;23:323-332.
182. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Immediate and delayed-onset systemic reactions after subcutaneous immunotherapy injections: ACAAI/AAAAI surveillance study of subcutaneous immunotherapy: year 2. *Ann Allergy Asthma Immunol*. 2011;107:426-431.
183. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Risk factors for fatal and nonfatal reactions to subcutaneous immunotherapy: national surveillance study on allergen immunotherapy (2008–2013). *Ann Allergy Asthma Immunol*. 2016;116:354-359.
184. Calderon MA, Vidal C, Rodrıguez del Rıo P, et al. on behalf of the EASSI Doctors' Group. European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a real-life clinical assessment. *Allergy*. 2017;72:462-472.
185. Rodríguez del Río P, Vidal C, Just J, et al. The European survey on adverse systemic reactions in allergen immunotherapy (EASSI): a paediatric assessment. *Pediatr Allergy Immunol*. 2017;28:60-70.
186. Kelso JM. The rate of systemic reactions to immunotherapy injections is the same whether or not the dose is reduced after a local reaction. *Ann Allergy Asthma Immunol*. 2004;92:225-227.

187. Nielsen L, Johnsen CR, Mosbech H, Poulsen LK, Malling HJ. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. *J Allergy Clin Immunol*. 1996;97:1207-1213.
188. Reimers A, Hari Y, Müller U. Reduction of side-effects from ultra-rush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial. *Allergy*. 2000;55:484-488.
189. Brehler R, Klimek L, Pfaar O, Hauswald B, Worm M, Bieber T. Safety of a rush immunotherapy build-up schedule with depigmented polymerized allergen extracts. *Allergy Asthma*. 2010;31:3138.
190. Cardona R, Lopez E, Beltran J, Sanchez J. Safety of immunotherapy in patients with rhinitis, asthma or atopic dermatitis using an ultra-rush buildup. A retrospective study. *Allergol Immunopathol (Madr)*. 2014;42:90-95.
191. Casanovas M, Martin R, Jimenez C, Caballero R, Fernandez-Caldas E. Safety of an ultra-rush immunotherapy build-up schedule with therapeutic vaccines containing depigmented and polymerized allergen extracts. *Int Arch Allergy Immunol*. 2006;139:153-158.
192. Casanovas M, Martin R, Jimenez C, Caballero R, Fernandez-Caldas E. Safety of immunotherapy with therapeutic vaccines containing depigmented and polymerized allergen extracts. *Clin Exp Allergy*. 2007;37:434-440.
193. Vogelbruch M, Nuss B, Körner M, Kapp A, Kiehl P, Bohm W. Aluminium-induced granulomas after inaccurate intradermal hyposensitization injections of aluminium-adsorbed depot preparations. *Allergy*. 2000;55:883-887.
194. Netterlid E, Hindsén M, Björk J, et al. There is an association between contact allergy to aluminium and persistent subcutaneous nodules in children undergoing hyposensitization therapy. *Contact Dermatitis*. 2009;60:41-49.
195. Frost L, Johansen P, Pedersen S, Veien N, Ostergaard PA, Nielsen MH. Persistent subcutaneous nodules in children hyposensitized with aluminium-containing allergen extracts. *Allergy*. 1985;40:368-372.
196. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev*. 2010;12:CD002893.
197. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J*. 2014;7:6.
198. Cox LS, Larenas Linnemann D, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol*. 2006;117:1021-1035.
199. Passalacqua G, Baena-Cagnani CE, Bousquet J, et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: speaking the same language. *J Allergy Clin Immunol*. 2013;132:93-98.
200. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol*. 2006;117:169-175.
201. Meadows A, Kaambwa B, Novielli N, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. *Health Technol Assess*. 2013;17:1–322.
202. Ariano R, Berto P, Tracci D, et al. Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma. *Allergy Asthma Proc*. 2006;27:159-163.
203. Berto P, Bassi M, Incorvaia C, et al. Cost effectiveness of sublingual immunotherapy in children with allergic rhinitis and asthma. *Allerg Immunol (Paris)*. 2005;37:303-308.
204. Hankin CS, Cox L, Lang D, et al. Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. *J Allergy Clin Immunol*. 2008;121:227-232.
205. Hankin CS, Cox L, Lang D, et al. Allergen immunotherapy and health care cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study. *Ann Allergy Asthma Immunol*. 2010;104:79-85.
206. Hankin CS, Cox L, Bronstone A, Wang Z. Allergy immunotherapy: reduced health care costs in adults and children with allergic rhinitis. *J Allergy Clin Immunol*. 2013;131:1084-1091.
207. Creticos PS, Reed CE, Norman PS, et al. Ragweed immunotherapy in adult asthma. *N Engl J Med*. 1996;334:501-506.
208. Berto P, Frati F, Incorvaia C, et al. Comparison of costs of sublingual immunotherapy and drug treatment in grass-pollen induced allergy: results from the SIMAP database study. *Curr Med Res Opin*. 2008;24:261-266.
209. Schadlich PK, Brecht JG. Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. *Pharmacoeconomics*. 2000;17:37-52.
210. Petersen KD, Gyrd-Hansen D, Dahl R. Health-economic analyses of subcutaneous specific immunotherapy for grass pollen and mite allergy. *Allergol Immunopathol (Madr)*. 2005;33:296-302.
211. Berto P, Passalacqua G, Crimi N, et al. Economic evaluation of sublingual immunotherapy vs symptomatic treatment in adults with pollen-induced respiratory allergy: the Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study. *Ann Allergy Asthma Immunol*. 2006;97:615-621.
212. Bachert C, Vestenbaek U, Christensen J, Griffiths UK, Poulsen PB. Cost-effectiveness of grass allergen tablet (GRAZAX) for the prevention of seasonal grass pollen induced rhinoconjunctivitis—a Northern European perspective. *Clin Exp Allergy*. 2007;37:772-779.
213. Nasser S, Vestenbaek U, Beriot-Mathiot A, Poulsen PB. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. *Allergy*. 2008;63:1624-1629.
214. Poulsen PB, Pedersen KM, Christensen J, Vestenbaek U. Economic evaluation of a tablet-based vaccination against hay fever in Denmark. *Ugeskr Laeger*. 2008;14:138-142.
215. Keiding H, Jorgensen KP. A cost-effectiveness analysis of immunotherapy with SQ allergen extract for patients with seasonal allergic rhinoconjunctivitis in selected European countries. *Curr Med Res Opin*. 2007;23:1113-1120.
216. Ronaldson S, Taylor M, Bech PG, Shenton R, Bufe A. Economic evaluation of SQ-standardized grass allergy immunotherapy tablet (Grazax) in children. *Clin Outcomes Res*. 2014;6:187-196.
217. Westerhout KY, Verheggen BG, Schreder CH, Augustin M. Cost effectiveness analysis of immunotherapy in patients with grass pollen allergic rhinoconjunctivitis in Germany. *J Med Econ*.. 2012;15:906-917.
218. Verheggen B, Westerhout K, Schreder C, Augustin M. Health economic comparison of SLIT allergen and SCIT allergoid immunotherapy in patients with seasonal grass-allergic rhinoconjunctivitis in Germany. *Clin Transl Allergy*. 2015;5:1.
219. Reinhold T, Brüggenjürgen B. Cost-effectiveness of grass pollen SCIT compared with SLIT and symptomatic treatment. *Allergo J Int*. 2017;26:7-15.
220. Asaria M, Dhami S, van Ree R, et al. Health economic analysis of allergen immunotherapy (AIT) for the management of allergic rhinitis, asthma, Food allergy and venom allergy: a systematic overview. *Allergy* 2018;73:269-283.
221. Nelson H, Cartier S, Allen-Ramey F, Lawton S, Calderon MA. Network meta-analysis shows commercialized subcutaneous and sublingual grass products have comparable efficacy. *J Allergy Clin Immunol*. 2015;3:256-266.
222. Shamji MH, Kappen JH, Akdis M, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. *Allergy*. 2017;72:1156-1173.

223. Stelmach I, Sobocińska A, Majak P, Smejda K, Jerzyńska J, Stelmach W. Comparison of the long-term efficacy of 3- and 5-year house dust mite allergen immunotherapy. *Ann Allergy Asthma Immunol*. 2012;109:274-278.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Roberts G, Pfaar O, Akdis CA, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. *Allergy*. 2018;73:765–798. https://doi.org/10.1111/all.13317

New developments in patients with eosinophilic gastrointestinal diseases presented at the CEGIR/ TIGERS

Antonella Cianferoni, USA

Rostrum

New developments in patients with eosinophilic gastrointestinal diseases presented at the CEGIR/TIGERS Symposium at the 2018 American Academy of Allergy, Asthma & Immunology Meeting

Jonathan M. Spergel, MD, PhD,[a,b]* Seema S. Aceves, MD, PhD,[c]* Kara Kliewer, PhD,[d] Nirmala Gonsalves, MD,[e] Mirna Chehade, MD,[f] Joshua B. Wechsler, MD, PhD,[g] Marion Groetch, MS,[f] Joshua Friedlander, DO,[h] Evan S. Dellon, MD, MPH,[i] Wendy Book, MD,[j] Ikuo Hirano, MD,[e] Amanda B. Muir, MD,[b,k] Antonella Cianferoni, MD, PhD,[a,b] Lisa Spencer, PhD,[l] Chris A. Liacouras, MD,[b,k] Edaire Cheng, MD, PhD,[m] Leah Kottyan, PhD,[n] Ting Wen, MD, PhD,[d] Thomas Platts-Mills, MD, PhD,[o] and Marc E. Rothenberg, MD, PhD[d]

Philadelphia, Pa, La Jolla, Calif, Cincinnati, Ohio, Chicago, Ill, New York, NY, Aurora, Colo, Chapel Hill, NC, Atlanta, Ga, Boston, Mass, Dallas, Tex, and Charlottesville, Va

The Consortium of Eosinophilic Gastrointestinal Diseases and the International Gastrointestinal Eosinophil Researchers organized a day-long symposium at the recent 2018 Annual Meeting of the American Academy of Allergy, Asthma & Immunology, which was coupled for the first time with the World Allergy Organization meeting to create an international platform. The symposium featured experts in many facets of eosinophilic gastrointestinal diseases, including allergy, immunology, gastroenterology, pathology, and nutrition, and was a well-attended event. The basic science, genetics, cellular immunology, and clinical features of the diseases, with a focus on epithelial, eosinophil, and mast cell responses, as well as current and emerging treatment options, were reviewed. Here we briefly review some of the highlights of the material presented at the meeting. (J Allergy Clin Immunol 2018;142:48-53.)

Key words: *Eosinophilic esophagitis, food allergy, treatment, diagnosis*

From [a]the Division of Allergy and Immunology and [k]the Division of Gastroenterology and Nutrition, Children's Hospital of Philadelphia; [b]the Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia; [c]the Division of Allergy, Immunology, Departments of Pediatrics and Medicine, University of California, San Diego, Rady Children's Hospital, San Diego, La Jolla; [d]the Division of Allergy and Immunology and [n]the Center for Autoimmune Genomics and Etiology, Cincinnati Children's Hospital Medical Center and Department of Pediatrics, University of Cincinnati; [e]the Division of Gastroenterology and Hepatology, Northwestern University–Feinberg School of Medicine, Chicago; [f]the Mount Sinai Center for Eosinophilic Disorders, Icahn School of Medicine at Mount Sinai, New York; [g]the Eosinophilic Gastrointestinal Diseases Program, Division of Gastroenterology, Hepatology, and Nutrition, Ann & Robert H. Lurie Children's Hospital of Chicago; [h]the Digestive Health Institute, Children's Hospital Colorado, and the Aerodigestive Program, University of Colorado School of Medicine, Aurora; [i]the Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, University of North Carolina School of Medicine, Chapel Hill; [j]the American Partnership for Eosinophilic Disorders, Atlanta; [l]Beth Israel Deaconess, Boston; [m]the Departments of Pediatrics and Internal Medicine, Children's Medical Center, University of Texas Southwestern Medical Center, Dallas; and [o]the Division of Asthma, Allergy, and Immunology, University of Virginia, Charlottesville.

*These authors contributed equally to this work as co-first authors.

Disclosure of potential conflict of interest: J. M. Spergel reports grants from the National Institutes of Health (NIH), End Allergy Together, and Aimmune Therapeutics; grants and personal fees from Regeneron, Shire, and DBV Technology; personal fees from UpToDate, Abbott, and the *Annals of Allergy Asthma and Immunology* outside the submitted work. S. S. Aceves reports a grant from the NIH and a UCSD patented licensed to Shire Pharma. M. Chehade reports receiving grants from NIH, PCORI, Nutricia, Regeneron, and Shire and consulting fees from Allakos and Shire. M. Groetch has received honoraria from Abbott, Nutricia North America and Mead Johnson for educational lectures. J. Friedlander reports personal fees and other from Triple Endoscopy and grants from the CURED Foundation, OEDIT-STATE of Colorado; in addition, J. Friedlander has a patent on Pediatric Nasal Endoscope/Aerodigestive Scope with royalties paid to University of Colorado. E. S. Dellon reports grants and personal fees from Adare, Banner, Celgene/Receptos, Regeneron, and Shire and personal fees from Alivio, Allakos, AstraZeneca, Enumeral, Robarts Clinical Trials; grants from Meritage, Miraca, Nutricia, and Holoclara. I. Hirano reports grants and consultant fees from Adare, Shire, Regeneron, and Receptos. A. Cianferoni reports grants and personal fees from DBV and grants from Shire. E. Cheng reports personal fees from Abbott Nutrition. L. Kottyan reports a pending patent WO2015142739A1. T. Wen and M. E. Rothenberg are co-inventors of issued and pending patents owned by CCHMC. M. E. Rothenberg reports grants from the NIH, a US-Israel Binational Grant, and PCORI; personal fees from Celgene and Genentech; equity in Immune Pharmaceuticals, PulmOne, and Spoon Guru; and personal fees from GlaxoSmithKline, Merck, Allakos, AstraZeneca, Celgene, and Regeneron; in addition, M. E. Rothenberg receives royalties from UpToDate and reslizumab (Teva Pharmaceuticals). The rest of the authors declare that they have no relevant conflicts to disclose.

Received for publication April 24, 2018; revised May 17, 2018; accepted for publication May 18, 2018.

Available online May 24, 2018.

Corresponding author: Marc E. Rothenberg, MD, PhD, Children's Hospital Medical Center, Department of Pediatrics, 3333 Burnet Ave, MLC7028, Cincinnati, OH 45229-3039. E-mail: Rothenberg@cchmc.org.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2018.05.005

Abbreviations used
CEGIR: Consortium of Eosinophilic Gastrointestinal Disease Researchers
EC: Eosinophilic colitis
EDP: EoE Diagnostic Panel
EG: Eosinophilic gastritis
EGID: Eosinophilic gastrointestinal disorder
EoE: Eosinophilic esophagitis
EoEe1: EoE endotype 1 (EDP identified)
EoEe2: EoE endotype 2 (EDP identified)
EoEe3: EoE endotype 3 (EDP identified)
iNKT: Invariant natural killer T
PPI: Proton pump inhibitor
PPI-REE: Proton pump inhibitor–responsive esophageal eosinophilia
TNE: Transnasal endoscopy

Knowledge related to the epidemiology of eosinophilic gastritis (EG), gastroenteritis, and eosinophilic colitis (EC) remains limited. The prevalence of these conditions ranges from 3.5 to 8.3 per 100,000, with approximately 50,000 cases total estimated in the United States.[1] There does not appear to be a male predominance, but there is an association with atopy.

No etiologic or risk factor studies have been done for EG, eosinophilic gastroenteritis, or EC. The epidemiology of eosinophilic esophagitis (EoE) is far better described.[2] The prevalence is approximately 1 per 2000, with an estimated 150,000 cases in the United States and large burden of disease (>$1 billion annually).[3,4] Both the incidence and prevalence of EoE are increasing rapidly, and there is much research interest in these evolving trends. Although no specific "cause" for this increase has been found, there are a number of potential risk factors, including the decrease in *Helicobacter pylori* infection, low population density, and early-life exposures, such as antibiotic use.[5] Gene-environment interactions, particularly between breast-feeding and single-nucleotide polymorphisms in calpain 14 *(CAPN14)*, have been identified recently as a predisposing factor.[6] EoE is a highly atopic disease with a high rate of asthma, allergic rhinitis, and IgE-mediated food allergy. For food allergy, it is also known that oral immunotherapy can induce EoE in about 5% of cases.[7]

CONSEQUENCES OF EoE: REMODELING

Unbridled T_H2 eosinophilic esophageal inflammation leads to esophageal rigidity in children and adults through tissue remodeling that includes histologic changes of basal zone hyperplasia, fibrosis, angiogenesis, and smooth muscle hyperplasia with hypertrophy.[8,9] Current data in adults demonstrate that uncontrolled EoE can result in a fibrostenotic state, with resultant strictures in the majority of patients.[10,11] The use of endoscopic functional lumen imaging probe technology provides a novel esophageal readout for compliance and motility.[12,13]

A rigid extracellular matrix has consequences in terms of both esophageal biomechanics and structural cell function.[14,15] Esophageal fibroblasts cultured on a rigid matrix have increased contractility and myofibroblast features, and smooth muscle cells become hypertrophic and have increased expression of contractility and fibrotic genes when cultured in a stiff matrix.[14,15] Therapies that reduce inflammation in children and adults can reverse histologic fibrosis and esophageal rigidity in a subset of subjects.[16,17] A future direction for EoE therapy will be to treat not only inflammation but also the complications of dysfunctional esophageal biomechanics.

RELATIONSHIP BETWEEN EoE AND OTHER FORMS OF ESOPHAGITIS WITH FOCUS ON PROTON PUMP INHIBITOR RESPONSES

The Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) is addressing a number of key issues in the field of eosinophilic gastrointestinal disorders (EGIDs), including the relationship between EoE and various other forms of esophagitis.[18] EoE and gastroesophageal reflux disease share a complex relationship, and previous assumptions used to dichotomize the 2 might be flawed.[18,19] Proton pump inhibitor (PPI)–responsive esophageal eosinophilia (PPI-REE) describes patients with esophageal eosinophilia; typical EoE symptoms, endoscopic features, and histology; and no evidence of gastroesophageal reflux disease, as determined by using endoscopy, but who exhibit clinical and histologic response to PPIs. There is still controversy surrounding the entity and extent to which it overlaps with or is a subtype of EoE.[20,21] Clinically, a number of conditions can cause esophageal eosinophilia. However, when patients present with typical symptoms of esophageal dysfunction, atopy, endoscopic findings suggestive of EoE and biopsy specimens with marked esophageal eosinophilia, they appear to have EoE. There are now extensive data that suggest the clinical, endoscopic, histologic, immunologic, and molecular features of these patients at baseline (before PPI treatment) are largely indistinguishable between PPI responders (PPI-REE) and nonresponders (classic EoE).[3,20-22] One possible mechanism for PPI-REE is that patients with EoE respond to the anti-inflammatory effects of PPIs unrelated to gastric acid inhibition. PPIs have been documented to induce histologic remission in approximately 50% of patients with symptomatic esophageal eosinophilia, block T_H2 cytokine–induced eotaxin-3 secretion in esophageal (and bronchial) epithelial cells, and reverse an allergic T_H2 inflammatory transcriptome signature.[23] Given the weight of evidence documenting that PPIs reduce esophageal eosinophilia, A Working Group on PPI-REE (AGREE) is putting forth an updated diagnostic algorithm for EoE that includes removal of the PPI trial requirement and suggests that PPIs are better classified as a treatment rather than as a diagnostic criterion for EoE.[19]

EoE THERAPY: DIET VERSUS STEROIDS?

The advantages of using diet therapy over steroid therapy to treat EoE (particularly over the long-term) were reviewed. Diet therapies achieve histologic remission, consistently resolve symptoms, and might mitigate long-term esophageal complications by reversing epithelial hyperplasia and subepithelial fibrosis.[17,24-26] Elimination diet therapies can be a practical treatment for patients of all ages, and with the assistance of dietitians, diet therapies might improve the nutritional quality of patients' diets.[27] In recent years, elimination diets have become easier to follow because food manufacturers have improved the palatability of foods used as substitutes for eliminated foods. Although therapies for EoE should be individualized and based on the patients' lifestyle and clinical needs, diet therapy has become an increasingly feasible treatment option for many patients.

EoE THERAPY: STEROIDS VERSUS DIET?

The advantages of using steroid therapy over diet for patients with EoE were reviewed (Table I). Important points favoring steroid therapy include that use of topical corticosteroids is effective at achieving histologic, endoscopic, and symptomatic end points while preventing complications, such as fibrosis and food impactions.[28-30] This treatment offers good tolerability with minimal effect on quality of life and without the use of multiple endoscopies. Topical corticosteroids have a good side effect profile, and complications are rare. Overall, the right choice on initial therapy is very individualized and patient driven, being based on consideration of the goals of care and what fits best with the subject's lifestyle and needs.

NUTRITIONAL IMPLICATIONS OF EoE

Children with EoE might be at increased nutritional risk. A number of studies have reported poor growth at diagnosis in the pediatric population with EoE.[31,32] Although there appears to be greater risk of stunting and being underweight in children with IgE-mediated food allergy on cow's milk or multiple food elimination diets, studies in children with EoE on elimination diets do not indicate growth consequences when the patient is under the care of a dietitian; receiving adequate energy, protein, and micronutrients; and/or using a supplemental formula to support the diet. Feeding difficulties in patients with EoE have also been reported, and data exist that many children with EoE have maladaptive eating behaviors on the basis of a validated behavioral feeding assessment scale. Tools have been developed through an American Academy of Allergy, Asthma & Immunology workgroup report to assist practitioners in minimizing the nutritional effect of EoE and the associated diet therapies used in disease management.[33]

IgG VERSUS IgE AND DISEASE PATHOGENESIS

The importance of IgE versus IgG_4 in the pathogenesis of EoE was discussed. On the one hand, it was concluded that IgE might not have a major role in EoE for several reasons, including the following: (1) symptoms are typically not temporally related to food triggers, (2) skin prick test results and serum IgE levels to foods are only weakly predictive of food triggers,[34,35] and (3) allergy test–based elimination diets (directed by skin prick tests, serum food-specific IgE levels, and IgE measurement of allergenic molecules by using component-resolved diagnostics) are not that effective in inducing EoE remission.[36,37] Furthermore, omalizumab, an antibody targeted against IgE, was not effective in inducing EoE remission in a double-blind, placebo-controlled clinical trial.[38] IgG_4 was thought to potentially have a role in EoE pathogenesis, although the current evidence for this is still preliminary. Serum, plasma, and esophageal tissue IgG_4 levels to common food triggers were shown to be increased in patients with EoE, although the increase was not predictive of food triggers in these patients.[39,40] Therefore it was concluded that higher levels of IgG_4 than IgE are produced in patients with EoE and that evidence to support IgG_4 involvement directly in disease pathogenesis is needed.

ROLE OF T CELLS IN EoE PATHOGENESIS

There is evidence of a T_H2 phenotype in blood and biopsy specimens, indicating that T-cell function might play a key role in disease pathogenesis.[41] Patients with active EoE have local T_H2 inflammation characterized by high levels of IL-13, IL-4, IL-5, and thymic stromal lymphopoietin, chemokines that attract eosinophils (eg, eotaxins), lymphocytes, mast cells, basophils, and invariant natural killer T (iNKT) cells.[41-43] T_H2 polarization can be favored by genetic background in patients with EoE with higher production of epithelial factors, such as thymic stromal lymphopoietin, thereby promoting differentiation of naive $CD4^+$ T cells into T_H2 cells.[44] Accumulating evidence suggests that both innate (ie, iNKTs) and conventional T cells are able to recognize and mount a T_H2 response against food antigens in patients with EoE. Mouse models have demonstrated that T, but not B, cells are essential for EoE development.[45] iNKT numbers are increased at the site of inflammation and have a T_H2 phenotype in patients with EoE.[46,47] Milk-derived lipid antigens are able to specifically activate iNKT cells and induce a T_H2 response in patients with EoE.[46,48]

In addition, patients with active EoE disease triggered by milk consumption have a significant increase in numbers of activated peripheral blood $CD4^+$ T cells expressing T_H2 cytokines compared with those seen in healthy control subjects or patients with inactive EoE.[41] This $CD4^+$ T-cell population is capable of *in vitro* milk-specific antigen responses.[41,49] These data confirm that both innate and adaptive T cells could have a central role in antigen recognition and initiation of T_H2 inflammation.

MAST CELL INVOLVEMENT

Mast cells are increased in patients with active EoE, and their counts correlate with eosinophil levels and decrease with treatment in a majority of patients with EoE.[50] Mast cells can have a role in symptoms through esophageal nerve activation and smooth muscle contraction, and the mast cell transcriptome correlates with dysphagia scores. Mast cells have a potential role in fibrosis and esophageal remodeling, and their esophageal density correlates with endoscopic furrows.

LESS INVASIVE TESTING

Less invasive testing for evaluating the esophagus is a rapidly growing area of clinical medicine and inquiry. Such testing includes methods that replace endoscopy or complement endoscopy with or without sedation. Most of these modalities are generally not currently available, except for the endoscopic functional lumen imaging probe (EndoFLIP), unsedated transnasal endoscopy (TNE), and the EoE Diagnostic Panel (EDP). Other technologies will likely becoming more clinically available soon, such as the esophageal string test, mucosal impedance, and cytosponge, which are currently only available in research settings. These technologies have the potential to enable improved monitoring of the esophagus with lower cost but have tradeoffs compared with a more complete, biopsy-centric mucosal examination with sedated endoscopy. Other complementary technologies might offer additional information regarding esophageal compliance or more rapid assessment of mucosa compared with mucosal pathology, but the usefulness of such testing is debated.

PATIENT ADVOCACY

The positions of patient advocacy groups were presented. In particular, the many challenges of rare diseases were discussed, from obtaining a correct diagnosis to limited treatment options to

TABLE I. Pros and cons of diet versus steroids

Diet therapy		Swallowed steroids	
Pro	**Con**	**Pro**	**Con**
"Natural"	Lower quality of life to adjust to dietary restrictions and poor palatability in case of elemental diet	Ease of use	Side effect: esophageal candidiasis (5% to 10%)
Removing upstream trigger of disease	Grocery cost of restricted diet	Not approved by FDA	Theoretic adrenal and growth suppression
Highest response rate with elemental diet	Multiple endoscopies	Improved quality of life	Cost of unapproved medication
Reverse fibrosis		Reverse fibrosis in children	
Reduce symptoms		Reduce symptoms and, in adults, improve complication of food impactions	
Decrease eosinophil count and improve histologic pathology		Decrease eosinophil count and improve histologic pathology	

FDA, US Food and Drug Administration.

TABLE II. Future needs in EGID

Need	Near future	Far future
Drug approval	Topical esophageal corticosteroid (adults)	Biologics for disease modification: anti–IL-13; anti–IL-4Rα; eosinophil-depleting antibodies and drugs Small-molecule inhibitors for mast cell, eosinophil, T-cell, and/or epithelial cell function and/or modification
Personalized medicine	Endotype-based therapy based on esophageal transcriptome profiling (eg, EDP) PPI-responsive patients	Genetic SNP-based therapy
Inflammation-dependent and independent remodeling therapy	Biologics (eg, anti–IL-13 in adults)	Inflammation-independent antifibrotic therapy
Understanding long-term complications and long-term response to therapy	Increased Multicenter Trials, across the United States (via CEGIR)	Genotype-phenotype variability Natural history in large cohorts of children
Less invasive or noninvasive biomarkers	Esophageal string test TNE Sponge test	Peripheral blood markers/panels
Improved diet therapy	One-food elimination (eg, milk elimination diets)	Induction of food tolerance

SNP, Single nucleotide polymorphism.

finding a knowledgeable physician.[51] Patients with EGIDs have limited treatment options for a lifelong disease that significantly affects quality of life. Patient advocacy groups, such as the American Partnership for Eosinophilic Disorders and the Campaign Urging Research for Eosinophilic Diseases (CURED), can help physicians by assisting patients in finding support, lay friendly educational materials, patient conferences, and practical tools for everything needed to live life to the fullest.

PILOT STUDIES WITH POTENTIAL TO AFFECT EGIDs

The CEGIR Pilot Study Program examines novel areas with the potential to create or change diagnostic and therapeutic paradigms concerning EoE, EG, and EC.[18] Currently, 4 pilot studies have been funded and are active: (1) a microbiome initiative examining the gastrointestinal mucosal and fecal bacterial genomes in patients with EoE, EG, and EC; (2) a prospective clinical trial of losartan in patients with EoE; (3) a prospective trial of elemental diet in adults with EG; and (4) a prospective study examining the utility of TNE in children with EoE. Characterization of dysbiosis of the intestinal tract should provide fundamental insight into the pathogenesis of EGIDs. The losartan and elemental diet trials are the first prospective evaluations of such treatments in patients with the indicated diseases. Finally, evaluation of TNE can reduce the necessity of anesthesia during endoscopy during food reintroduction, a major limitation of the elimination diet approach in patients with EoE.

ENDOTYPES IN PATIENTS WITH EoE

Three EoE endotypes have been identified based on probing esophageal biopsy specimens from pediatric and adult patients with EoE across sites associated with CEGIR by using the EDP, a set of 96 informative transcripts.[52] Of histologic features, basal zone hyperplasia correlated relatively strongly with the EDP, and of different endoscopic features, furrows correlated relatively strongly with the EDP.

The EDP identified 3 clusters associated with distinct endotypes (termed EoE endotype 1 [EoEe1] to EoE endotype 3 [EoEe3]) despite similar eosinophil levels. EoEe1 was strongly associated with a normal-appearing esophagus and showed

relatively mild histologic, endoscopic, and molecular changes. EoEe2 demonstrated an inflammatory and steroid-refractory phenotype and showed the greatest expression of cytokines and steroid-responding genes. EoEe3 was associated strongly with a narrow-caliber esophagus and showed the highest degree of endoscopic and histologic severity and the lowest expression of epithelial differentiation genes. These endotypes have potential to allow tailoring of EoE-specific therapy, as well as prognostic predictions.

PREDICTING THE FUTURE IN EGIDs

The potential needs for patients, researchers, and physicians were discussed for the immediate future and the next 10 years (Table II). The major developments will be availability of US Food and Drug Administration–approved medications for patients with EoE and less invasive biomarkers for diagnosis. In the more distant future, personalized medicine based on genetics and genomics on esophageal biopsy specimens, as well as disease endotypes, is likely to advance patient care and understanding.

REFERENCES

1. Jensen ET, Martin CF, Kappelman MD, Dellon ES. Prevalence of eosinophilic gastritis, gastroenteritis, and colitis: estimates from a national administrative database. J Pediatr Gastroenterol Nutr 2016;62:36-42.
2. Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. Gastroenterology 2018;154:319-32.e3.
3. Dellon ES, Jensen ET, Martin CF, Shaheen NJ, Kappelman MD. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol 2014; 12:589-96.e1.
4. Jensen ET, Kappelman MD, Martin CF, Dellon ES. Health-care utilization, costs, and the burden of disease related to eosinophilic esophagitis in the United States. Am J Gastroenterol 2015;110:626-32.
5. Jensen ET, Dellon ES. Environmental and infectious factors in eosinophilic esophagitis. Best Pract Res Gastroenterol 2015;29:721-9.
6. Jensen ET, Kuhl JT, Martin LJ, Langefeld CD, Dellon ES, Rothenberg ME. Early-life environmental exposures interact with genetic susceptibility variants in pediatric patients with eosinophilic esophagitis. J Allergy Clin Immunol 2018;141:632-7.
7. Petroni D, Spergel JM. Eosinophilic esophagitis and symptoms possibly related to eosinophilic esophagitis in oral immunotherapy. Ann Allergy Asthma Immunol 2018;120:237-40.e4.
8. Aceves SS. Unmet therapeutic needs in eosinophilic esophagitis. Dig Dis 2014; 32:143-8.
9. Cheng E, Souza RF, Spechler SJ. Tissue remodeling in eosinophilic esophagitis. Am J Physiol Gastrointest Liver Physiol 2012;303:G1175-87.
10. Schoepfer AM, Safroneeva E, Bussmann C, Kuchen T, Portmann S, Simon HU, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology 2013;145:1230-6, e1-e2.
11. Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc 2014;79:577-85.e4.
12. Menard-Katcher C, Benitez AJ, Pan Z, Ahmed FN, Wilkins BJ, Capocelli KE, et al. Influence of age and eosinophilic esophagitis on esophageal distensibility in a pediatric cohort. Am J Gastroenterol 2017;112:1466-73.
13. Kwiatek MA, Hirano I, Kahrilas PJ, Rothe J, Luger D, Pandolfino JE. Mechanical properties of the esophagus in eosinophilic esophagitis. Gastroenterology 2011; 140:82-90.
14. Tkachenko E, Rawson R, La E, Doherty TA, Baum R, Cavagnero K, et al. Rigid substrate induces esophageal smooth muscle hypertrophy and eosinophilic esophagitis fibrotic gene expression. J Allergy Clin Immunol 2016;137:1270-2.e1.
15. Muir AB, Dods K, Henry SJ, Benitez AJ, Lee D, Whelan KA, et al. Eosinophilic esophagitis-associated chemical and mechanical microenvironment shapes esophageal fibroblast behavior. J Pediatr Gastroenterol Nutr 2016;63:200-9.
16. Rajan J, Newbury RO, Anilkumar A, Dohil R, Broide DH, Aceves SS. Long-term assessment of esophageal remodeling in patients with pediatric eosinophilic esophagitis treated with topical corticosteroids. J Allergy Clin Immunol 2016; 137:147-56.e8.
17. Carlson DA, Hirano I, Zalewski A, Gonsalves N, Lin Z, Pandolfino JE. Improvement in esophageal distensibility in response to medical and diet therapy in eosinophilic esophagitis. Clin Transl Gastroenterol 2017;8:e119.
18. Cheng K, Gupta SK, Kantor S, Kuhl JT, Aceves SS, Bonis PA, et al. Creating a multi-center rare disease consortium—the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR). Transl Sci Rare Dis 2017;2:141-55.
19. Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. Am J Gastroenterol 2007;102:1301-6.
20. Eluri S, Runge TM, Cotton CC, Burk CM, Wolf WA, Woosley JT, et al. The extremely narrow-caliber esophagus is a treatment-resistant subphenotype of eosinophilic esophagitis. Gastrointest Endosc 2016;83:1142-8.
21. Molina-Infante J, Prados-Manzano R, Gonzalez-Cordero PL. The role of proton pump inhibitor therapy in the management of eosinophilic esophagitis. Expert Rev Clin Immunol 2016;12:945-52.
22. Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. J Allergy Clin Immunol 2015;135:187-97.
23. Molina-Infante J, Bredenoord AJ, Cheng E, Dellon ES, Furuta GT, Gupta SK, et al. Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. Gut 2016;65: 524-31.
24. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol 2012;130:461-7.e5.
25. Kagalwalla AF, Shah A, Li BU, Sentongo TA, Ritz S, Manuel-Rubio M, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. J Pediatr Gastroenterol Nutr 2011;53:145-9.
26. Lieberman JA, Morotti RA, Konstantinou GN, Yershov O, Chehade M. Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: a historical cohort. Allergy 2012;67:1299-307.
27. Wang R, Hirano I, Doerfler B, Zalewski A, Gonsalves N, Taft T. Assessing adherence and barriers to long-term elimination diet therapy in adults with eosinophilic esophagitis. Dig Dis Sci 2018[Epub ahead of print].
28. Abu-Sultaneh SM, Durst P, Maynard V, Elitsur Y. Fluticasone and food allergen elimination reverse sub-epithelial fibrosis in children with eosinophilic esophagitis. Dig Dis Sci 2011;56:97-102.
29. Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterology 2010;139:418-29.
30. Aceves SS, Newbury RO, Chen D, Mueller J, Dohil R, Hoffman H, et al. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. Allergy 2010;65:109-16.
31. Moawad FJ, Dellon ES, Achem SR, Ljuldjuraj T, Green DJ, Maydonovitch CL, et al. Effects of race and sex on features of eosinophilic esophagitis. Clin Gastroenterol Hepatol 2016;14:23-30.
32. Pelz BJ, Wechsler JB, Amsden K, Johnson K, Singh AM, Wershil BK, et al. IgE-associated food allergy alters the presentation of paediatric eosinophilic esophagitis. Clin Exp Allergy 2016;46:1431-40.
33. Groetch M, Venter C, Skypala I, Vlieg-Boerstra B, Grimshaw K, Durban R, et al. Dietary therapy and nutrition management of eosinophilic esophagitis: a work group report of the American Academy of Allergy, Asthma, and Immunology. J Allergy Clin Immunol Pract 2017;5:312-24.e29.
34. Spergel JM, Brown-Whitehorn T, Beausoleil JL, Shuker M, Liacouras CA. Predictive values for skin prick test and atopy patch test for eosinophilic esophagitis. J Allergy Clin Immunol 2007;119:509-11.
35. Lucendo AJ, Arias A, Gonzalez-Cervera J, Yague-Compadre JL, Guagnozzi D, Angueira T, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. J Allergy Clin Immunol 2013;131: 797-804.
36. Arias A, Gonzalez-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology 2014; 146:1639-48.
37. van Rhijn BD, Vlieg-Boerstra BJ, Versteeg SA, Akkerdaas JH, van Ree R, Terreehorst I, et al. Evaluation of allergen-microarray-guided dietary intervention as treatment of eosinophilic esophagitis. J Allergy Clin Immunol 2015;136: 1095-7.e3.
38. Clayton F, Fang JC, Gleich GJ, Lucendo AJ, Olalla JM, Vinson LA, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology 2014;147:602-9.

39. Erwin EA, Kruszewski PG, Russo JM, Schuyler AJ, Platts-Mills TA. IgE antibodies and response to cow's milk elimination diet in pediatric eosinophilic esophagitis. J Allergy Clin Immunol 2016;138:625-8.e2.
40. Erwin EA, Tripathi A, Ogbogu PU, Commins SP, Slack MA, Cho CB, et al. IgE antibody detection and component analysis in patients with eosinophilic esophagitis. J Allergy Clin Immunol Pract 2015;3:896-904.e3.
41. Cianferoni A, Ruffner MA, Guzek R, Guan S, Brown-Whitehorn T, Muir A, et al. Elevated expression of activated TH2 cells and milk-specific TH2 cells in milk-induced eosinophilic esophagitis. Ann Allergy Asthma Immunol 2018;120:177-83.e2.
42. Rothenberg ME, Spergel JM, Sherrill JD, Annaiah K, Martin LJ, Cianferoni A, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. Nat Genet 2010;42:289-91.
43. Sherrill JD, Gao PS, Stucke EM, Blanchard C, Collins MH, Putnam PE, et al. Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. J Allergy Clin Immunol 2010;126:160-5.e3.
44. Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. Nat Immunol 2002;3:673-80.
45. Mishra A, Schlotman J, Wang M, Rothenberg ME. Critical role for adaptive T cell immunity in experimental eosinophilic esophagitis in mice. J Leukoc Biol 2007;81:916-24.
46. Jyonouchi S, Smith CL, Saretta F, Abraham V, Ruymann KR, Modayur-Chandramouleeswaran P, et al. Invariant natural killer T cells in children with eosinophilic esophagitis. Clin Exp Allergy 2014;44:58-68.
47. Rayapudi M, Rajavelu P, Zhu X, Kaul A, Niranjan R, Dynda S, et al. Invariant natural killer T-cell neutralization is a possible novel therapy for human eosinophilic esophagitis. Clin Transl Immunol 2014;3:e9.
48. Brennan PJ, Tatituri RV, Heiss C, Watts GF, Hsu FF, Veerapen N, et al. Activation of iNKT cells by a distinct constituent of the endogenous glucosylceramide fraction. Proc Natl Acad Sci U S A 2014;111:13433-8.
49. Cianferoni A, Spergel JM. Eosinophilic esophagitis and gastroenteritis. Curr Allergy Asthma Rep 2015;15:58.
50. Abonia JP, Blanchard C, Butz BB, Rainey HF, Collins MH, Stringer K, et al. Involvement of mast cells in eosinophilic esophagitis. J Allergy Clin Immunol 2010;126:140-9.
51. Eluri S, Book WM, Kodroff E, Strobel MJ, Gebhart JH, Jones PD, et al. Lack of knowledge and low readiness for health care transition in eosinophilic esophagitis and eosinophilic gastroenteritis. J Pediatr Gastroenterol Nutr 2017;65:53-7.
52. Shoda T, Wen T, Aceves SS, Abonia JP, Atkins D, Bonis PA, et al. Esophageal transcript analysis across the Consortium of Eosinophilic Gastrointestinal Disease Researchers identifies clinical-histopathologic correlates and endotypes of eosinophilic esophagitis. Lancet Gastroenterol Hepatol 2018;3:477-88.

Eosinophilic esophagitis is characterized by a non-IgEmediated food hypersensitivity;

Antonella Cianferoni, USA

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy

REVIEW ARTICLE

Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity§

D. Simon[1,*], A. Cianferoni[2,3,*], J. M. Spergel[2,3], S. Aceves[4], M. Holbreich[5], C. Venter[6,7], M. E. Rothenberg[6], I. Terreehorst[8], A. Muraro[9], A. J. Lucendo[10], A. Schoepfer[11], A. Straumann[12] & H.-U. Simon[13]

[1]Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [2]Division of Allergy and Immunology, Children's Hospital Philadelphia, University of Pennsylvania; [3]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [4]Division of Allergy and Immunology, Department of Pediatrics and Medicine, Center for Infection, Inflammation, and Immunology, La Jolla, CA; [5]Allergy and Asthma Consultants, Indianapolis, IN; [6]Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [7]School of Health Sciences and Social Work, University of Portsmouth, Portsmouth, UK; [8]Department of ENT and Pediatrics, AMC, Amsterdam, The Netherlands; [9]Food Allergy Referral Centre Veneto Region, Padua General University Hospital, Padua, Italy; [10]Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso, Spain; [11]Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois/CHUV, Lausanne; [12]Swiss EoE Research Network, Olten; [13]Institute of Pharmacology, University of Bern, Bern, Switzerland

To cite this article: Simon D, Cianferoni A, Spergel JM, Aceves S, Holbreich M, Venter C, Rothenberg ME, Terreehorst I, Muraro A, Lucendo AJ, Schoepfer A, Straumann A, Simon HU. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. *Allergy* 2016; **71**: 611–620.

Keywords
eosinophilic esophagitis; epithelial barrier; food allergy; immune response; immunoglobulin E.

Correspondence
Dagmar Simon, MD, Department of Dermatology, Inselspital, Bern University Hospital, CH-3010 Bern, Switzerland.
Tel.: +41 31 632 2278
Fax: +41 31 632 2233
E-mail: dagmar.simon@insel.ch

§Review initiated by the EAACI Eosinophilic Esophagitis Interest Group
*These authors contributed equally to this paper.

Accepted for publication 17 January 2016

DOI:10.1111/all.12846

Edited by: Thomas Bieber

Abstract

Eosinophilic esophagitis (EoE) is a chronic disease characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation. EoE is frequently associated with concomitant atopic diseases and immunoglobulin E (IgE) sensitization to food allergens in children as well as to aeroallergens and cross-reactive plant allergen components in adults. Patients with EoE respond well to elemental and empirical food elimination diets. Recent research has, however, indicated that the pathogenesis of EoE is distinct from IgE-mediated food allergy. In this review, we discuss the individual roles of epithelial barrier defects, dysregulated innate and adaptive immune responses, and of microbiota in the pathogenesis of EoE. Although food has been recognized as a trigger factor of EoE, the mechanism by which it initiates or facilitates eosinophilic inflammation appears to be largely independent of IgE and needs to be further investigated. Understanding the pathogenic role of food in EoE is a prerequisite for the development of specific diagnostic tools and targeted therapeutic procedures.

Abbreviations
ACD, allergic contact dermatitis; AD, atopic dermatitis; APT, atopy patch test; DHR, drug hypersensitivity reactions; EoE, eosinophilic esophagitis; FPIES, food protein-induced enterocolitis; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IBD, inflammatory bowel disease; Ig, immunoglobulin; OAS, oral allergy syndrome; PPI-REE, proton pump inhibitor-responsive esophageal eosinophilia; SFED, six-food elimination diet; SPT, skin prick test; TCR, T-cell receptor; TNF, tumor necrosis factor.

Current definition of EoE

As a consequence of intense research in the field of esophageal eosinophilia, our understanding of eosinophilic esophagitis (EoE) has developed from strict clinic–pathologic criteria leading toward a conceptual definition which includes pathogenic aspects (1–3). According to current recommendations, EoE represents a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation (2). EoE has been recognized as having a spectrum of clinical signs and symptoms, endoscopic findings as well as pathologic features. However, the term 'immune/antigen-mediated' does not address the question where EoE should be positioned in the wide range between autoimmune and allergic diseases. In addition, there are likely subgroups of patients who do not meet this strict definition; for example, some have less than 15 eosinophils per high power field (hpf), but otherwise fulfill the criteria of EoE (2).

The two most common causes of eosinophilia in the esophagus, normally devoid of eosinophils in healthy humans, are gastroesophageal reflux (GERD) and EoE (2). However, yet another form of esophageal eosinophilia has recently emerged having clinical manifestations and histological features indistinguishable from EoE, but distinct from GERD, apart from the fact that it is responsive to high dose of PPI whereas EoE is histologically refractory to PPI. Hence, it is called PPI-responsive esophageal eosinophilia (PPI-REE) (4, 5). Patients with PPI-REE frequently exhibit environmental and/or food allergen sensitizations like patients with EoE, whereas the atopy rate in patients with GERD is similar to that of the general population. Moreover, the inflammatory markers of PPI-REE are more similar to those of EoE than of GERD: positive for factors involved in eosinophil chemotaxis (eotaxin-3, CCL26), barrier integrity (desmoglein-1, DSG1), tissue remodeling (periostin, POSTN), and mast cell-specific activity (carboxypeptidase A, CPA3) (4). The molecular signature typical of PPI-REE and EoE could be reversed by PPI therapy only in PPI-REE (4), suggesting the molecular signature is either a sign of disease or marker of eosinophilic inflammation. Mechanisms proposed to explain the PPI response include an acid-independent, anti-inflammatory action of PPIs on the one hand, or a PPI-induced restoration of esophageal barrier function on the other (6). In summary, it is possible that PPI-REE and EoE are the consequence of the same underlying immunologic mechanism, but additional research is required to confirm this concept.

Already early reports on EoE mentioned concomitant allergic diseases and elevated total serum immunoglobulin E (IgE) levels in about 70% of the patients (7, 8). After receiving elemental formulas, children with esophageal eosinophilia not responding to pharmacological and/or surgical antireflux therapy, showed marked improvements (9). This observation suggested that EoE could represent an allergic disease in which food proteins play an important role. However, further research revealed that EoE seems not to be simply an IgE-mediated food allergy. What, then, are the underlying causes of EoE and what role might food and/or other antigens play in the pathogenesis? In this review initiated by the EAACI Eosinophilic Esophagitis Interest Group, we will discuss recently published work on EoE in the context of an immune/antigen-mediated disease.

EoE-associated IgE sensitization to food and aeroallergens

EoE is associated with elevated total IgE levels as well as IgE sensitization to food and aeroallergens (10). In a pediatric EoE cohort, sensitizations to food and environmental allergens have been observed in 75% and 79%, respectively (11). Skin prick testing in children with EoE revealed increasing reactivity with inhalant allergen with age, while the reactivity to foods decreased (12). Children with EoE were mainly sensitized to milk, eggs, soy, wheat/rye, beef and peanuts (13). In adult patients with EoE, specific IgEs to food and inhalant allergen components have been detected in 91% (14). These patients were mainly sensitized to pollens, in particular cross-reactive plant allergen components such as profilins and pathogenesis-related (PR) 10 proteins (14). Noteworthy is the observation of local immunoglobulin class switching and production of IgE in the esophageal mucosa of pediatric patients with EoE (15). Considering all these findings, EoE was initially suspected of being an IgE-mediated allergy to food and cross-reactive plant allergens.

On the other hand, clinical trials of targeted food elimination diets, as well as of IgE blocking, failed to show an IgE-mediated mechanism. Measuring specific IgE levels and/or skin prick testing were not sufficient to clearly identify causative food allergens (13, 14, 16, 17). Moreover, elimination diets based solely on IgE sensitization to food allergens as determined by skin prick tests (SPTs) and/or specific IgE determinations could not improve EoE in a significant number of patients (16, 18, 19). The positive predictive values for causative food identified by SPT ranged from 26% to 96%, with an average of 47% (16). Based on the assumption that IgE plays a key role in pathogenesis, a therapy with an anti-IgE antibody for 12 weeks in pediatric and adult patients with EoE was initiated in a non-placebo-controlled study resulting in a remission rate of only 33% despite an effective reduction of IgE levels observed in the esophageal tissue (20). In a double-blind placebo-controlled study, anti-IgE treatment was not better than placebo in inducing EoE remission (21). Taken together, recent clinical and research data lead us to conclude that EoE, while often associated with IgE sensitization, is not simply an IgE-mediated food allergy.

EoE exhibits features of a Th2-predominant inflammation

The inflammation of EoE is predominantly eosinophilic, but is also characterized by increased numbers of T cells and mast cells infiltrating the esophageal mucosa, as well as high expression levels of IL-5 and TNF-α (Fig. 1) (22). Transcriptome analysis of EoE tissue showed a distinct Th2 pattern with significantly elevated mRNA levels of eotaxin-3, IL-5, IL-5 receptor α-chain and IL-13 (23, 24). In experimental models, both

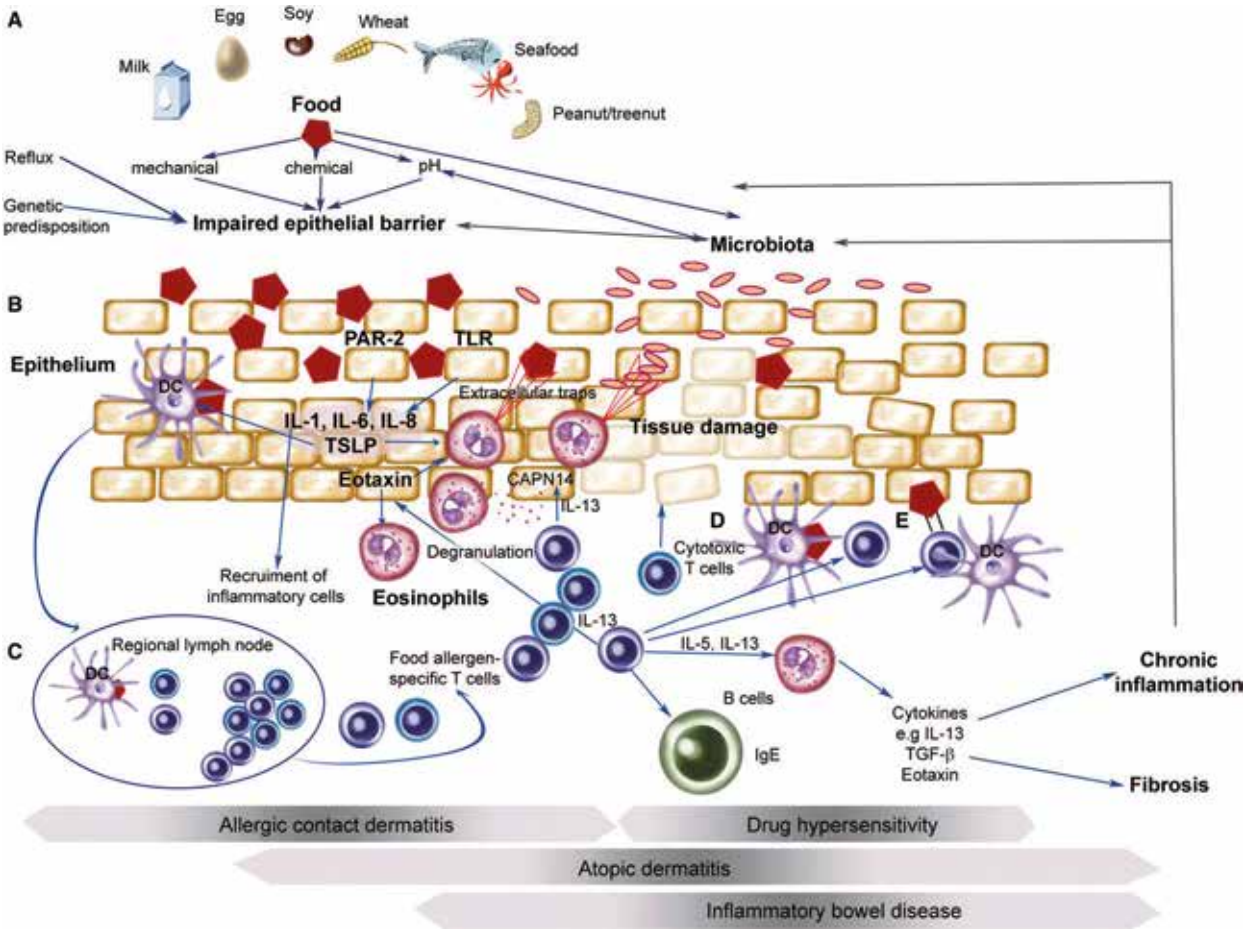


Figure 1 Food as a trigger in the pathogenesis of EoE. (A) In addition to the presence of a genetic predisposition or reflux disease, a food allergy would further disrupt the epithelial barrier and affect the microbiota. (B) Food allergens could then penetrate also in the skin, bind to pathogen-related receptors and activate epithelial cells to produce pro-inflammatory cytokines responsible for the recruitment and activation of inflammatory cells including eosinophils. (C) Antigen-presenting cells capturing food antigens would migrate to the regional lymph nodes where they stimulate food-specific T cells. Food proteins may induce T-cell responses either as a consequence of antigen presentation by dendritic cells (D) or directly (E) with subsequent eosinophil activation. By releasing toxic granule proteins and cytokines, eosinophils defend against invading pathogens, but cause tissue damage, stimulating fibrosis and perpetuating inflammation. The pathomechanisms of EoE overlapping with other diseases are indicated.

eotaxin and IL-5 were essential for eosinophil recruitment, accumulation and activation in the esophagus as well as for epithelial hyperplasia and remodeling (25–28). Moreover, IL-13 can induce eotaxin-3 production by esophageal epithelial cells (29). In addition to the Th2 cytokines, patients with EoE show elevated blood levels of IL-1α, IL-6 and IL-8, but lower levels of IL-12, IL-17 and CD40L as compared with healthy controls, while the gene expression of receptors for IL-1, IL-9 and IL-17 is also upregulated in EoE lesions (23, 24).

Treatment with corticosteroids resulted in a reduced expression of eotaxin-3, IL-5 and IL-13 and was followed by a decrease of eosinophil numbers in the esophagus of patients with EoE (29). Although reducing eosinophil inflammation in the esophagus, blocking IL-5 or IL-13 with therapeutic antibodies has yet to be proven to be clinically useful, although trends have been seen in preliminary studies (30, 31). In summary, Th2 immune responses are a striking feature and most likely contribute to the pathogenesis of EoE, but are not the sole players as pro-inflammatory cytokines are also expressed that may regulate additional responses.

Lessons learnt from hypersensitivity reactions of the skin

EoE shares many similarities with dermatoses that are due to T-cell responses of the skin independent of IgE. Therefore, it appears logical to consider antigen-triggered T cell-mediated mechanisms for the pathogenesis of EoE (Fig. 1).

T-cell responses in allergic contact dermatitis

In allergic contact dermatitis (ACD), chemical allergens penetrate into the skin where they form complexes or bind covalently to proteins of immune and structural cells in the skin

and, thus, may induce innate immune responses as well as generate T-cell epitopes (32). Contact allergens, for example, nickel, are recognized by pattern recognition receptors (PRRs) resulting in the production of pro-inflammatory cytokines such as IL-1 and IL-18. This irritant effect of contact allergens is essential for the subsequent activation of the adaptive immune system leading to a Tc1/Th1 and Tc17/Th17 effector/memory T-cell response (33). Contact hypersensitivity is dependent on T cell-mediated cytotoxicity via FAS/FASL and perforin pathways (34). In ACD, Th1/Th17 cells may amplify the cytotoxic cascade as they increase T cell–keratinocyte adhesiveness and promote ICAM-1-dependent non-antigen-specific keratinocyte killing by T lymphocytes (35). However, there is little evidence for an IL-17-mediated process in EoE (36).

T cells in drug hypersensitivity

While immediate allergic drug hypersensitivity reactions (DHR) are mediated by specific IgE bound to mast cells and basophils, delayed (nonimmediate) allergic DHR are T cell-mediated. Analogous to haptens, drugs are presented either covalently bound to peptides in the binding grove of MHC molecules on antigen-presenting cells or complexed to amino acids in MHC molecules and TCR (37). Recently, a concept for the pharmacological interaction of drugs with immune receptor (p-i concept) has been proposed, suggesting a non-covalent binding enabling a direct interaction with immunological receptors such as MHC and TCR (38, 39). Thus, the antigen might bind either to the MHC complex, thereby modifying the structure that is recognized by the TCR leading to a specific T-cell activation, or directly to a specific TCR requiring additional MHC interaction for full T-cell activation (38). In cutaneous reactions, drug-specific cytotoxic T cells have been demonstrated that can contribute to tissue damage via perforin/granzyme B or FAS/FASL mechanisms (40, 41). In DRESS, an oligoclonal expansion of activated CD8+ T cells directed against viral antigens derived from *Herpes* viruses, whose replication is enhanced by the culprit drug, has been observed in the skin and visceral organs (42).

Food-specific T-cell responses in the skin

Over 80% of patients with atopic dermatitis (AD) have increased IgEs to foods and inhalant allergens in the peripheral blood (43). However, the positive predictive value of IgE specific to food allergens is low (44). Interestingly, in 45% of patients reacting upon food allergen challenge, eczematous reactions with or without prior immediate reactions have been observed, suggesting the occurrence of late, most likely T cell-mediated reactions against foods (44). Indeed, in patients with food-triggered AD exacerbations, relevant food allergen-specific T cells have been detected in the peripheral blood as well as the skin (45, 46). Moreover, positive atopy patch test (APT) reactions to inhalant and food allergens can be detected in the absence of corresponding IgE responses (47). Although widely used, the APT has limited value in the diagnosis of food allergy in EoE (16) perhaps owing to the fact that here the skin and not the esophagus is tested. Upon food allergen, but not nonspecific stimulation, peripheral blood mononuclear cells from EoE patients with or without allergen-specific IgE produce significant amounts of IL-5 (48). In peanut-allergic children, skin- and gut-homing T cells expressing Th2 and Th9 genes as well as IL-9 and IL-5 production by distinct T helper cell populations have been reported (49).

To date, the presence of food allergen-specific T cells in EoE has not been demonstrated. Furthermore, it remains uncertain when and where the sensitization to food allergens occurs. In adult patients with EoE, airway allergy precedes EoE (50). Recent data suggest that an epicutaneous sensitization with ovalbumin may result in an antigen-induced gastrointestinal food allergy via the TSLP–basophil axis or in an IL-17-mediated response depending on the animal model (51, 52). Furthermore, filaggrin mutations as risk factors for eczema, the atopic march and peanut allergy have been reported, indicating that an impaired epithelial barrier function may predispose to allergen sensitization and atopy (53, 54).

Epithelial barrier and innate immune responses in EoE

There is increasing evidence that EoE is associated with a dysfunction at the epithelial barrier followed by an eosinophilic inflammation similar to AD which is concomitant in over half of patients with EoE (Fig. 1). In esophageal epithelial cells, the expression of epidermal differentiation complex (EDC) genes, for example, filaggrin, SPRR3 and keratins, is downregulated in response to IL-13 and in active EoE, where it could be only partially normalized upon therapy (55, 56). Desmoglein (DSG)-1, an intercellular adhesion molecule responsible for epithelial integrity and barrier function was one of the most strongly downregulated genes in EoE (29). A downregulation of DSG-1 gene, for example, by IL-13, was shown to result in the separation of epithelial cells (spongiosis) followed by impaired barrier function as well as by periostin induction further potentiating inflammation (57). Ultrastructural analysis revealed a significantly decreased number of desmosomes per cell in EoE biopsies as compared to healthy controls, which was reversible after treatment (58). Furthermore, the expression of filaggrin and the tight junction proteins zonula occludens (ZO)-3 and claudin-1 is decreased in EoE, correlating with spongiosis (59). Consistent with this finding, mutations in filaggrin are overrepresented in patients with EoE (55) and homozygous mutations of DSG1 cause a severe atopy syndrome which includes EoE (60).

In stratified epithelia, the activity of proteases is tightly regulated by protease inhibitors. The loss of inhibition results in cleavage of desmosomal proteins and loss of barrier integrity, facilitating the penetration of allergens and microbes as well as the subsequent generation of danger signals and protease activated receptor (PAR)-2 activation (61). In active EoE, a significantly decreased expression of the protease inhibitor LEKTI has been observed (36).

TSLP that is produced by epithelial cells in response to PAR-2, Toll-like receptor (TLR) stimulation or mechanical injury, strongly induces Th2 immune responses by stimulating dendritic cells, T cells, eosinophils, mast cells and basophils (62). Upon stimulation with TSLP, eosinophils that bear the TSLP receptor on their surface generate extracellular DNA traps associated with granule proteins that are able to kill bacteria (63). Interestingly, the expression of TSLP is increased in EoE and correlates with the number of eosinophils generating eosinophil extracellular traps (36). Genetic variants of TSLP and its receptor have been associated with an increased susceptibility to EoE overall, and in males, respectively (64, 65). Furthermore, the gene of esophageal selective calpain (CAPN) 14, a member of the calpain protease family involved in the cleavage of inflammatory mediators such as IL-33, was upregulated in active EoE, while the calpain inhibitor CAST was downregulated (66). In line with these findings, genetic variants in the CAPN 14 gene locus are linked with EoE susceptibility (67) and increased expression of innate cytokines including IL-33 by epithelial cells has been detected in EoE (36).

Immense efforts have been undertaken to identify the role of the microbiota in the immune system, in particular in association with immune-mediated diseases. Microbiota research aims at elucidating their role in initiating and perpetuating inflammation and, conversely, the effect of diseases and treatment procedures on the microbiota. Compared to healthy controls, the bacterial load of the esophagus is increased in patients with EoE regardless of treatment and disease activity, with a relative abundance of gram-negative bacteria in active EoE (68, 69). Recently, IgE sensitization to *Candida albicans* has been reported in pediatric and adult patients with EoE (14, 70). Whether an esophageal colonization with *Candida albicans* and later sensitization is owing to EoE inflammation or corticosteroid therapy remains to be investigated. Furthermore, any potential role of IgE specific for *Candida albicans* in the pathogenesis of EoE is uncertain.

Taken together, recent research suggests that impaired epithelial barrier function plays a major role in initiating and perpetuating EoE inflammation as it facilitates the penetration of allergens and microbes and generates danger signals leading to an activation of epithelial cells as well as innate and adaptive immune cells with subsequent chemokine and cytokine production resulting in Th2 immune responses. There is evidence of a dysbiosis of microbiota in EoE; however, the consequences in terms of microbial-triggered eosinophilic inflammation and the particular role of diet on the microbiome in the esophagus remain to be investigated.

Similarities and differences between EoE and IBD

With inflammatory bowel diseases (IBDs), such as Crohn's disease (CD) and ulcerative colitis (UC), the pathogenesis is determined by genetic factors, environmental and microbial factors together with an epithelial barrier dysfunction and subsequent innate and adaptive immune responses (71). The susceptibility to IBD is determined by genetic variants related to innate immunity, autophagy and phagocytosis in CD and to barrier function in UC (72). Due to an increased intestinal epithelial permeability, food antigens and microbes may activate pattern recognition receptors on epithelial cells resulting in a release of pro-inflammatory cytokines such as TNF-α, IL-1, IL-18 and IL-33 (Fig. 1) (71). In contrast to EoE, predominantly Th1 cells and the IL-23/Th17 axis are activated in IBD (71). It has been hypothesized that due to a dysregulated innate intestinal immunity and barrier function, affecting both the diversity and composition of the microbiota, the immune response is initiated to eliminate invading antigens (e.g. microbes, food) and to restore epithelial barrier integrity, but may later turn into a chronic inflammation leading to the clinical manifestations of IBD (71, 73).

Thus, the principal pathomechanisms of IBD seem congruent with those of EoE, although it is currently not clear which tissue-specific characteristics, including immune responses, environmental factors such as microbiota and food, as well as genetic predispositions favor a chronic Th1/Th17 inflammation as in IBD or a Th2-predominant inflammation as in EoE with corresponding clinical phenotypes. While both diseases have common mechanisms, the upstream events are likely to be different as EoE is associated with unique genetic susceptibility (TSLP and CAPN14) and atopy; whereas IBD is more related to innate immunity to microbial flora.

EoE is distinct from IgE-mediated food allergies

If one were to consider EoE as a kind of food allergy, how would its symptoms agree with the current concept of gastrointestinal (GI) allergies? A food allergy is defined as an abnormal immunologic response to a food substance occurring in a susceptible host and causing some type of GI inflammation. The vast majority of food allergies affecting the GI tract are characterized by a Th2 inflammation with predominant Th2 cytokine expression (that is IL-4, IL-13, and IL-5). Th2 inflammation can cause B cells to produce IgE antibodies specific to certain foods or can lead to a chronic cellular inflammation frequently characterized by the presence of Th2 cell and eosinophils (74).

According to the immunological mechanism elicited, food allergies can be classified into (1) IgE-mediated, which are immediate, short-lived reactions mediated by antibodies belonging to the IgE class; (2) cell-mediated, which usually have a delayed/chronic course, typically involving the GI tract and the cell component of the immune system responsible for inflammation; or (3) mixed, IgE- and cell-mediated (75). IgE-mediated reactions to foods are acute and highly reproducible. They are initiated by the cross-linking of two or more allergen-specific IgE antibodies bound to their high-affinity receptor (FcεRI) expressed on mast cells and basophils as a result of a specific food allergen engagement. Such cross-linking determines the release of preformed mediators, in particular, histamine, that cause vasodilatation, angioedema, smooth muscle constriction, and increased mucus production (76).

Examples of typical IgE-mediated allergic reactions affecting the GI tract are the oral allergy syndrome (OAS) and the more severe GI food allergy, also known as 'gastrointestinal anaphylaxis'. When comparing IgE-mediated OAS and GI

food allergies with EoE, the following differences become evident: EoE symptoms might be instant, but they are not transient, EoE inflammation is chronic, anaphylaxis is not a feature of EoE, and pollen-associated food allergens are not a typical trigger of EoE. It should be noted, however, that patients with EoE can concurrently suffer from OAS and/or a GI food allergy.

Food protein-induced enterocolitis (FPIES), an increasingly recognized form of non-IgE-mediated food hypersensitivity, is characterized by a delayed onset of vomiting with or without diarrhea, typically occurring in infants and toddlers from 2 to 6 h postingestion of the trigger food (77, 78). FPIES is usually a transient disease which starts at 4–9 months of life or when solid foods are first introduced, and resolves by age 2–5 years (77). The foods most commonly involved in FPIES are milk, soy, rice, oats and eggs. IgEs specific to the trigger foods are usually not detectable (77, 79). Although FPIES and EoE seem to share some clinical (symptoms, age of onset) and pathogenic (causative food triggers, increased TNF-α, epithelial barrier defects) features (80), other characteristics such as disease course, endoscopic and histologic findings discriminate FPIES from EoE.

Experience with omalizumab: Its lack of clinical efficacy in EoE

Omalizumab is an anti-IgE humanized monoclonal antibody that binds to the fragment crystallizable (Fc) region of the IgE molecule and thus prevents its binding to the high-affinity IgE receptor (Fc epsilon RI, FcεRI). In the only published prospective, randomized, double-blind placebo-controlled study in 30 adult patients with EoE (16 treated with omalizumab and 14 with placebo) omalizumab was given every 2–4 weeks for 16 weeks, based on weight and serum level of IgE. Before starting the treatment and at the end of the trial (16 weeks of treatment) symptoms evaluation, EGD and histological assessment of the eosinophil density (peak eos/hpf) in esophageal biopsies were performed. Patients treated with omalizumab had neither a significant improvement in symptoms nor a decrease of the eosinophil infiltration of the esophageal mucosa compared with placebo (21). This study confirmed anecdotal data from clinical cases reported in which omalizumab had been considered to improve IgE-mediated symptoms of food allergy, but not of EoE (81). Overall, these data support the notion that EoE is not IgE-mediated. Clayton et al. (21) speculated that IgG4 antibodies specific for a food allergen are blocking IgE responses. Indeed, in allergic diseases, an IgG4 response follows an IgE-mediated response and does block IgE-mediated mast cell activation (21). In EoE, extracellular granular deposits of IgG4 and abundant IgG4-containing plasma cells in the tissue, as well as increased serum levels of IgG4 reactive with specific foods have been observed, suggesting that in adults, EoE might be an IgG4- and IgE-associated disease and perhaps the balance between the two antibodies could be a key determinant (21). However, B cell-deficient mice also develop typical EoE, suggesting that antibodies may simply be nonpathogenic (82). Moreover, the antifood IgG4 levels did not correlate with the age and duration of disease symptoms (21). Further studies will be necessary to really understand the pathogenic role of IgG4 in EoE.

EoE is characterized by a non-IgE-mediated food hypersensitivity

Since the first description of a series of clinical cases of EoE, food allergies have appeared to play a major role in causing a severe esophageal eosinophilia that resolved on elemental diet, but not on aggressive GERD treatment, including Nissen fundoplication (6). In view of this, food allergens have been identified as triggers of EoE in most children and adults (6, 16, 82, 83).

Thus, food as a trigger of EoE fulfills Koch's postulates as the addition or subtraction of foods can cause disease or eliminate EoE in nearly all patients. The most effective treatment in patients with EoE is an elemental diet that induces histological and clinical resolution in over 95% of pediatric and adult patients (83–86). Noteworthy is that IBD may also resolve upon elemental diet (87) with a mechanism that involves both bowel rest and a change in microbiome. So far, the explanation for remission of EoE on an elemental diet has always been linked to the avoidance of food allergens, rather than bowel rest/change in microbiome, but this possibility needs to be investigated further. This presumption was supported by the fact that elimination diets based on removal of the six most common food allergens (SFED – six-food elimination diet) (82) or of the foods to which patients were sensitized (targeted elimination diets) have been shown to induce and maintain EoE remission in 72% and 45% of patients with EoE, respectively (13, 16). According to biopsy confirmation, the most common food proteins causing EoE are milk, followed by wheat, eggs, beef, soy and legumes, and chicken (16, 83, 88, 89). Interestingly, peanuts, tree nuts, fish and shellfish are rare as causes for EoE despite being common causes of IgE-mediated reactions in adults.

The evidence that EoE is generally non-IgE-mediated is based on both clinical and research findings:

1 Despite the fact that the majority of patients with EoE have specific IgEs to food allergens and/or aeroallergens, the detection of specific IgEs for food allergens, either by SPT or by specific sera IgE (sIgE), has not proven successful for the identification of causative foods in EoE (84, 85). Indeed, removal of SPT- or sIgE-positive foods is not superior to SFED (2, 16, 17, 83, 90). Moreover, it has been reported that the introduction of skin test-negative foods into the diet sometimes induces clinical disease (6, 16).
2 Clinical trials and case series have shown that therapy with omalizumab is not effective in inducing remission of EoE (21, 81).
3 Oral immunotherapy, which has been used successfully in IgE-mediated food allergy, is associated with an increased risk of developing EoE (e.g. in 2 to 10% of treated patients) (91–93).

4 Children who outgrow IgE-mediated food allergy and therefore are able to reintroduce these foods in their diet can later develop EoE to the same food (94).
5 In experimental models in which food allergens are able to induce an EoE-like disease, mice with depleted IgE and devoid of mast cells still could develop esophageal inflammation and consequent food impaction similar to the wild-type mice (95, 96).

Confirmation of EoE diagnosis and the practical search for offending foods

EoE is a clinicopathological diagnosis. However, EoE and GERD have a substantial overlap of clinical and of histological features. For instance, the presence of heartburn and marked esophageal eosinophilia might be fairly common in both entities (2). To solve this diagnostic conundrum, updated consensus recommendations for diagnosis and management of EoE advocate performing a PPI trial in patients having symptoms suggestive of EoE and esophageal eosinophilia (2). Accordingly, a diagnosis of GERD was recommended for those patients responding to PPI therapy, whereas patients whose symptoms and inflammation persist were regarded as having EoE (2). Unfortunately, this diagnostic PPI trial did not fulfill the expectation of differentiating EoE from GERD, but unexpectedly uncovered a third category of patients, called PPI-REE, presenting with symptoms of EoE, but responding to PPI (5). With the exception of the responsiveness to PPI, PPI-REE, and EoE have common clinical, endoscopic, histological and molecular features.

EoE is a chronic and progressive disease. If left untreated complications, such as food impaction, esophageal stricture, narrow-caliber esophagus, and esophageal perforation, are common (97, 98). Therefore, once the diagnosis is confirmed, it is important to treat the eosinophilic inflammation not only to control the presenting symptoms, but also to preserve the morphological and functional integrity of the esophagus (2, 10, 87, 98). Beside medications, diets avoiding culprit foods are an important therapeutic option (99). Of note, before an elimination diet can be established, it is necessary to identify the triggering foods, ideally with the help of a dietitian specialized in dealing with this disease. Currently culprit foods are identified by demonstrating histological and clinical remission of EoE after the establishment of an elimination diet. In practice, after avoidance and after reintroduction of any food category, the effect must be controlled endoscopically and histologically (82, 83). Serial endoscopies are therefore required to figure out an individual elimination diet. This approach is time-consuming, inconvenient for patients, expensive, and affects the quality of life (100). Therefore, there is a need to develop noninvasive methods for the identification of the offending foods. The determination of food-specific IgG4 in the serum is a method currently under evaluation. Further phenotyping patients based on their esophageal gene expression, using a 94 gene transcript profile, is promising to be helpful (101).

Conclusions

There is strong evidence that foods, most likely food proteins, are triggers of EoE, as elimination of culprit food categories as well as protein-free elemental diets results in an improvement of histological and endoscopic signs as well as of symptoms. Furthermore, the observation that the eosinophilic inflammation and the Th2 inflammation pattern reappear rapidly after reintroduction of the culprit foods is a strong evidence that EoE is likely a food-driven disorder with features of food allergy. However, the spectrum of clinical presentations of EoE, the results of IgE-based diagnostic procedures, and the lack of efficacy of anti-IgE treatment suggest that EoE cannot be regarded as an IgE-mediated food allergy.

The mechanism by which food elicits EoE is not yet understood. It seems likely that a cellular mechanism similar to contact allergy of the skin or drug hypersensitivity plays a role. IgG4 formed against foods has been suspected of playing a role in EoE, perhaps as a blocking antibody. Analogous to AD and IBD, an impairment of the epithelial barrier, alterations of the microbiota and subsequent chronic inflammation might be the underlying pathogenic factors for EoE. Given this scenario, food might interfere either as an irritant, modulator of the microbiota or as an antigen/allergen to initiate and perpetuate inflammation (Fig. 1). The identification of offending foods by empirical elimination diets and controlled reintroduction of foods is inconvenient for patients, time-consuming, and in the clinical routine hardly applicable. Nevertheless, this procedure is currently the only reliable method to identify food triggers in patients with EoE. Elucidating the exact mechanism of how foods affect EoE would allow the development of novel diagnostic tests. For instance, the determination of food-specific markers including T-cell responses to specific foods could possibly overcome the limitations of SPT, APT, and empirical diets. As in IBD and atopic diseases, EoE should be considered as a complex disease with a disordered interplay between the epithelial barrier, innate and adaptive immune responses together with the composition of the microbiota.

Conflict of interest

J. M. Spergel has consultant contracts with DBV Technology and Danone and received a grant from Aimmune Therapeutics. M. E. Rothenberg is a consultant for Receptos and NKT Therapeutics, and has an equity interest in Immune Pharmaceuticals and NKT Therapeutics. He has received speaking honorarium from Merck. He is an inventor of eosinophilic esophagitis-related patents owned by Cincinnati Children's Hospital Medical Center, some of which have been licensed to Miraca Life Sciences. He has a royalty interest in reslizumab, a drug being developed by Texas Pharmaceuticals. A. Schoepfer has consultant contracts with Falk, Receptos, and Regeneron. A. Straumann has consultant contracts with Actelion, Falk, Genentech-Roche, Nutricia, Receptos, and Regeneron. The remaining authors have no potential conflict of interest.

References

1. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;**133**:1342–1363.
2. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;**128**:3–20.
3. Furuta GT, Katzka DA. Eosinophilic esophagitis. *N Engl J Med* 2015;**373**:1640–1648.
4. Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. *J Allergy Clin Immunol* 2015;**135**:187–197.
5. Molina-Infante J, Bredenoord AJ, Cheng E, Dellon ES, Furuta GT, Gupta SK et al. Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. *Gut* 2015;**65**:524–531.
6. Eluri S, Dellon ES. Proton pump inhibitor-responsive oesophageal eosinophilia and eosinophilic oesophagitis: more similarities than differences. *Curr Opin Gastroenterol* 2015;**31**:309–315.
7. Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia, a distinct clinicopathologic syndrome. *Dig Dis Sci* 1993;**38**:109–116.
8. Straumann A, Spichtin HP, Bernoulli R, Loosli J, Vögtlin J. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings. *Schweiz Med Wochenschr* 1994;**124**:1419–1429.
9. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995;**109**:1503–1512.
10. Straumann A, Aceves SS, Blanchard C, Collins MH, Furuta GT, Hirano I et al. Pediatric and adult eosinophilic esophagitis: similarities and differences. *Allergy* 2012;**67**:477–490.
11. Assa'ad AH, Putnam PE, Collins MH, Akers RM, Jameson SC, Kirby CL et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol* 2007;**119**:731–738.
12. Sugnanam KK, Collins JT, Smith PK, Connor F, Lewindon P, Cleghorn G et al. Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. *Allergy* 2007;**62**:1257–1260.
13. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol* 2002;**109**:363–368.
14. Simon D, Straumann A, Dahinden C, Simon HU. Frequent sensitization to Candida albicans and profilins in adult eosinophilic esophagitis. *Allergy* 2013;**68**:945–948.
15. Vicario M, Blanchard C, Stringer KF, Collins MH, Mingler MK, Ahrens A et al. Local B cells and IgE production in the oesophageal mucosa in eosinophilic oesophagitis. *Gut* 2010;**59**:12–20.
16. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol* 2012;**130**:461–467.
17. Henderson CJ, Abonia JP, King EC, Putnam PE, Collins MH, Franciosi JP et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2012;**129**:1570–1578.
18. Simon D, Straumann A, Wenk A, Spichtin H, Simon HU, Braathen LR. Eosinophilic esophagitis in adults–no clinical relevance of wheat and rye sensitizations. *Allergy* 2006;**61**:1480–1483.
19. Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol* 2005;**95**:336–343.
20. Loizou D, Enav B, Komlodi-Pasztor E, Hider P, Kim-Chang J, Noonan L et al. A pilot study of omalizumab in eosinophilic esophagitis. *PLoS One* 2015;**10**:e0113483.
21. Clayton F, Fang JC, Gleich GJ, Lucendo AJ, Olalla JM, Vinson LA et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. *Gastroenterology* 2014;**147**:602–609.
22. Straumann A, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001;**108**:954–961.
23. Blanchard C, Wang N, Stringer KF, Mishra A, Fulkerson PC, Abonia JP et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006;**116**:536–547.
24. Blanchard C, Stucke EM, Rodriguez-Jimenez B, Burwinkel K, Collins MH, Ahrens A et al. A striking local esophageal cytokine expression profile in eosinophilic esophagitis. *J Allergy Clin Immunol* 2011;**127**:208–217.
25. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001;**107**:83–90.
26. Mishra A, Rothenberg ME. Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism. *Gastroenterology* 2003;**125**:1419–1427.
27. Kohan M, Puxeddu I, Reich R, Levi-Schaffer F, Berkman N. Eotaxin-2/CCL24 and eotaxin-3/CCL26 exert differential profibrogenic effects on human lung fibroblasts. *Ann Allergy Asthma Immunol* 2010;**104**:66–72.
28. Zuo L, Fulkerson PC, Finkelman FD, Mingler M, Fischetti CA, Blanchard C et al. IL-13 induces esophageal remodeling and gene expression by an eosinophil-independent, IL-13R alpha 2-inhibited pathway. *J Immunol* 2010;**185**:660–669.
29. Blanchard C, Mingler MK, Vicario M, Abonia JP, Wu YY, Lu TX et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol* 2007;**120**:1292–1300.
30. Straumann A, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut* 2010;**59**:21–30.
31. Rothenberg ME, Wen T, Greenberg A, Alpan O, Enav B, Hirano I et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. *J Allergy Clin Immunol* 2015;**135**:500–507.
32. Martin SF. Allergic contact dermatitis: xenoinflammation of the skin. *Curr Opin Immunol* 2012;**24**:720–729.
33. Martin SF. New concepts in cutaneous allergy. *Contact Dermatitis* 2015;**72**:2–10.
34. Kehren J, Desvignes C, Krasteva M, Ducluzeau MT, Assossou O, Horand F et al. Cytotoxicity is mandatory for CD8(+) T cell-mediated contact hypersensitivity. *J Exp Med* 1999;**189**:779–786.
35. Pennino D, Eyerich K, Scarponi C, Carbone T, Eyerich S, Nasorri F et al. IL-17 amplifies human contact hypersensitivity by licensing hapten nonspecific Th1 cells to kill autologous keratinocytes. *J Immunol* 2010;**184**:4880–4888.
36. Simon D, Radonjic-Hösli S, Straumann A, Yousefi S, Simon HU. Active eosinophilic esophagitis is characterized by epithelial

barrier defects and eosinophil extracellular trap formation. *Allergy* 2015;**70**:443–452.
37. Martin SF, Esser PR, Schmucker S, Dietz L, Naisbitt DJ, Park BK et al. T-cell recognition of chemicals, protein allergens and drugs: towards the development of *in vitro* assays. *Cell Mol Life Sci* 2010;**67**:4171–4184.
38. Pichler WJ, Naisbitt DJ, Park BK. Immune pathomechanism of drug hypersensitivity reactions. *J Allergy Clin Immunol* 2011;**127**:74–81.
39. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA et al. International Consensus on drug allergy. *Allergy* 2014;**69**:420–437.
40. Yawalkar N, Egli F, Hari Y, Nievergelt H, Braathen LR, Pichler WJ. Infiltration of cytotoxic T cells in drug-induced cutaneous eruptions. *Clin Exp Allergy* 2000;**30**:847–855.
41. Schmid S, Kuechler PC, Britschgi M, Steiner UC, Yawalkar N, Limat A et al. Acute generalized exanthematous pustulosis: role of cytotoxic T cells in pustule formation. *Am J Pathol* 2002;**161**:2079–2086.
42. Picard D, Janela B, Descamps V, D'Incan M, Courville P, Jacquot S et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. *Sci Transl Med* 2010;**2**:46–62.
43. Akdis CA, Akdis M, Simon D, Dibbert B, Weber M, Gratzl S et al. T cells and T cell-derived cytokines as pathogenic factors in the nonallergic form of atopic dermatitis. *J Invest Dermatol* 1999;**113**:628–634.
44. Breuer K, Heratizadeh A, Wulf A, Baumann U, Constien A, Tetau D et al. Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy* 2004;**34**:817–824.
45. Reekers R, Beyer K, Niggemann B, Wahn U, Freihorst J, Kapp A et al. The role of circulating food antigen-specific lymphocytes in food allergic children with atopic dermatitis. *Br J Dermatol* 1996;**135**:935–941.
46. Reekers R, Busche M, Wittmann M, Kapp A, Werfel T. Birch pollen-related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens. *J Allergy Clin Immunol* 1999;**104**:466–472.
47. Darsow U, Laifaoui J, Kerschenlohr K, Wollenberg A, Przybilla B, Wüthrich B et al. The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study. *Allergy* 2004;**59**:1318–1325.
48. Yamazaki K, Murray JA, Arora AS, Alexander JA, Smyrk TC, Butterfield JH et al. Allergen-specific *in vitro* cytokine production in adult patients with eosinophilic esophagitis. *Dig Dis Sci* 2006;**51**:1934–1941.
49. Brough HA, Cousins DJ, Munteanu A, Wong YF, Sudra A, Makinson K et al. IL-9 is a key component of memory Th cell peanut-specific responses from children with peanut allergy. *J Allergy Clin Immunol* 2014;**134**:1329–1338.
50. Simon D, Marti H, Heer P, Simon HU, Braathen LR, Straumann A. Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases. *J Allergy Clin Immunol* 2005;**115**:1090–1092.
51. Noti M, Kim BS, Siracusa MC, Rak GD, Kubo M, Moghaddam AE et al. Exposure to food allergens through inflamed skin promotes intestinal food allergy through the thymic stromal lymphopoietin-basophil axis. *J Allergy Clin Immunol* 2014;**133**:1390–1399.
52. He R, Kim HY, Yoon J, Oyoshi MK, MacGinnitie A, Goya S et al. Exaggerated IL-17 response to epicutaneous sensitization mediates airway inflammation in the absence of IL-4 and IL-13. *J Allergy Clin Immunol* 2009;**124**:761–770.
53. Marenholz I, Nickel R, Rüschendorf F, Schulz F, Esparza-Gordillo J, Kerscher T et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J Allergy Clin Immunol* 2006;**118**:866–871.
54. Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao Y, Liao H et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol* 2011;**127**:661–667.
55. Blanchard C, Stucke EM, Burwinkel K, Caldwell JM, Collins MH, Ahrens A et al. Coordinate interaction between IL-13 and epithelial differentiation cluster genes in eosinophilic esophagitis. *J Immunol* 2010;**184**:4033–4041.
56. Kiran KC, Rothenberg ME, Sherrill JD. *In vitro* model for studying esophageal epithelial differentiation and allergic inflammatory responses identifies keratin involvement in eosinophilic esophagitis. *PLoS One* 2015;**10**:e0127755.
57. Sherrill JD, Kc K, Wu D, Djukic Z, Caldwell JM, Stucke EM et al. Desmoglein-1 regulates esophageal epithelial barrier function and immune responses in eosinophilic esophagitis. *Mucosal Immunol* 2014;**7**:718–729.
58. Capocelli KE, Fernando SD, Menard-Katcher C, Furuta GT, Masterson JC, Wartchow EP. Ultrastructural features of eosinophilic oesophagitis: impact of treatment on desmosomes. *J Clin Pathol* 2015;**68**:51–56.
59. Katzka DA, Tadi R, Smyrk TC, Katarya E, Sharma A, Geno DM et al. Effects of topical steroids on tight junction proteins and spongiosis in esophageal epithelia of patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2014;**12**:1824–1829.
60. Samuelov L, Sarig O, Harmon RM, Rapaport D, Ishida-Yamamoto A, Isakov O et al. Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting. *Nat Genet* 2013;**45**:1244–1248.
61. Hovnanian A. Netherton syndrome: skin inflammation and allergy by loss of protease inhibition. *Cell Tissue Res* 2013;**351**:289–300.
62. Roan F, Bell BD, Stoklasek TA, Kitajima M, Han H, Ziegler SF. The multiple facets of thymic stromal lymphopoietin (TSLP) during allergic inflammation and beyond. *J Leukoc Biol* 2012;**91**:877–886.
63. Morshed M, Yousefi S, Stöckle C, Simon HU, Simon D. Thymic stromal lymphopoietin stimulates the formation of eosinophil extracellular traps. *Allergy* 2012;**67**:1127–1137.
64. Rothenberg ME, Spergel JM, Sherrill JD, Annaiah K, Martin LJ, Cianferoni A et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat Genet* 2010;**42**:289–291.
65. Sherrill JD, Gao PS, Stucke EM, Blanchard C, Collins MH, Putnam PE et al. Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. *J Allergy Clin Immunol* 2010;**126**:160–165.
66. Kottyan LC, Davis BP, Sherrill JD, Liu K, Rochman M, Kaufman K et al. Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease. *Nat Genet* 2014;**46**:895–900.
67. Sleiman PM, Wang ML, Cianferoni A, Aceves S, Gonsalves N, Nadeau K et al. GWAS identifies four novel eosinophilic esophagitis loci. *Nat Commun* 2014;**5**:5593.
68. Harris JK, Fang R, Wagner BD, Choe HN, Kelly CJ, Schroeder S et al. Esophageal microbiome in eosinophilic esophagitis. *PLoS One* 2015;**10**:e0128346.
69. Benitez AJ, Hoffmann C, Muir AB, Dods KK, Spergel JM, Bushman FD et al. Inflammation-associated microbiota in pediatric eosinophilic esophagitis. *Microbiome* 2015;**3**:23.
70. Erwin EA, James HR, Gutekunst HM, Russo JM, Kelleher KJ, Platts-Mills TA. Serum IgE measurement and detection of food allergy in pediatric patients with eosinophilic esophagitis. *Ann Allergy Asthma Immunol* 2010;**104**:496–502.
71. Corridoni D, Arseneau KO, Cominelli F. Inflammatory bowel disease. *Immunol Lett* 2014;**161**:231–235.

72. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007;**448**:427–434.
73. Huttenhower C, Kostic AD, Xavier RJ. Inflammatory bowel disease as a model for translating the microbiome. *Immunity* 2014;**40**:843–854.
74. Cianferoni A, Spergel JM. Food allergy: review, classification and diagnosis. *Allergol Int* 2009;**58**:457–466.
75. Nowak-Wegrzyn A, Sampson HA. Adverse reactions to foods. *Med Clin North Am* 2006;**90**:97–127.
76. Simons FE. Anaphylaxis. *J Allergy Clin Immunol* 2010;**125**:161–181.
77. Nowak-Wegrzyn A, Muraro A. Food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol* 2009;**9**:371–377.
78. Venter C, Groetch M. Nutritional management of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol* 2014;**14**:255–262.
79. Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: insights from review of a large referral population. *J Allergy Clin Immunol Pract* 2013;**1**:343–349.
80. Berin MC. Immunopathophysiology of food protein-induced enterocolitis syndrome. *J. Allergy Clin Immunol* 2015;**135**:1108–1113.
81. Rocha R, Vitor AB, Trindade E, Lima R, Tavares M, Lopes J et al. Omalizumab in the treatment of eosinophilic esophagitis and food allergy. *Eur J Pediatr* 2011;**170**:1471–1474.
82. Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;**4**:1097–1102.
83. Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* 2012;**142**: 1451–1459.
84. Liacouras CA, Spergel JM, Ruchelli E, Verma R, Mascarenhas M, Semeao E et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005;**3**:1198–1206.
85. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, Franciosi J, Shuker M, Verma R et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr* 2009;**48**:30–36.
86. Arias A, Gonzalez-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology* 2014;**146**:1639–1648.
87. Lee D, Albenberg L, Compher C, Baldassano R, Piccoli D, Lewis JD et al. Diet in the pathogenesis and treatment of inflammatory bowel diseases. *Gastroenterology* 2015;**148**:1087–1106.
88. Kagalwalla AF, Shah A, Li BU, Sentongo TA, Ritz S, Manuel-Rubio M et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. *J Pediatr Gastroenterol Nutr* 2011;**53**:145–149.
89. Molina-Infante J, Arias A, Barrio J, Rodríguez-Sánchez J, Sanchez-Cazalilla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. *J Allergy Clin Immunol* 2014;**134**:1093–1099.
90. van Rhijn BD, Vlieg-Boerstra BJ, Versteeg SA, Akkerdaas JH, van Ree R, Terreehorst I et al. Evaluation of allergen-microarray-guided dietary intervention as treatment of eosinophilic esophagitis. *J Allergy Clin Immunol* 2015;**136**:1095–1097.
91. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2014;**113**:624–629.
92. Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. *Ann Allergy Asthma Immunol* 2011;**106**: 73–74.
93. Miehlke S, Alpan O, Schroeder S, Straumann A. Induction of eosinophilic esophagitis by sublingual pollen immunotherapy. *Case Rep Gastroenterol* 2013;**7**:363–368.
94. Maggadottir SM, Hill DA, Ruymann K, Brown-Whitehorn TF, Cianferoni A, Shuker M et al. Resolution of acute IgE-mediated allergy with development of eosinophilic esophagitis triggered by the same food. *J Allergy Clin Immunol* 2014;**133**:1487–1489.
95. Niranjan R, Mavi P, Rayapudi M, Dynda S, Mishra A. Pathogenic role of mast cells in experimental eosinophilic esophagitis. *Am J Physiol Gastrointest Liver Physiol* 2013;**304**:1087–1094.
96. Noti M, Wojno ED, Kim BS, Siracusa MC, Giacomin PR, Nair MG et al. Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. *Nat Med* 2013;**19**:1005–1013.
97. Schoepfer AM, Safroneeva E, Bussmann C, Kuchen T, Portmann S, Simon HU et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology* 2013;**145**:1230–1236.
98. Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc* 2014;**79**:577–585.
99. Straumann A. Treatment of eosinophilic esophagitis: diet, drugs, or dilation? *Gastroenterology* 2012;**142**:1409–1411.
100. Lucendo AJ, Arias A, Gonzalez-Cervera J, Yague-Compadre JL, Guagnozzi D, Angueira T et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study in the food cause of the disease. *J Allergy Clin Immunol* 2013;**131**:797–804.
101. Wen T, Stucke EM, Grotjan TM, Kemme KA, Abonia JP, Putnam PE et al. Molecular diagnosis of eosinophilic esophagitis by gene expression profiling. *Gastroenterology* 2013;**145**:1289–1299.

Biomarkers of desensitization and tolerance in food allergy

Carmen Riggioni, Spain

BIOMARKERS OF DESENSITIZATION AND TOLERANCE IN FOOD ALLERGY

Food allergy has been on the rise for the past 10 years in both developed and developing countries, becoming a growing global health concern. Food-induced anaphylaxis represents an economic liability on public health systems and measures should be taken by allergy specialists worldwide to anticipate and address this growing burden. (1)

Similarly, food allergy has profound repercussions in patients and their families. Highly restrictive diets can result in complications ranging from parental anxiety to children coping with social acceptance, resulting in a reduced quality of life. (2)

Present-day therapy in clinical practice relies solely on allergen avoidance and treatment of adverse reactions, but these strategies are not sufficient to address the current food allergy epidemic. International allergy societies, particularly EACCI, are moving rapidly forward in this area of research. (3)

Because of a growing understanding of food allergy mechanisms and pathways, new therapeutic strategies are currently under investigation. A shift towards induction of tolerance, through low-dose allergen exposure, has been a constant study subject. However, there are still important steps to take before food allergy oral immunotherapy (FA-OIT) is ready for an everyday clinical setting. (4)

There is great heterogeneity in FA-OIT protocols when it comes to induction and maintenance phases. (5) Most FA-OIT protocols report frequent adverse reactions and even severe anaphylaxis, thus the overall risk of OIT could, in some patients, out-weight the benefits. Further on, even if patients can undertake these obstacles, a complete clinical remission is not guaranteed. An effort should be made to find solid data that identifies these subjects early on. (6)

When addressing efficacy in FA-OIT there are two pathways: desensitization and sustained unresponsiveness. Desensitization addresses short-term efficacy and accounts for the change in dose threshold needed to cause an allergic reaction, resulting in the ability to safely consume a determined amount of food allergen, while on immunotherapy to this offender allergen. The concept of sustained unresponsiveness tackles long-term efficacy and is used in patients that have achieved tolerance to the allergen without being on active immunotherapy. (3,4)

A decrease in Th2 phenotype is important for successful FA-OIT. Children who achieve tolerance overturn the Th1/Th2 imbalance and launch a predominant TH1 cytokine reaction. The induction of allergen specific T regs also correlates with clinical reactivity. (7,8)

Research in effectiveness and safety of FA-OIT trials, reports that desensitization is associated with a reduction of skin prick test responses to the relevant food with a mean reduction

of 2.96mm and an increase in specific IgG4 levels average 19.9 μg/ml. Most studies do not report a decrease in allergen-specific IgE. (9)

Many studies report high rates of initial desensitization but neglect to report long term tolerance. Desensitization, ranges from 57% to 94% for egg-white oral immunotherapy (EW-OIT), and 36% to 91% for cow´s milk oral immunotherapy (CM-OIT). (4)

A EAACI meta-analysis, describes trials that measure efficacy of FA-OIT in regard to desensitization, revealing a benefit for patients undergoing OIT. However, there is incomplete data concerning sustained unresponsiveness and an insufficient number of trials assess tolerance following a period of allergen avoidance after successful desensitization. (3)

In a double-blind placebo-controlled randomized (DBPCR) EW-OIT trial, Caminiti *et al* described desensitization to egg in 94% of patients (17 completed EW-OIT) against 0% in placebo. However, after 3 months of avoidance, only 30 % of patients achieved sustained unresponsiveness, compared to 7% of placebo. (10) For CM-OIT, only one trial addressed sustained tolerance. Keet *et al* showed results for 30 subjects (20 on CM-OIT) of which 70% were desensitized but only 40 % sustained tolerance after 6 week avoidance period. (11,12) Limitations on both the studies include a small sample size and a short maintenance phase of approximately a year, which could account for the drop in sustained efficacy.

A longer follow up was done by The Consortium of Food Allergy Research EW- OIT trial, which reported 75% desensitization and 27.5% sustained unresponsiveness at 2 years. Recently updated results for 4-year follow-up reported 50% of patients achieved unresponsiveness after a 4-6 week avoidance period, thus concluding that efficacy is possibly enhanced with longer duration of therapy. (13)

Limited evidence is available for biomarkers that can recognize tolerant patients. For EW-OIT, baseline specific IgE to ovomucoid (IgE-OVM) and specific IgE to egg white (IgE-EW) were lower in tolerant patients. A higher IgG4/IgE-OVM and IgG4/IgE-EW ratios were seen in patients that achieved unresponsiveness, as well as increases in IgG4-EW and IgA-EW. (14,15)

Novel peptide biomarkers are currently under investigation. Sensitization to linear epitopes is more common in patients with persistent allergies and more severe reactions. (16) For CM-OIT, it is suggested that the development of tolerance to milk is associated with reduced IgE levels and increased IgG4 levels against linear epitopes. However, a major limitation to the clinical use of microarray is the automated analysis of the data. (17,18)

Basophil activation test (BAT) has been performed before and after CM-OIT, showing a complete suppression of cow's milk protein's induced CD63 regulation in desensitized patients, however the sample was very small and no long-term assessment was carried out. (19)

Future studies are needed to evaluate and validate these potential biomarkers and search for parameters that distinguish between temporarily desensitized patients and those who have acquired sustained unresponsiveness.

To date it remains unclear if therapy needs to be continued permanently and patients sentenced to enduring life-long maintenance. There is limited evidence with regard to post-immunotherapy outcomes and likelihood of allergic relapse following cessation of treatment. All of these interrogations need to be well defined before FA-OIT is ready for routine clinical practice. (3,4)

REFERENCES:

(1) Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn JK, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. World Allergy Organ J 2013 Dec 4;6(1):21-4551-6-21.

(2) DunnGalvin A, Dubois AE, Flokstra-de Blok BM, Hourihane JO. The effects of food allergy on quality of life. Chem Immunol Allergy 2015;101:235-252.

(3) Nurmatov U, Dhami S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy. 2017 Aug;72(8):1133-1147.

(4) Peters RL, Dang TD, Allen KJ. Specific oral tolerance induction in childhood. Pediatr Allergy Immunol 2016 Dec;27(8):784-794.

(5) Vazquez-Ortiz M, Turner PJ. Improving the safety of oral immunotherapy for food allergy. Pediatr Allergy Immunol 2016 Mar;27(2):117-125.

(6) Vazquez-Ortiz M, Alvaro M, Piquer M, Giner MT, Dominguez O, Lozano J, et al. Life-threatening anaphylaxis to egg and milk oral immunotherapy in asthmatic teenagers. Ann Allergy Asthma Immunol 2014 Oct;113(4):482-484.

(7) Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, Ishida S, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). J Allergy Clin Immunol 2014 Feb;133(2):500-510.

(8) Wood RA. Food allergen immunotherapy: Current status and prospects for the future. J Allergy Clin Immunol 2016 Apr;137(4):973-982.

(9) Nurmatov U, Devereux G, Worth A, Healy L, Sheikh A. Effectiveness and safety of orally administered immunotherapy for food allergies: a systematic review and meta-analysis. Br J Nutr 2014 Jan 14;111(1):12-22.

(10) Caminiti L, Pajno GB, Crisafulli G, Chiera F, Collura M, Panasci G, et al. Oral Immunotherapy for Egg Allergy: A Double-Blind Placebo-Controlled Study, with Postdesensitization Follow-Up. J Allergy Clin Immunol Pract 2015 Jul-Aug;3(4):532-539.

(11) Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol 2012 Feb;129(2):448-55, 455.e1-5.

(12) Keet CA, Seopaul S, Knorr S, Narisety S, Skripak J, Wood RA. Long-term follow-up of oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol 2013 Sep;132(3):737-739.e6.

(13) Jones SM, Burks AW, Keet C, Vickery BP, Scurlock AM, Wood RA, et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. J Allergy Clin Immunol 2016 Apr;137(4):1117-27.e1-10.

(14) Wright BL, Kulis M, Orgel KA, Burks AW, Dawson P, Henning AK, et al. Component-resolved analysis of IgA, IgE, and IgG4 during egg OIT identifies markers associated with sustained unresponsiveness. Allergy 2016 Nov;71(11):1552-1560.

(15) Vazquez-Ortiz M, Alvaro M, Piquer M, Dominguez O, Machinena A, Martin-Mateos MA, et al. Baseline specific IgE levels are useful to predict safety of oral immunotherapy in egg-allergic children. Clin Exp Allergy 2014 Jan;44(1):130-141.

(16) Martinez-Botas J, de la Hoz B. IgE and IgG4 Epitope Mapping of Food Allergens with a Peptide Microarray Immunoassay. Methods Mol Biol 2016;1352:235-249.

(17) Savilahti EM, Kuitunen M, Valori M, Rantanen V, Bardina L, Gimenez G, et al. Use of IgE and IgG4 epitope binding to predict the outcome of oral immunotherapy in cow's milk allergy. Pediatr Allergy Immunol 2014 May;25(3):227-235.

(18) Martinez-Botas J, Rodriguez-Alvarez M, Cerecedo I, Vlaicu C, Dieguez MC, Gomez-Coronado D, et al. Identification of novel peptide biomarkers to predict safety and efficacy of cow's milk oral immunotherapy by peptide microarray. Clin Exp Allergy 2015 Jun;45(6):1071-1084.

(19) Nucera E, Pecora V, Buonomo A, Rizzi A, Aruanno A, Pascolini L, et al. Utility of Basophil Activation Test for monitoring the acquisition of clinical tolerance after oral desensitization to cow's milk: Pilot study. United European Gastroenterol J 2015 Jun;3(3):272-276.

Egg immunotherapy workshop summary

Carmen Riggioni, Spain

Alberto Alvarez, Spain

EGG IMMUNOTHERAPY WORKSHOP SUMMARY

Speakers: Dr. A Alvarez and Dr. C Riggioni

Definitions:

- Allergen immunotherapy

  Repeated allergen exposure at regular intervals to modulate immune response to reduce symptoms and the need for medication for clinical allergies.

- Desensitization

  The ability to safely consume foods containing the culprit allergen while on allergen immunotherapy. This clinical response is dependent on ongoing allergen exposure. If the administration of the allergen is discontinued; the previous level of clinical reactivity may return.

- Tolerance or sustained unresponsiveness

  Post-discontinuation effectiveness. The ability to safely consume a normal serving of food containing the trigger allergen despite a period of absence of exposure.

EAACI Recommendations on efficacy of OIT in children with hen's egg allergy

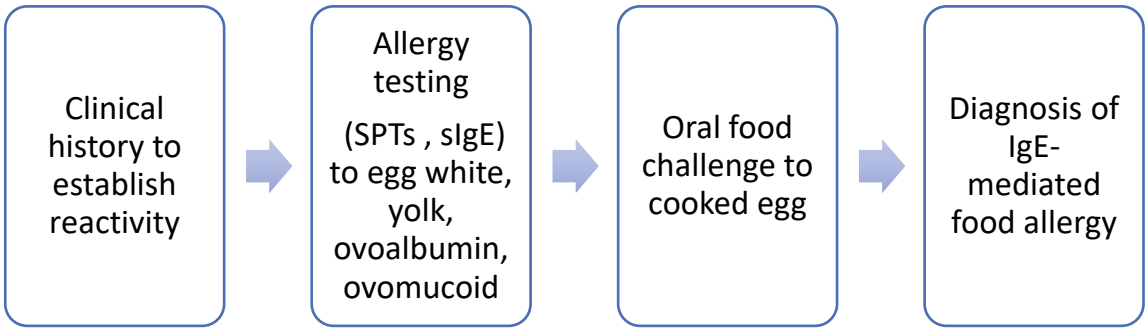
(IB Moderate recommendation) OIT can be recommended as a treatment option to increase the threshold of reaction while on OIT in children with persistent hen´s egg allergy, from around 4 - 5 years of age. Desensitization is achieved in approximately 75% of patients. However, studies are all small with some heterogeneity in results and risk of adverse reactions needs to be considered.

(IB Strong recommendation) A recommendation cannot currently be made for OIT as a treatment option to achieve post-discontinuation effectiveness in children with persistent hen´s egg allergy. After 4 years of OIT 50% of subjects achieved sustained unresponsiveness 4-6 weeks after stopping OIT.

STEPS BEFORE INITIATING FA-AIT

STEP 1

CONFIRM PERSISTENT, SYSTEMIC IgE- MEDIATED FA.



STEP 2

NATURAL HISTORY OF ALLERGY

Consider the likelihood of spontaneous resolution of the egg allergy. Remember benefit over risk every time.

STEP 3

APPROPIATE SETTING

Make sure your center has the expertise and facilities to safely deliver this therapy. Use checklists for equipment and personnel.

Personnel:

- ✓ Medical doctor and nurse trained and experienced in the diagnosis of food allergy and allergic reactions including anaphylaxis.
- ✓ At least 12 hours of observation in case of adverse reactions.
- ✓ Team trained in resuscitation on call (within 5 minutes), anesthesiology or intensive care.

Equipment:

- ✓ Stethoscope
- ✓ Sphygmomanometer
- ✓ Oxygen and Pulse oximeter
- ✓ Spirometer, peak flow meter
- ✓ Laryngoscope(s), intubation tube(s), ventilation bag(s)
- ✓ Heart defibrillator and crash trolley

Medication

- ✓ Adrenaline (epinephrine)
- ✓ Antihistamine (oral and parenteral)
- ✓ Inhaled beta2-agonist
- ✓ Corticosteroids (oral, parenteral)
- ✓ IV lines and IV fluids

STEP 4

EDUCATION:

Interview and explain to patients and their families the importance of motivation and adherence. The family needs to understand the commitment required to undertake a FA-AIT protocol.

The child and family need to be capable of administering emergency treatment (especially intramuscular adrenaline) in case of adverse effects.

Give oral and written instructions to the family and have an easy contact number for adverse reactions and questions.

Always Provide:

- ✓ Individualized schedule, clearly written in simple non-medical language and a copy for his/her caregiver(s), and their family doctor.
- ✓ Clear identification of food allergen to be administered during FA-AIT.
- ✓ Clear explanation that FA-AIT escalation dose(s) has to be administered in clinical specialized setting under strict medical supervision.
- ✓ Emergency kit with copy of emergency action plan and adrenaline auto-injector.

STEP 5

RULE OUT CONTRAINDICATIONS.

FA-AIT should only be used with caution in an individual patient when benefits outweigh potential risks.

Absolute	Relative
Poor adherence	Severe systemic illness or medical conditions
Uncontrolled or severe asthma	Autoimmune disorders in remission
Active malignant neoplasia(s)	Uncontrolled active atopic dermatitis
Active systemic, autoimmune disorders	Chronic urticaria

Active EoE or GI eosinophilic disorders	ACE inhibitors, Beta-blockers
Initiation during pregnancy	Mastocytosis

Routes of administration

There has been no consistent formulation of food in FA-AIT studies conducted to date with wide heterogeneity between protocols.

The most frequent of FA-AIT is the oral route where the allergen is either immediately swallowed (oral immunotherapy, OIT) or held under the tongue for a period of time (sublingual immunotherapy, SLIT). Studies using the subcutaneous route (SCIT) and epicutaneous immunotherapy (EPIT) with application of patches containing food allergen onto the skin are ongoing.

In the case of egg OIT some protocols have used dilutions of unprocessed egg white, pasteurized egg white, extensively heated egg (hard boiled or very well cooked) and baked egg.

Some studies have been carried out with powdered or lyophilized products.

Recommendations

• Take dose daily

• Do not take dose on an empty stomach

• Do not go to the bed in the hour following a dose

• Do not do exercise the 2-3 hours following a dose

• Reduce or withhold the dose during infections, asthma exacerbations, gastrointestinal diseases or menses.

Recommended reading:

1. Antonella Muraro, Graham Roberts (ed.) Allergen Immunotherapy Guidelines Part 1 and 2, Zurich, European Academy of allergy and Clinical Immunology.
2. Nurmatov U, Dhami S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A et al. Allergen immunotherapy for IgE mediated food allergy: a systematic review and metaanalysis. Allergy 2017;72:1133-1147.
3. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med 2012;367:233-243.
4. Caminiti L, Pajno GB, Crisafulli G, Chiera F, Collura M, Panasci G et al. Oral immunotherapy for egg allergy: a double blind placebo controlled study, with postdesensitization followup. J Allergy Clin Immunol Practice 2015;70:99.
5. Jones SM, Burks AW, Keet C, Vickery BP, Scurlock AM, Wood RA et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. J Allergy Clin Immunol 2016;137:1117-1127.
6. Vazquez Ortiz M, Alvaro-Lozano M, Piquer Gibert M,Dominguez Sánchez O, Machinena A, Martín- Mateos M et al. Baseline specific IgE levels are useful to predict safety of oral immunotherapy in egg allergic children. Clin Exp Allergy 2014;44:130-141

Persistent regulatory T cell response 2 years after 3 years of grass tablet SLIT: links to reduced eosinophil counts, sIgE levels and clinical benefit

Domingo Barber Hernández, Spain

Persistent regulatory T cell response 2 years after 3 years of grass tablet SLIT: links to reduced eosinophil counts, sIgE levels and clinical benefit

Varona R[1], Ramos T[2], Escribese MM[3,4,5], Jimeno L[6], Galán A[6], Würtzen PA[7], Vega F[2], Marín A[6], Martín S[6], Carrera AC[1], Blanco C[2,5], Barber D[3,5]

Author information

1. Department of Immunology and Oncology, Centro Nacional de Biotecnología (CNB-CSIC), Madrid, Spain.

2. Servicio de Alergia, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IP), Madrid, Spain.

3. Institute for Applied Molecular Medicine. School of Medicine, Universidad CEU San Pablo, Madrid, Spain.

4. Department of Basic Medical Sciences. School of Medicine, Universidad CEU San Pablo, Madrid, Spain.

5. RETIC ARADYAL RD16, , 0006/0015, Instituto de Salud Carlos III.

6. Departamento Médico e I+D, ALK-Abelló, Madrid, Spain.

7. Translational Research. ALK-Abelló, Hørsholm, Denmark.

Background

In the first 2 years of grass tablet sublingual immunotherapy treatment, we have previously demonstrated a progressive development of a regulatory T-cell response, which was preceded by an early decrease in the frequency of both IL-4+ cells and sIgE levels. A progressive increase of sIgG4 levels and FAB blockage were also found.

Methods

By monitoring immunological kinetics during 3 years of active treatment + 2 follow-up years, we aimed to identify key immunological parameters that could explain sustained clinical benefit of grass tablet sublingual immunotherapy.

Results

Thirty patients completed the 5-yr clinical trial protocol. Although individual responses were heterogeneous, reduction in both sIgE and circulating IL-4+ cells compared the initial 1- to 4-month peak, was maintained throughout the 3-yr treatment period and for two years after discontinuation. Meanwhile, after a 2-yr increase in sIgG4, the levels were stabilized during the 3rd year and decreased post-therapy. FAB inhibition remained significantly inhibited throughout the study

compared to pre-immunotherapy in 83% of patients. A sustained regulatory T cell response, after IT cessation, occurs in two thirds of the patients. There was a statistical association between this regulatory response, the maintenance of lower eosinophil counts during grass pollen seasons, and sIgE titers lower than before immunotherapy treatment, and the latter were significantly associated with clinical response.

Conslusion

Our results suggest that the immunological mechanisms underlying the sustained response after two years of cessation of immunotherapy (3-yr treatment period), is linked to the acquisition and maintenance of a regulatory T cell response.

Keywords

sIgE ; Allergic rhinitis; IL-4; Regulatory T cells; Sublingual immunotherapy; sIgG4

Profilin-mediated food-induced allergic reactions are associated with oral epithelial remodelling;

Domingo Barber Hernández, Spain

Profilin-mediated food-induced allergic reactions are associated with oral epithelial remodeling

Rosace D[1], Gomez-Casado C[1], Fernandez P[1], Gordo MP[2], Dominguez MDC[3], Vega A[3], Belver MT[4], Ramos T[4], Vega F[4], Marco G[5], de Pedro M[5], Sanchez L[5], Arnas MLM[6], Santaolalla M[6], Saez MÁ[7], Benedé S[8], Fernandez-Rivas M[5], Blanco C[4], Alvarado MI[3], Escribese MM[9], Barber D[1]

Author information

1. Instituto de Medicina Molecular Aplicada, Grupo Hospital de Madrid, Universidad San Pablo-CEU, Madrid, Spain.

2. Departamento de Ciencias Médicas Básicas, Facultad de Medicina, Universidad San Pablo-CEU, Madrid, Spain.

3. Hospital Virgen del Puerto, Plasencia, Cáceres, Spain.

4. Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IP), Madrid, Spain.

5. Hospital Universitario Clínico San Carlos, Madrid, Spain.

6. Hospital HM Sanchinarro, Madrid, Spain.

7. Hospital Central de la Defensa "Gómez Ulla", Madrid, Spain.

8. Facultad de Ciencias Químicas, Universidad Complutense de Madrid, Madrid, Spain.

9. Instituto de Medicina Molecular Aplicada, Grupo Hospital de Madrid, Universidad San Pablo-CEU, Madrid, Spain; Departamento de Ciencias Médicas Básicas, Facultad de Medicina, Universidad San Pablo-CEU, Madrid, Spain. Electronic address: mariamarta.escribesealonso@ceu.es.

Background

In areas of high exposure to grass pollen, allergic patients are frequently sensitized to profilin, and some experience severe profilin-mediated food-induced reactions. This specific population of patients is ideal to study the relationship between respiratory and food allergies.

Objective

We sought to determine the role of oral mucosal epithelial barrier integrity in profilin-mediated allergic reactions.

Methods

Thirty-eight patients with profilin allergy stratified into mild or severe according to their clinical history and response to a profilin challenge test and 6 nonallergic subjects were recruited. Oral mucosal biopsies were used for measurement of CD11c, CD3, CD4, tryptase, claudin-1, occludin, E-cadherin, and vascular endothelial growth factor A levels; Masson trichrome staining; and POSTN, IL33, TPSAB, TPSB, and CMA gene expression analysis by using quantitative RT-PCR. Blood samples were used for basophil activation tests.

Results

Distinct features of the group with severe allergy included the following: (1) impaired epithelial integrity with reduced expression of claudin-1, occludin, and E-cadherin and decreased numbers of epithelial cells, which is indicative of acanthosis, higher collagen deposition, and angiogenesis; (2) inflammatory immune response in the mucosa, with an increased number of CD11c+ and CD4+ infiltrates and increased expression of the cytokine genes POSTN and IL33; and (3) a 10-fold increased sensitivity of basophils to profilin.

Conclusion

Patients with profilin allergy present with significant damage to the oral mucosal epithelial barrier, which might allow profilin penetration into the oral mucosa and induction of local inflammation. Additionally, severely allergic patients presented with increased sensitivity of effector cells.

Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study

Giovanni Pajno, Italy

Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study

Giovanni Battista Pajno, MD*; Lucia Caminiti, MD*; Paolo Ruggeri, MD†; Raffaele De Luca, MD‡; Daniela Vita, MD*; Mario La Rosa, MD§; and Giovanni Passalacqua, MD¶

Background: Cow's milk allergy (CMA) in children is a important problem in medical practice. Oral desensitization has been proposed as a therapeutic approach, but current protocols are time-consuming and impractical.

Objectives: To establish a patient-friendly desensitization regimen with weekly up-dosing and to evaluate it in a randomized controlled trial.

Methods: Thirty children with IgE-mediated CMA confirmed by double-blind placebo-controlled food challenge were equally randomized to desensitization with CM or soy milk as control. The weekly up-dosing lasted 18 weeks. The occurrence and severity of reactions after each dose was evaluated, and the desensitization was stopped if severe reactions occurred. Specific IgE and IgG4 levels to CM were measured at baseline, after 8 weeks, and at the end of the study. The double-blind food challenge was repeated once the desensitization was completed or after premature discontinuation.

Results: Two active and 1 control patient dropped out. Full tolerance to CM (200 mL) was achieved in 10 active patients and partial tolerance in 1. Two active patients discontinued the desensitization after experiencing severe reactions, whereas no reactions occurred in controls, whose sensitivity to CM remained unchanged. A significant increase in specific IgG4 levels was found only in the active group.

Conclusions: This weekly up-dosing desensitization protocol for CMA performed under medical supervision was effective and reasonably safe and induced consistent immunologic changes.

Ann Allergy Asthma Immunol. 2010;105:376–381.

INTRODUCTION

Among food allergies, cow's milk allergy (CMA) is the most relevant in the pediatric age group owing to its prevalence, the practical difficulties in management, the emotional burden for children and parents, and the nutritional implications. Currently, the management of CMA is primarily based on the complete avoidance of CM. This approach is associated with impaired quality of life for allergic children and their families.[1,2] In addition, it is difficult to achieve complete avoidance because milk proteins can be present in small amounts or even as hidden allergens in a variety of processed foods. This may lead to unexpected exposure and possibly severe reactions. The present interventions for CMA include avoidance maneuvers and education regarding the proper indications for and use of autoinjectable epinephrine. Among the CM substitutes most frequently used are soy formulas and extensively hydrolyzed formulas of casein and whey. These substitutes have an acceptable nutritional value, but hydrolyzed formulas often have an unpleasant taste and are expensive and soy formulas have themselves the potential to evoke allergic reactions.

It has been shown that infants with CMA but without detectable specific IgE levels to CM have a higher spontaneous recovery rate compared with infants with high levels of specific IgE toward milk proteins (IgE-mediated CMA).[3-5] Oral desensitization or immunotherapy, also referred to as "tolerance induction," has been suggested as a suitable approach to reduce clinical symptoms and modify the immune response to allergens, and this was also confirmed in the case of CMA.[6-11] Oral immunotherapy is usually performed starting with very low amounts of milk, which are then slowly increased until an amount comparable with the usual daily intake is reached. Afterward, milk is given daily to maintain the tolerant state. The protocols that have been published usually have a very long duration[6,12] or require hospitalization of the child for several days.[6,7] As such, they are considered, to some extent, to be impractical. Based on these considerations, we attempted to set up a more patient-friendly and easy-to-perform oral desensitization using a weekly up-dosing regimen. The feasibility of this approach was demonstrated in a previous open exploratory study.[13] The present trial was undertaken to confirm in a randomized and con-

Affiliations: * Allergy Unit, Department of Pediatrics, University of Messina, Messina, Italy; † Department of Respiratory Diseases, University of Messina, Messina, Italy; ‡ Department of Emergency Medicine, University of Messina, Messina, Italy; § Allergy and Respiratory Unit, Department of Pediatrics, University of Catania, Catania, Italy; ¶ Allergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa, Genoa, Italy.

Disclosures: Authors have nothing to disclose.

Received for publication January 14, 2010; Received in revised form March 11, 2010; Accepted for publication March 23, 2010.

doi:10.1016/j.anai.2010.03.015

trolled manner the clinical efficacy and safety of this approach.

METHODS

Overall Design

This study was designed as a randomized, single-blind, soy milk–controlled trial with 2 parallel groups. Children 4 years or older with demonstrated IgE-mediated CMA were enrolled and were randomized to receive either active oral immunotherapy or matched soy formula**.** The efficacy of the desensitization was evaluated during a 4-month period by identifying the maximum tolerated dose of milk or, ideally, 200 mL. The ethics committee of the Department of Pediatrics, University of Messina, approved the study, and all the parents of the children signed an informed consent form.

Patients and Diagnosis

Children of both sexes aged 4 to 10 years with demonstrated IgE-mediated CMA were enrolled at the allergy units of the departments of pediatrics of Messina and Catania university hospitals between January 1, 2006, and and December 31, 2008. The diagnosis of CMA was based on (1) clinical history, (2) demonstration of the presence of CM specific IgE by means of skin testing and CAP-RAST assay, and (3) a positive double-blind placebo-controlled food challenge (DBPCFC) result. None of the patients had a positive clinical history or suspected adverse reactions to soy formula or positive skin test results or serum specific IgE levels to soy. This was required to ensure the safety of DBPCFC and the desensitization protocol with soy formula as controls. Sensitization to other foods was an exclusion criteria as well.

Skin prick tests were performed on the volar surface of the forearm with commercial extracts of whole milk, α-lactalbumin, β-lactoglobulin, and casein (all f rom Lofarma Spa, Milan, Italy). A prick-prick test with undiluted fresh CM and soy formula was also performed. A wheal of 3 mm or greater was considered positive. The DBPCFC was conducted before randomization and at the end of treatment, before revealing the blinding. It was performed at the clinics under medical supervision and with resuscitation facilities immediately available. Fresh CM or soy formula (Humana Sinelac, Milan) was administered at increasing doses of 0.1, 0.3, 1, 3, 10, 30, and 100 mL in a double-blind manner, with 30 minutes between doses. The challenge procedure was stopped when the highest dose was reached or if any of the following occurred: urticaria, angioedema, wheezing, rhinitis, vomiting, diarrhea, abdominal pain, exacerbation of atopic dermatitis, wheezing, rhinitis, or anaphylactic shock. After completing the DBPCFC procedure, children were observed for at least 6 hours and then were discharged. Rescue medications, to be given according to medical judgment, included diphenhydramine, prednisolone, adrenaline, and inhaled salbutamol.

Oral Immunotherapy Protocol

Oral immunotherapy involved the administration of increasing amounts of CM (or soy milk) at weekly intervals starting with 1 drop of whole milk diluted 1:25. The dose was doubled every week at the clinic until week 18 to achieve an intake of 200 mL in approximately 4.5 months. Soy milk was the control treatment. The doses were prepared blinded to the investigators by a nurse according to a computer-generated randomization list so that the physicians remained blinded to the treatment. The desensitization protocol, entirely performed at the clinics in an ambulatory regimen, is summarized in Table 1.

After receiving the dose, the children were observed and were considered to have a positive reaction if 1 or more of the following symptoms appeared: urticaria, exacerbation of eczema ($\geq$10-point increase in SCORing Atopic Dermatitis score), angioedema or generalized urticaria, vomiting, diarrhea, rhinitis, severe conjunctivitis, or anaphylactic reactions. If symptoms were judged as mild (abdominal pain, erythema, throat itching, or gritty eyes), no action was taken and the protocol was continued. When moderate or severe symptoms appeared, an appropriate medical treatment was given.

CM had to be avoided in the desensitization protocol. Oral antihistamine use was not permitted until the up-dosing period was completed. If an illness occurred (eg, the common cold or fever) during the desensitization, appropriate therapy was given and the weekly increase in the dose was postponed.

Immunologic Assays

Blood samples were collected before randomization, when the dose of 8 mL was reached (week 13), and at the end of the study. Specific IgE and specific IgG4 to CM, α-lactalbumin, β-lactoglobulin, and casein were assayed using the ImmunoCAP System (Phadia Diagnostics, Uppsala, Sweden).

IgG4 to CM could not be directly measured because of interfering IgG antibodies specific for bovine albumin in

Table 1. Oral Immunotherapy Protocol

Day/week	Dose No.	Volume
1/1	1	1 drop[a]
7/2	2	2 drops[a]
14/3	3	4 drops[a]
21/4	4	8 drops[a]
28/5	5	16 drops[a]
35/6	6	32 drops[a]
42/7	7	64 drops[a]
49/8	8	5 drops[b]
56/9	9	10 drops[b]
63/10	10	20 drops[b]
70/11	11	2 mL[b]
77/12	12	4 mL[b]
84/13	13	8 mL[b]
91/14	14	16 mL[b]
98/15	15	32 mL[b]
105/16	16	64 mL[b]
112/17	17	128 mL[b]
119/18	18	200 mL[b]

[a] Cow's milk diluted 1:25.
[b] Undiluted CM.

most sera. Therefore, the sum of α-lactalbumin, β-lactoglobulin, and casein specific IgG4 antibody levels was used as a surrogate measure of IgG4 to CM. The lower limit of assay detection was 0.35 kU/L for specific IgE and 0.3 μg/mL for specific IgG4.

Statistical Analysis

No formal calculation of the sample size could be made because no quantitative data about the clinical outcome could be hypothesized. The number of patients was chosen according to similar articles available in the literature. The Fisher exact test was used to compare the clinical characteristics of the 2 groups at baseline, except for age, which was compared using the *t* test. Immunologic variables were analyzed using the Wilcoxon and Mann-Whitney signed rank tests for intragroup and intergroup comparisons, respectively. All the tests were 2-tailed, and $P < .05$ was considered significant.

RESULTS

Clinical Results

The disposition of all patients considered for the study is summarized in Figure 1. Thirty children who fulfilled the inclusion and exclusion criteria were enrolled in the study and were equally randomized to active desensitization or control intervention. The clinical characteristics of the participants at randomization are given in Table 2. There were 2 dropouts in the active group and 1 in the control group (their parents withdrew their consent early in the study for personal reasons and not because of the desensitization procedure).

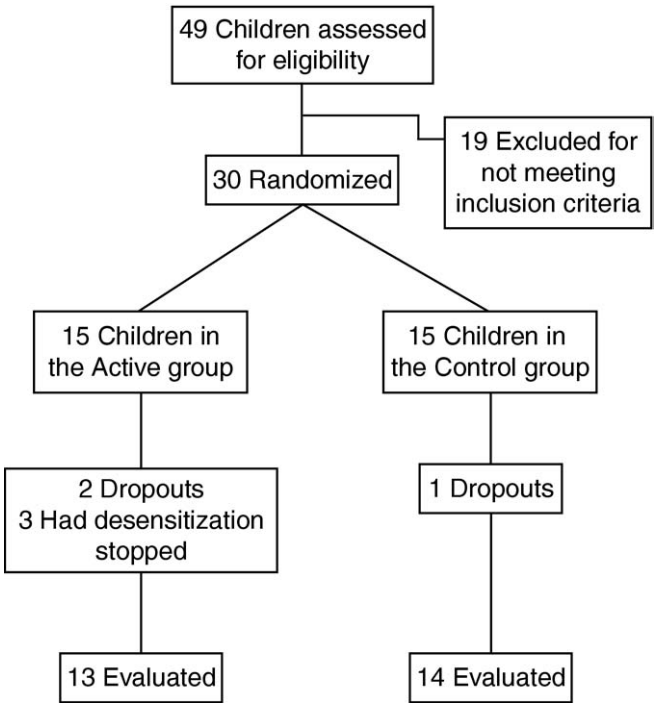


Figure 1. Study design and patient disposition.

Table 2. Demographic and Clinical Characteristics of the 30 Enrolled Children at Baseline[a]

	Active group (CM) (n = 15)	Control group (soy milk) (n = 15)
Sex, M/F, No.	8/7	9/6
Age, median (range), y	9 (4–12)	10 (4–13)
Duration of CM allergy, mean (SD), y	6.9 (3.2)	7.4 (3.7)
Atopic dermatitis, No.	3	3
Urticaria/angioedema, No.	4	3
Asthma, No.	1	1
Multiple symptoms, No.	5	7
Anaphylaxis, No.	2	1
Baseline CM specific IgE, median (range), kU/L	32.7 (8.8–124.6)	25.4 (5.3–97.3)
Baseline CM specific IgG4, median (range), μg/mL	4.5 (1.1–7.9)	3.1 (1.4–4.7)

Abbreviation: CM, cow's milk.

[a] The *P* values are not significant for all between-group comparisons.

The clinical results of the desensitization are summarized in Table 3. One patient achieved only partial tolerance because at the dose of 64 mL she developed urticaria, angioedema, and cough and received intramuscular antihistamines and corticosteroids. In this patient, the desensitization was stopped for ethical reasons. This patient, who previously experienced symptoms even with minimal amounts of CM, can now eat CM-containing cakes, snacks, delicatessen foods, and ice cream and can drink moderate amounts of CM without symptoms. At the DBPCFC, his threshold dose increased from 1 to 30 mL (cumulative, 45 mL). One patient experienced urticaria, rhinitis, throat pruritus, vomiting, and circulatory collapse with 4 mL. He promptly recovered after intramuscular adrenaline and antihistamine administration and intravenous corticosteroid treatment. A third patient failed to achieve tolerance because 2 mL of CM provoked rhinitis, cough, asthma, generalized urticaria, and laryngeal edema. He received intramuscular adrenaline and corticosteroids, oral antihistamines, and inhaled salbutamol and promptly recovered. In the 2 latter children, there was no appreciable change in the threshold dose in the DBPCFC (Table 4).

The remaining 10 children (77%) reached the 200-mL dose and, therefore, achieved full tolerance without adverse effects (Table 3). None of the 15 controls receiving soy milk had symptoms during the study. The results of the DBPCFC are given in Table 4. It is apparent that the control patients maintained unchanged their clinical response to CM, whereas the 10 children with successful desensitization had a negative DBPCFC result. The DBPFC was also repeated in the 3 children who had discontinued the protocol, and it remained positive in 2 of them. Approximately 6 months after the trial, no clinical changes had occurred in the patients, who continued to tolerate CM well.

Table 3. Results of Specific Oral Immunotherapy With CM

Patient No.	Age at the desensitization	Symptoms during CM desensitization	Dose of CM that elicited symptoms, mL	Action taken	Outcome of CM desensitization
1	10 y 3 mo	Rhinitis, cough, asthma, generalized urticaria	2	Adrenaline, corticosteroids, antihistamines, salbutamol, protocol stopped	Failed
2	9 y 2 mo	Abdominal pain, throat pruritus	128	Antihistamine, corticosteroid	Tolerated 200 mL of whole CM
3	5 y 9 mo	Generalized urticaria, angioedema, cough	64	Antihistamine, corticosteroid, protocol stopped	Partial tolerance, up to approximately 100 mL
4	7 y 1 mo	Throat pruritus, gritty eyes	32	None	Tolerated 200 mL of whole CM
5	6 y 4 mo	Abdominal pain, gritty eyes, watery eyes	128	None	Tolerated 200 mL of whole CM
6	9 y 5 mo	Transient erythema (face and hands)	128	None	Tolerated 200 mL of whole CM
7	10 y 1 mo	None	NA	None	Tolerated 200 mL of whole CM
8	6 y 3 mo	Abdominal pain, gritty eyes	64	None	Tolerated 200 mL of whole CM
9	5 y 4 mo	None	NA	None	Tolerated 200 mL of whole CM
10	8 y 4 mo	Rhinitis, urticaria, cough, hypotension, dyspnea	4	Adrenaline, corticosteroids, salbutamol, antihistamine, protocol stopped	Failed
11	4 y 8 mo	None	NA	None	Tolerated 200 mL of whole CM
12	6 y 2 mo	Abdominal pain	64	None	Tolerated 200 mL of whole CM
13	7 y 5 mo	Abdominal pain, gritty eyes	32	None	Tolerated 200 mL of whole CM

Abbreviations: CM, cow's milk; NA, not applicable.

Immunologic Variables

No significant difference in IgE levels between the active and control groups was observed at 13 or 18 weeks vs baseline (Fig. 2). However, in 5 children in the active group, specific IgE levels displayed a clear increase when the intermediate dose of 8 mL was reached, but they returned to near baseline values at the end of the study. The 3 children with serious adverse events during desensitization had an increase in specific IgE levels from baseline of approximately 85% (mean [SD] before vs after: 34.8 [7.6] vs 66.6 [8.1] kU/L). In the active group, mean (SD) serum IgG4 levels increased from baseline (4.52 [3.4] μg/mL) to week 18 (23.8 [5.3] μg/mL) ($P = .003$). Such an increase was not seen in the control group (3.13 [1.6] vs 4.37 [1.7] μg/mL, respectively) (Fig. 3). The intergroup comparison also confirmed a significant difference in favor of the active CM group vs controls at 18 weeks (mean [SD], 23.8 [5.3] vs 4.3 [1.7] μg/mL; $P < .01$).

Table 4. Results of the Double-Blind, Placebo-Controlled Food Challenge[a]

Patient No.	Active group		Control group	
	Baseline	End of the study	Baseline	End of the study
1	0.3	3 mL	3	10
2	3	Negative	3	1
3	1	30	1	1
4	3	Negative	3	3
5	10	Negative	10	10
6	3	Negative	3	10
7	10	Negative	0.3	1
8	3	Negative	30	30
9	10	Negative	3	3
10	0,3	3	10	10
11	30	Negative	30	30
12	1	Negative	1	1
13	1	Negative	3	3
14	10	Dropout	10	3
15	30	Dropout	3	Dropout

[a] Data are given as milliliters of milk that elicited symptoms.

Safety Data

The safety results during the double-blind treatment are summarized in Table 3. As mentioned previously herein, in 3 patients, severe events occurred and the desensitization was stopped. Three patients concluded the desensitization without symptoms. The remaining 7 children had mild adverse effects, mostly abdominal pain, throat pruritus, and gritty eyes, during the desensitization. Most reactions were transient and required no treatment. Antihistamines were given to only 1 patient to control symptoms. In patients who completed the protocol, the reactions invariably occurred with a dose greater than 32 mL. No adverse effects were observed in the control group.

DISCUSSION

There is currently no specific curative treatment available for IgE-mediated food allergy, for which total avoidance of the offending food is the only effective approach. It was previously suggested that CMA tends to disappear in older age in

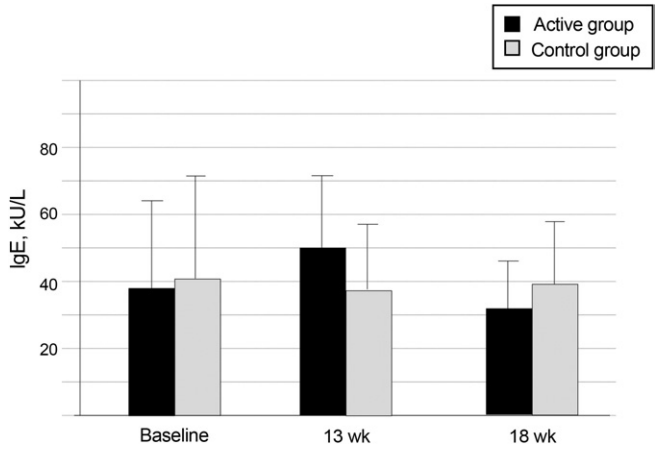


Figure 2. Mean cow's milk specific IgE levels at the 3 time points in active and control patients. No significant differences between and within groups were detected. Error bars represent SD.

most children and that approximately 85% of patients become tolerant by age 3 years. However, more recent studies[14,15] provided a less optimistic view. The burden of the disease and its tendency to persist across time in some individuals highlight the need for curative treatment, which can, in principle, reduce clinical symptoms and modify the natural history of the disease. In this regard, specific immunotherapy given by the oral route is regarded as a promising candidate.[16] Several attempts have been made to induce a tolerance to CM by administering progressively increasing doses of the food until intake of a full serving is achieved. These attempts have provided, overall, encouraging results, with an efficacy rate of 75% to 86%.[7,10,12,17] In a recent study[7] in children with severe CM-induced reactions, 36% became completely tolerant and 54% could ingest limited amounts of CM.

Currently, rush[18,19] and slow[7,11] protocols are used to achieve food tolerance. The first approach carries a certain risk of adverse events, and the second is, to some extent, impractical and time-consuming. In addition, part of the tolerance induction is conducted at home, without medical supervision,[7,11] and parents need to be carefully instructed on how to manage adverse reactions that can be also severe. The aim of the present study was to optimize the tolerance induction by identifying a more practical and patient-friendly approach. In this regard, weekly up-dosing oral immunotherapy seemed to be an acceptable compromise because it requires neither a complex protocol or hospitalization of the child. In fact, with the mentioned protocol, the dose increasing is performed every week at the clinic, and the patient is discharged within a few hours. In addition, the whole procedure lasts approximately 4 months, for a total of 28 visits. The study was designed as blinded and controlled, according to the requirements of evidence-based medicine. Soy milk cannot be strictly considered as a placebo, but in the case of CM, a "true" placebo is not available. In addition, it is true that patients can distinguish between soy milk and CM, but the procedure kept at least the investigator blinded. In such a study, the use of a control arm may be questionable because the absence of a reaction to control treatment (soy milk) was ascertained at the beginning of the study. On the other hand, a control arm was required to evaluate the occurrence, if any, of spontaneous tolerance development. In the control patients, no adverse effects occurred during the trial, but they maintained their sensitization to CM, as testified by the DBPCFC.

In this study, oral immunotherapy was effective: full specific tolerance was achieved in 10 of 13 actively treated children and partial tolerance in 1 of 13. In 2 patients, the desensitization had to be discontinued owing to severe adverse events. Therefore, the overall safety of the protocol is similar to that previously described.[7,18] The procedure is not devoid of adverse events, but the risk of having a reaction due to inadvertent ingestion is certainly higher than the risk of a reaction during a medically supervised desensitization. The results obtained in this study are, in addition, comparable in terms of clinical outcome with those reported in other studies[7,8,11,18,19] using daily protocols. Concerning immunologic outcomes, CM specific IgE levels remained unchanged overall. However, at the 8-mL dose, there was a transient increase in the IgE level, which returned to baseline levels when 200 mL of CM was reached. On the other hand, IgG4 levels against CM proteins exhibited a significant increase in the actively treated group. This is in agreement with the results described in other studies with milk[20] and peanuts[21] and is in line overall with the effects of specific immunotherapy for respiratory allergens. Also, in peanut allergy, it has been shown that oral desensitization induces down-regulation of the T_H2 response.[21] Thus, it can be speculated that the procedure described in the trial is a true immunotherapy inducing

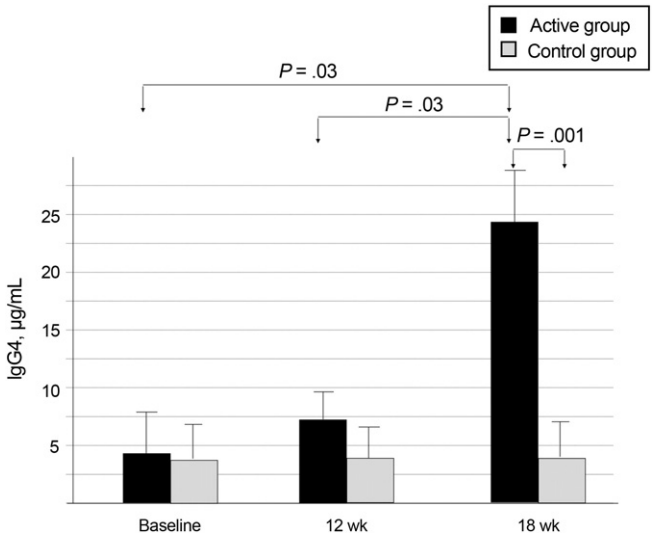


Figure 3. Mean cow's milk specific IgG4 levels at the 3 time points in the active and control patients. The significant intragroup and intergroup differences are shown at the top of the bars. Error bars represent SD.

immunologic changes. Whether the induced desensitization is permanent or transient is still unclear.[22] Staden and coworkers[11] reported that permanent tolerance could be achieved in 36% of patients with desensitized CMA. However, when children who achieved partial tolerance were included, efficacy increased to 64%. The latter group included patients who required a regular intake of CM to maintain tolerance or those who can tolerate lower-than-standard maximum doses.

In summary, these clinical data suggest that desensitization to CM can be successfully achieved in children with IgE-mediated food allergy. The proposed protocol is not time-consuming and is safe if performed in the hospital. It may represent a new therapeutic opportunity for children with IgE-mediated allergy to CM.

ACKNOWLEDGMENT

We thank Dr Harold Nelson for revising the English language of the manuscript and for his helpful comments and suggestions.

REFERENCES

1. Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *J Allergy Clin Immunol.* 2007;119: 1018–1019.
2. Vandenplas Y, Koletzko S, Isolauri E, et al. Guidelines for the diagnosis and management of cow's milk protein allergy in infants. *Arch Dis Child.* 2007;92:902–908.
3. Niggemann B, Staden U, Rolinck-Werninghaus C, Beyer K. Specific oral tolerance induction in food allergy. *Allergy.* 2006;61:808–811.
4. Saarinen KM, Pelkonen AS, Mäkelä MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J Allergy Clin Immunol.* 2005;116:869–875.
5. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol.* 2010;125(suppl 2):S116–S125.
6. Longo G, Barbi E, Berti I, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol.* 2008;121:343–347.
7. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. *Allergy.* 2004;59:980–987.
8. Morisset M, Moneret-Vautrin DA, Guenard L, et al. Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases: a randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. *Eur Ann Allergy Clin Immunol.* 2007;39:12–19.
9. Patriarca G, Nucera E, Pollastrini E, et al. Oral specific desensitization in food-allergic children. *Dig Dis Sci.* 2007;52:1662–1672.
10. Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB. Food allergy in children: results of a standardized protocol for oral desensitization. *Hepatogastroenterology.* 1998;45:52–58.
11. Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy.* 2007;62:1261–1269.
12. Patriarca G, Nucera E, Roncallo C, et al. Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther.* 2003;7:459–465.
13. Caminiti L, Passalacqua G, Barberi S, et al. A new protocol for specific oral tolerance induction in children with IgE-mediated cow's milk allergy. *Allergy Asthma Proc.* 2009;30:443–448.
14. Saarinen KM, Pelkonen AS, Makela MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J Allergy Clin Immunol.* 2005;116:869–875.
15. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol.* 2007;120: 1172–1177.
16. Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol.* 2008;121:1331–1336.
17. Wüthrich B. Oral desensitization with cow's milk in cow's milk allergy: Pro! *Monogr Allergy.* 1996;32:236–240.
18. Bauer A, Ekanayake Mudiyanselage S, Wigger-Alberti W, Elsner P. Oral rush desensitization to milk. *Allergy.* 1999;54:894–895.
19. Patriarca G, Nucera E, Pollastrini E, et al. Oral rush desensitization in peanut allergy: a case report. *Dig Dis Sci.* 2006;51:471–473.
20. Skripak JM, Nash SD, Rowley H, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol.* 2008;122:1154–1160.
21. Jones MS, Pons L, Roberts LJ, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol.* 2009:124:292–300.
22. Rolinck-Werninghaus C, Staden U, Mehl A, Hamelmann E, Beyer K, Niggemann B. Specific oral tolerance induction with food in children: transient or persistent effect on food allergy? *Allergy.* 2005;60: 1320–1322.

What is the evidence in AIT for allergic rhinitis in children?

Graham Roberts, United Kingdom

What is the evidence in AIT for allergic rhinitis in children?

Graham Roberts, Professor and Consultant in Paediatric Allergy and Respiratory Medicine, University of Southampton

Allergic rhinoconjunctivitis (AR) is an allergic disorder of the nose and eyes affecting many children and teenager. Symptoms of AR can be controlled with allergen avoidance measures and pharmacotherapy. However, many patients continue to have ongoing symptoms and an impaired quality of life; pharmacotherapy may also induce some side-effects. Allergen immunotherapy (AIT) represents the only currently available treatment that targets the underlying pathophysiology, and it may have a disease-modifying effect. Either the subcutaneous (SCIT) or sublingual (SLIT) routes may be used.

The European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on AIT has recently published a guideline on AIT for AR. The Guideline provides evidence-based clinical recommendations and has been informed by a formal systematic review and meta-analysis. Its generation has followed the Appraisal of Guidelines for Research and Evaluation (AGREE II) approach. There is broad evidence for the clinical efficacy of AIT for AR exists but a product-specific evaluation of evidence is recommended as not all have been shown to be effective. In general, SCIT and SLIT are recommended for both seasonal and perennial AR for its short-term benefit. The strongest evidence for long-term benefit is documented for grass AIT (especially for the grass tablets) where long-term benefit is seen. To achieve long-term efficacy, it is recommended that a minimum of 3 years of therapy is used. Many gaps in the evidence base exist, particularly around long-term benefit and use in children.

References:

Roberts G, Pfaar O, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy 2018; 73: 765-98.

Dhami S et al. Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. Allergy 2017; 72: 1597-1631.

Pro-con debate - To treat or not to treat.

Food AIT: is it worth it? CON.

Margitta Worm, Germany

Cons to be discussed based on the literature

- risk of acute severe systemic reactions
- onset of EOE
- limited (long-term) efficacy
- reduction of QoL
- onset of peanut aversion

Provocation Tests to Inhalant Allergens

Ozlem Cavkaytar, Turkey

Oliver Pfaar, Germany

Ozlem Cavkaytar [1] Oliver Pfaar [2,3]

[1]Department of Pediatric Allergy

Istanbul Medeniyet University Göztepe Training & Research Hospital

İstanbul, Turkey

[2]Department of Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.

[3]Center for Rhinology and Allergology, Wiesbaden, Germany.

Provocation Tests to Inhalant Allergens

Allergic Rhinoconjunctivitis (AR) and allergic asthma affect a nonnegligible portion of children and adolescents worldwide and aeroallergens are responsible from emergence of the symptoms. Besides history, a correct diagnosis is established with the use of adequate and standardized tests as basis for an optimized treatment strategy. In some clinical conditions establishment of the accurate diagnosis of allergy is not possible with the use of common tests like skin prick test or serum specific IgE only. In these cases the next step to take is the use of more straightforward techniques like inhalant allergen challenge tests (ACT). Allergen challenge tests are currently being used for both research and diagnostic purposes with reproducible and reliable results. Nasal (NPT), conjunctival (CPT), and bronchial aeroallergen provocation (BPT) tests are performed to provoke allergic reactions of the nasal, conjunctival and bronchial mucosa under standardized and controlled conditions (1-3). For scientific purposes and clinical development programs allergen exposure chambers (AEC) are also used (4).

During inhalant ACTs, a quantified concentration of allergen is applied to the mucosal surface that provokes both an immediate type I hypersensitivity and a late phase reaction (5). The indications of NPT are to diagnose persistant and intermittent allergic rhinitis, local and occupational rhinitis, to correlate with extranasal symptoms, to differentially diagnose ocular symptoms, to design allergen composition and to monitor clinical efficacy of allergen immunotherapy (AIT). The indications for a CPT are as well to

demonstrate the causal role of a suspected allergen or to define clinically relevant allergen(s) in case of polysensitization and to diagnose occupational disease (3). In case of a BPT the indications are to diagnose occupational asthma, to demonstrate the causal role of the suspected allergen or to demonstrate late airway bronchial response. However, BPT are only performed in selected centers with great expertise in this challenge method. All ACTs may also be performed for research purposes.

Several prerequistes are needed in order to provide a controlled and standardized test environment and to achieve reproducible results during an ACT (2). Additionally it is obviously recommended to use standardized solutions in all types of ACTs. In case of NPT different methods have been used in the past but most reliable and easiest way is to use pump-aerosol spray bottles which repels 50 µl of solution per puff (1, 2). During a nasal ACT both subjective symptom scores and objective patency assessment methods of the nose are used to interprete the outcome of an ACT, a strong increase in the objective measurement or a strong increase in the subjective measurement or a moderate increase in both the objective and the subjective measurement are accepted as positive ACT result and criteria have been recently harmonized by the European Academy of Allergy and Clinical Immunology (EAACI) in a Position Paper (1) (2). Comparison of the baseline measurements, control and allergen challenge measurements should be done for an appropriate interpretation. At the end of the test the patients should be treated accordingly and followed up until the reaction ceases including the late phase reactions. The workshop will make participants familiar with the standardized operation procedures (SOPs) of different provocation models, their specific advantages and pitfalls.

References

1. Auge J, Vent J, Agache I, Airaksinen L, Campo Mozo P, Chaker A, et al. EAACI Position paper on the standardization of nasal allergen challenges. *Allergy* 2018;**73**(8):1597-1608.
2. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. *Allergy* 2014;**69**(7):854-867.
3. Fauquert JL, Jedrzejczak-Czechowicz M, Rondon C, Calder V, Silva D, Kvenshagen BK, et al. Conjunctival allergen provocation test : guidelines for daily practice. *Allergy* 2017;**72**(1):43-54.
4. Pfaar O, Calderon MA, Andrews CP, Angjeli E, Bergmann KC, Bonlokke JH, et al. Allergen exposure chambers: harmonizing current concepts and projecting the needs for the future - an EAACI Position Paper. *Allergy* 2017;**72**(7):1035-1042.
5. Agache I, Bilo M, Braunstahl GJ, Delgado L, Demoly P, Eigenmann P, et al. In vivo diagnosis of allergic diseases--allergen provocation tests. *Allergy* 2015;**70**(4):355-365.

What is the evidence in AIT for asthma in children?

Pablo Rodríguez del Río, Spain

What is the evidence in AIT for asthma in children?

EAACI Allergy School: Immunotherapy in children for the treatment of respiratory and food allergy

Author: Pablo Rodríguez del Río.

Niño Jesús Hospital, Madrid, Spain

Asthma is one of the most common chronic diseases in childhood and despite Allergen immunotherapy (AIT) is being prescribed to treat this condition, the evidence in children is still a matter of debate. To analyse the evidence of the efficacy of AIT in paediatric asthma, it can be interesting to differentiate in what stage of the disease severity-spectrum AIT can be useful.

With only very few studies addressing the ability of AIT to prevent the apparition of asthma in non-allergic patients, and according to the EAACI guidelines on AIT, the evidence does not support its use for this porpoise. In an interesting study by Zolkipli et al, a group of 111 non-allergic high risk infants were randomized to receive an oral house dust mite (HDM) extract for 12 months and the onset of eczema and wheeze, along with the apparition of skin prick test (SPT) positivities was evaluated. The treatment only showed efficacy to reduce the risk for the sensitization to any common allergen, but failed to minimize the risk of HDM SPT positivity, as well as new-onset wheeze.

It has been previously described that around 45% of children suffering allergic rhinitis will eventually also develop allergic asthma. There are very interesting studies addressing the efficacy of AIT to prevent the apparition of asthma in allergic rhinitis, and maybe, one of the largest and with a better methodology is that published by Valovirta et al. In their trial, 812 children with history of grass allergic rhinitis but without asthma, received a grass tablet and evaluated its effect on the prevention of asthma onset, that had to be confirmed on the basis of a positive bronchodilator test. Unfortunately, the primary outcome wasn´t reached, but a nice positive effect of the SLIT treatment was recorded as a reduction in both medication and asthma symptoms. This study along with others, provides enough evidence as to show that the risk of asthma symptoms in allergic rhinitis patients can be decreased by the use of AIT.

The largest body of evidence for AIT in asthma is built for children suffering mild to moderate asthma. In this field, we can find several studies and metanalysis supporting the use of AIT in children showing improvement in asthma severity, asthma exacerbations, asthma symptoms, reduction in the dose of inhaled corticosteroids and also in some cases improvement of bronchial hyperreactivity. However, evidence should be evaluated with caution and despite that the pooling of studies done in metanalysis is a great tool to understand the body of evidence, it can also be a source

of confusion due to the heterogeneity between studied populations, treatment modalities (extracts, allergens, schemes, protein content…) and variables used to analyse efficacy.

For decades, severe asthma has been a contraindication for AIT due to the higher ratio and more severe adverse events that these patients might encounter in the course of AIT. Due to a better product design and standardization, in the last position paper on AIT contraindications, severe asthma is not considered anymore an absolute contraindication as long as it is well controlled, widening the potential candidates for this treatment. Additionally, the use of Omalizumab along with AIT in severe asthmatic children is being explored, and despite only a few publications with low number of patients is available, the results in terms of safety are very encouraging.

REFERENCES

Meltzer EO, Blaiss MS, Derebery J, Mahr TA, Gordo BR, Sheth KK, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. J Allergy Clin Immunol 2009;124:s43-70.

Halken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Pfaar O, et al. EAACI Guidelines on Allergen Immunotherapy: Prevention of allergy. Pediatr Allergy Immunol 2017 Dec;28(8):728-745

Kristiansen M, Dhami S, Netuveli G, Halken S, Muraro A, Roberts G et al. Allergen immunotherapy for the prevention of allergy: A systematic review and metaanalysis. Pediatr Allergy Immunol 2017;28:18-29

Zolkipli Z, Roberts G, Cornelius V, Clayton B, Pearson S, Michaelis L et al. Randomized controlled trial of primary prevention of atopy using house dust mite allergen oral immunotherapy in early childhood. J Allergy Clin Immunol 2015;136:1541-1547.

Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A et al. Specific immunotherapy has longterm preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007; 62:943-948.

Valovirta E, Petersen TH, Piotrowska T, Laursen MK, Andersen JS, Sorensen HF et al. Results from the 5-year SQ grass SLIT-tablet asthma prevention (GAP) trial in children with grass pollen allergy. J Allergy Clin Immunol 2017. pii: S0091-6749(17)31088-6.

Pifferi M, Baldini G, Marrazzini G, Baldini M, Ragazzo V, Pietrobelli A, Boner AL. Benefits of immunotherapy with a standardized Dermatophagoides pteronyssinus extract in asthmatic children: a three-year prospective study. Allergy 2002;57:785-90.

Roberts G, Hurley C, Turcanu V, Lack G. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. J Allergy Clin Immunol 2006;117:263-8.

Ibero M, Castillo MJ. Significant improvement of specific bronchial hyperreactivity in asthmatic children after 4 months of treatment with a modified extract of dermatophagoides pteronyssinus. J Investig Allergol Clin Immunol 2006;16:194-202.

Cantani A, Arcese G, Lucenti P, Gagliesi D, Bartolucci M. A three-year prospective study of specific immunotherapy to inhalant allergens: evidence of safety and efficacy in 300 children with allergic asthma. J Investig Allergol Clin Immunol 1997;7:90-7.

Tabar AI, Lizaso MT, Garcia BE, Gomez B, Echechipia S, Aldunate MT, Madariaga B, Martínez A. Double-blind, placebo-controlled study of Alternaria alternata immunotherapy: clinical efficacy and safety. Pediatr Allergy Immunol 2008;19:67-75.

Kuna P, Kaczmarek J, Kupczyk M. Efficacy and safety of immunotherapy for allergies to Alternaria alternata in children. J Allergy Clin Immunol 2011;127:502-8.e1-6.

Tsai TC, Lu JH, Chen SJ, Tang RB. Clinical efficacy of house dust mite-specific immunotherapy in asthmatic children. Pediatr Neonatol 2010;51:14-8.

Zielen S, Kardos P, Madonini E. Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: a randomized controlled trial. J Allergy Clin Immunol 2010;126:942-9.

Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization Position Paper 2009. Allergy 2009;64 Suppl 91:1-59.

De Castro G, Zicari AM, Indinnimeo L, Tancredi G, di Coste A, Occasi F, et al. Efficacy of sublingual specific immunotherapy on allergic asthma and rhinitis in children's real life. Eur Rev Med Pharmacol Sci 2013;17:2225-31.

Peng W, Liu E. Factors influencing the response to specific immunotherapy for asthma in children aged 5-16 years. Pediatr Int 2013;55:680-4.

Penagos M, Passalacqua G, Compalati E, Baena-Cagnani CE, Orozco S, Pedroza A, Canonica GW. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. Chest 2008;133:599-609

Olaguíbel JM, Alvarez Puebla MJ. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. J Investig Allergol Clin Immunol 2005;15:9-16

Nelson HS, Calderon MA, Bernstein DI, Casele TB, Durham SR, Andersen JS et al. Allergen Immunotherapy Clinical Trial Outcomes and Design: Working Toward Harmonization of Methods and Principles. Curr Allergy Asthma Rep (2017) 17: 18

Dominguez-Ortega J, Delgado J, Blanco C, Prieto L, Arroabarren E, Cimarra M, et al. Specific allergen immunotherapy for the treatment of allergic asthma: a review of current evidence. J Investig Allergol Clin Immunol 2017; Vol. 27, Suppl. 1: 1-35

Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E, EAACI, Immunotherapy Task Force. Standards for practical allergen-specific immunotherapy. Allergy 2006;61(Suppl 82):1–20.

Pitsios C, Demoly P, Biló MB, Gerth van Wijk R, Pfaar O, Sturm GJ, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy 2015; 70: 897–909.

Lambert N, Guiddir T, Amat F, Just J. Pre-treatment by omalizumab allows allergen immunotherapy in children and young adults with severe allergic asthma. Pediatr. Allergy Immunol. 25(8), 829–832 (2014).

Stelmach I, Majak P, Jerzynska J, Bojo M, Cichalewski L, Smejda K. Children with severe asthma can start allergen immunotherapy after controlling asthma with omalizumab: a case series from Poland. Arch Med Sci. 2015;11:901-4.

Pro-con debate - To treat or not to treat.

Food AIT: is it worth it? PRO.

Pablo Rodríguez del Río, Spain

Pro-con debate - To treat or not to treat. Food AIT: is it worth it? PRO.

EAACI Allergy School: Immunotherapy in children for the treatment of respiratory and food allergy

Author: Pablo Rodríguez del Río.

Niño Jesús Hospital, Madrid, Spain

Food allergy represents the second wave of the allergy pandemic according to some authors and is experiencing an increase in prevalence affecting between 5 to 8% of the general population. Despite the burden of food allergy, current standard of care is mainly based upon patient and family education, avoidance of the offending food and the treatment of reactions resulting from accidental exposures.

Regardless of regulatory and academic efforts to improve foodstuff labeling, analysis performed in a selection of products with no allergen declaration disclosed that in some cases, these contained enough allergen residues to endanger allergic patients. When avoiding the culprit food fails, patients are at risk of suffering anaphylaxis, a life-threatening event. According to the records in the UK, the number of hospitalizations for food-triggered anaphylaxis increased from 1992 to 2010. Food allergy causes significant impairment in the quality of life of patients and guardians due to anxiety of accidental reactions, limitations in diet and social life, emotional impact and bullying at school.

The aforementioned reasons underscore the need of a treatment to ameliorate the impact of food allergy. Food immunotherapy, first described in 1908, but really being used in the last decades, represents a promising option of an etiological treatment for patients suffering persistent food allergy. It has awakened the interest of the scientific community and an increasing body of evidence has been created over the last few years that has lead to a positioning of the EAACI towards its use in experienced centers outside the framework of clinical trials.

Food AIT has shown its capability to increase the reactivity thresholds for milk, egg and peanut allergy whilst receiving the treatment. The post-discontinuation efficacy of Food AIT is still a matter of debate, but current evidence suggest that the achieved protection decreases with longer off diet periods.

The most relevant weak point of food-AIT, specially when oral route is used, is the safety of the treatment. Frequent adverse reactions appear in the course of AIT, and in some cases these can be severe. This fact has boosted the research of safer delivery routes. First the sublingual route, but more recently the epicutaneos route, that has already been used in large trials to treat peanut allergic patients, exhibited a more benign safety profile. Other initiatives to decrease side effects is the concomitant use of omalizumab, that has proven to ease the treatment successfully.

In conclusion, and considering that some aspects of the treatment as safety already deserve more study, the treatment provides a satisfactory solution to a problem that is suffering a quite large percentage of the population.

References

Prescott S, Allen KJ. Food allergy: Riding the second wave of the allergy epidemic. Pediatr Allergy Immunol 2011; 22: 155–160.

Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics. 2009 124:1549-55

Muraro A, Dubois AE, DunnGalvin A, et al. EAACI Food Allergy and Anaphylaxis Guidelines. Food allergy health-related quality of life measures Allergy. 2014 Jul;69(7):845-53

Muraro A, Hoffmann-Sommergruber K, Holzhauser T, Poulsen LK, Gowland MH, Akdis CA, et al. EAACI Food Allergy and Anaphylaxis Guidelines. Protecting consumers with food allergies: understanding food consumption, meeting regulations and identifying unmet needs. Allergy 2014; 69: 1464–1472.

Remington BC, Baumert JL, Blom WM, Houben GF, Taylor SL, Kruizinga AG. Unintended allergens in precautionary labelled and unlabeled products pose significant risks to UK allergic consumers. Allergy 2015; 70: 813–819

Turner PJ, Gowland M, Sharma V, Ierodiakonou D, harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: An analysis of United Kingdom national anaphylaxis data, 1992-2012. J Allergy Clin Immunol 2015;135:956-63

Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. Allergy. 2010 Aug;65(8):933-45

Egan M, Sicherer S. Doctor, my child is bullied: food allergy management in schools. Curr Opin Allergy Clin Immunol. 2016 Jun;16(3):291-6.

Schofield AT. A case of egg poisoning. Lancet 1908;1: 716

Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI Guidelines on allergen immunotherapy: IgE mediated food allergy. Allergy. 2017;00:1–17.

Nurmatov U, Dhami S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy. 2017 Aug;72(8):1133-1147.

Factor JM, Mendelson L, Lee J, Nouman G, Lester MR. Effect of oral immunotherapy to peanut on food-specific quality of life. Ann Allergy Asthma Immunol. 2012;109:348–352.

Otani IM, Bégin P, Kearney C, Dominguez TL, Mehrotra A, Bacal LR, et al. Multiple-allergen oral immunotherapy improves quality of life in caregivers of food-allergic pediatric subjects. Allergy Asthma Clin Immunol. 2014;10(1):25.

Vázquez-Ortiz M, Álvaro M, Piquer M, Domínguez O, Giner MT, Lozano J, et al. Impact of oral immunotherapy on quality of life in egg-allergic children. Pediatr Allergy Immunol. 2015 May;26(3):291-294

Vickery BP. Does clinical protection persist after food allergen oral immunotherapy? Immunotherapy. 2015;7(8):851-3.

Jones SM, Sicherer SH, Burks AW, Leung DYM, Lindblad RW, Dawson P, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol. 2017;139:1242–1252.e9.

Sampson HA, Shreffler WG, Yang WH, Sussman GL, Brown-Whitehorn TF, Nadeau KC, et al. Effect of Varying Doses of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Exposure Among Patients With Peanut Sensitivity: A Randomized Clinical Trial. JAMA. 2017;318:1798–809.

Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2011;127:640–646.e1

Wood RA. Food allergen immunotherapy: Current status and prospects for the future. J Allergy Clin Immunol. 2016 Apr;137(4):973-982.

Mechanisms of inhalant allergen immunotherapy and predictive biomarkers

Shamji Mohamed, United Kingdom

Title: Mechanisms of inhalant allergen immunotherapy and predictive biomarkers

Authors: Mohamed H Shamji PhD FAAAI and Stephen R Durham MD FRCP

Immunomodulation and Tolerance Group, Allergy and Clinical Immunology, Section Inflammation, Repair and Development, National Heart and Lung Institute, Imperial College London. MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, London, United Kingdom.

Correspondence

Professor Stephen R. Durham
Allergy and Clinical Immunology
National Heart & Lung Institute,
Imperial College London
Dovehouse Street,
London SW3 6LY
+442073518024
s.durham@imperial.ac.uk

Abstract

Allergen immunotherapy is effective in patients with IgE-dependent allergic rhinitis and asthma. In contrast to anti-allergic drugs, when immunotherapy is given continuously for 3 years, there is persistent clinical benefit for several years after its discontinuation. This disease-modifying effect is both antigen-specific and antigen-driven. Clinical improvement is accompanied by decreases in effector cells in target organs including mast cells, basophils, eosinophils and type 2 innate lymphoid cells. Immunotherapy also results in the production of blocking IgG/IgG4 antibodies that can inhibit IgE-dependent activation mediated via both Fc□RI (mast cells and basophils) and Fc□RII (facilitated antigen presentation). This suppression of Th2 immunity may occur as a consequence of either deletion and/or anergy of antigen-specific T cells, the induction of antigen-specific T regulatory cells and/or immune deviation in favour of Th1 responses. It is not clear whether the altered long-term memory resides within the T cell and/or B cell compartment. Recent data highlight the role of IL-10 producing regulatory B cells that produce 'protective' antibodies that likely contribute to long-term tolerance. Understanding mechanisms underlying the induction and persistence of tolerance should identify predictive biomarkers of clinical response and discover novel more effective strategies for immunotherapy.

Key words:

Immunotherapy, Mechanisms, Allergic rhinitis, Allergic asthma, Long-term tolerance, T cells, B cells, Type 2 Innate Lymphoid cells, IgE-FAB, Biomarkers

Abbreviations

Bregs	B regulatory cells
CCL	CC chemokine ligands
CCR	CC chemokine receptors
CD	Cluster of differentiation
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DAO	Diamine oxidase
DC	Dendritic cell
DCreg	Regulatory dendritic cell
ELIFAB	Enzyme-linked immunosorbent-facilitated antigen binding assay
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FAB	Facilitated antigen binding assay
Fc□RI	High affinity IgE receptors
FOXP3	Forkhead box P3
GATA3	GATA binding protein-3

GITR	Glucocorticoid-induced TNF receptor
GRASS	Gauging Responses in Allergic rhinitis to SCIT versus SLIT trial study
ICAM	Intercellular Adhesion Molecule
Ig	Immunoglobulin
IL	Interleukin
ILC	Innate lymphoid cell
ISAC	Immuno-solid-phase allergen chip
iTregs	Inducible Tregs
LT	Leukotriene
mRNA	Messenger RNA
nTregs	Natural T regulatory cells
PBMC	Peripheral blood mononuclear cells
Phlp	*Phleum pratense*
RIPK4	Receptor-interacting serine/threonine-protein kinase 4
ROR	RAR-related orphan receptors
RT-PCR	Reverse transcription-polymerase chain reaction
SAR	Untreated seasonal allergic rhinitis individuals
SCIT	Subcutaneous immunotherapy
sIg	Allergen-specific immunoglobulin
SLIT	Sublingual immunotherapy
TAME-Esterase	Tosyl l-arginine methyl ester-esterase
TCR	T cell receptor
Tfh	T follicular helper
Tfr	T follicular regulatory
TGF	Transforming growth factor
Th	T helper cells
TLR	Toll-like receptors
Tregs	T regulatory cells
TSLP	Thymic-stromal lymphopoetin
VCAM	Vascular cell adhesion protein
VLA4	Very late antigen-4, Integrin $\alpha 4\beta 1$

Introduction

Allergen immunotherapy is effective in selected patients with allergic rhinitis including those with mild/moderate asthma (1, 2). There is heterogeneity in the populations studied, the different allergen products and protocols employed and the clinical outcomes used to document efficacy and safety (3). None-the-less recent guidelines (4) confirm that immunotherapy is particularly effective in seasonal rhinitis and recent data strongly support its use in perennial allergy due to house dust mites (5). Subcutaneous immunotherapy involves weekly up-dosing injections followed by monthly maintenance injections for at least 3 years (1, 6, 7). In view of occasional systemic allergic side effects, subcutaneous immunotherapy requires administration in a specialist allergy clinic with access to resuscitative measures. Sublingual immunotherapy involves daily drops or tablets placed under the tongue. Sublingual immunotherapy is effective and safer than subcutaneous immunotherapy such that it may be self-administered by the patient at home (1, 8). Sublingual and subcutaneous immunotherapy are effective generally within 2-4 months of initiating treatment and may be given pre/co-seasonally for short term benefit. Indirect comparisons have suggested that immunotherapy may be more effective than anti-allergic drugs. In contrast to anti-allergic drugs and currently available monoclonal antibody therapies, when immunotherapy is given continuously for 3 years both routes have been shown to be disease modifying, manifest as long-term remission of symptoms for at least 2-3 years following their discontinuation (9, 10). In this review, we explore historical and recent data on the mechanisms of immunotherapy for inhalant allergens. Our expectation is that a greater understanding of the underlying mechanisms of tolerance will identify potential biomarkers that could predict and/or monitor the response to treatment. Such knowledge could inform new potential treatment strategies.

Overview of mechanisms of allergic rhinitis and asthma

IgE and mast cells

Cardinal features of allergic rhinitis include elevated allergen-specific IgE concentrations to clinically relevant allergens, the IgE-dependent activation of mast cells and local eosinophilia in target organs. In addition to systemic and regional lymphatic sources of IgE, specific IgE may be synthesised and produced locally by B cells within the respiratory mucosa (11) thereby accounting for the occasional phenomenon of 'local allergic rhinitis' with symptoms on allergen exposure in the absence of detectable serum specific-IgE or positive immediate skin tests to relevant allergens (12).

IgE-dependent activation is detectable during the immediate (0-60 minute) response following nasal allergen provocation. Allergen crosslinking of adjacent surface IgE molecules on mast cells and basophils triggers within seconds or minutes the release of pre-formed mediators such as histamine (13) and tryptase (14) contained within intra-cytoplasmic granules. Newly-formed mediators derived from arachidonic acid within the membrane lipid include sulphido-peptide leukotrienes (12). (LTC4, LTD4 and the terminal metabolite LTE4), platelet-activating factor and prostaglandin D2. The biological properties of these mediators are consistent with the local vasodilatation, edema formation, local neurogenic stimulation and mucus secretion that characterise typical nasal allergen-induced immediate type I hypersensitivity. In the lower airways, bronchial smooth contraction as well as edema and mucus hyper-secretion contribute to acute bronchoconstriction. A proportion of subjects develop a late response at 2-10 hours after challenge. The late response is characterised by tissue eosinophilia, nasal congestion and mucosal hyperreactivity to both allergic and non-allergic triggers that may last for days or even weeks following a single nasal allergen challenge. In contrast to findings in allergic asthma and in nasal polyposis, morphologic and immunohistochemical features of airway remodelling are not a consistent feature of even moderate/severe allergic rhinitis (15).

Th2 lymphocytes and group 2 innate lymphoid cells

The above pathophysiologic events are under the regulation of a distinct subset of T helper type 2 (Th2) cells. Th2 cells produce interleukin (IL)-4, the key cytokine responsible for Th2 cell differentiation (16-18). IL-4 and IL-13 induce B lymphocytes to produce □-germline gene transcripts (19). the first step in heavy chain gene rearrangement in favour of IgE production. IL-4 and IL-13 upregulate VCAM-1 expression on the vascular endothelium, promoting adhesion of VLA-4-expressing eosinophils. Both stimulate mucus production from glands in the upper and lower airways. IL-5 is responsible for terminal differentiation and release of eosinophils from the bone marrow and prolongs eosinophil survival by inhibiting eosinophil apoptosis in tissues (20). Along with stem cell factor, IL-9 is a key cytokine for the differentiation and maturation of mast cells (21). The release of Th2 cytokines and tissue eosinophilia are apparent during the late-phase response that occurs at 4-12 hours after allergen challenge (22).

Type 2 Innate lymphoid cells (ILC2s) represent an alternative source of 'Th2' cytokines in the nasal mucosa. ILCs are morphologically similar to lymphocytes although are distinct in not expressing surface antigen receptors or other cell lineage markers and act in an antigen-independent manner (23, 24). ILCs consist of three different groups referred to as ILC1, ILC2, and ILC3. ILC1s constitutively express Tbet and produce the Th1 cytokines IFN-γ and TNF and provide protection against intracellular bacteria and parasites. ILC2s constitutively express ROR-□ and GATA3, produce Th2 cytokines, particularly IL-5 and IL-13 and provide immunity to helminths, as well as stimulating allergic responses. ILC3s are characterised by the transcripton factor ROR-□t, express IL-17a and/or IL-22, afford protection against extracellular bacteria and are involved in tissue repair processes. The role of ILC2s in allergic rhinitis was first identified in cat allergic subjects who showed increases in peripheral blood ILC2s at 4 hours following a cat allergen nasal challenge (25). Subsequently increases in circulating ILC2s have been identified in both grass allergic rhinitic (26) and asthmatic subjects (27) during the grass pollen season. ILC2s represent an abundant alternative source of Th2 cytokines and likely serve to amplify and maintain local Th2-driven allergic inflammation. In view of recently identified plasticity within ILC2s in tissues of patients with chronic obstructive pulmonary disease and chronic rhinosinusitis (28), this concept requires to be revisited in the context of allergic rhinitis (18).

The respiratory epithelium and dendritic cells

Whereas IgE-dependent mast cell activation and tissue eosinophilia are driven by Th2 lymphocytes, the differentiation of Th2 cells is dependent on the local cytokine milieu provided by interactions between the respiratory epithelium, local dendritic cells and regional lymph glands.

In an atopic individual, aeroallergens pass through the inflamed nasal epithelium and activated epithelial cells release chemokines (CCL2 and CCL20) that recruit immature dendritic cells (Fig.1A). Activated DCs migrate to regional draining lymph nodes and polarize naïve T cells into Th2 cells. DC migration is primed by IL-13 produced by ILC2s and also by IL-4 produced principally by basophils. Within the germinal centre of the lymph node, a subset of T helper cells differentiates into T follicular helper cells (Tfh cells). Tfh cells produce both IL-4 and IL-21 that along with Th2 cell-derived IL-4 promote immunoglobulin heavy chain class switching to IgE in B cells.

The respiratory epithelium of atopic allergic subjects expresses cytokines that include IL-25 (29), IL-33 (30) and Thymic-stromal Lymphocyte activating Protein (TSLP) (31). These epithelial cytokines favour development of a pro-allergic dendritic cell phenotype (32, 33) that provides help for Th2 cell differentiation. Additionally, these epithelial-derived cytokines are major growth factors for ILC2s that amplify and maintain local Th2-driven allergic inflammation (34-36). During subsequent allergen exposure, IgE-facilitated allergen recognition via FceRI on dendritic cells and FceRII on B cells amplifies the development of Th2 responses to inhaled allergens (Fig 1B).

Dendritic cells (DCs), depending on their phase of maturation, their location and the associated local cytokine milieu, can either initiate and maintain allergic inflammation (pro-allergic, DC2) (32, 33, 37, 38) or alternatively promote a state of immune tolerance (tolerogenic, DCregs) (32, 33, 39-42) to sensitising allergens. DC2 cells express the markers CD141, GATA3, OX40 ligand, and receptor-interacting serine/threonine-protein kinase 4 (RIPK4) (33). When DC2s were exposed to allergen and subsequently co-cultured with T cells they promoted preferential Th2 T lymphocyte responses (35-39).

Mechanisms of allergen immunotherapy (Fig.2)

IgE, IgG and IgA responses

Sublingual and subcutaneous immunotherapy have both been associated with transient early increases in serum allergen-specific IgE antibodies that are followed by blunting of the usual seasonal increases in IgE during natural allergen exposure (66). These early increases are not accompanied by untoward side effects and it has been suggested that an early 'Th2 priming' by high allergen exposure may be important for successful immunotherapy. Prolonged subcutaneous immunotherapy over several years may result in a decrease in allergen specific IgE concentrations (43, 44), an event that may contribute to long-term tolerance.

Robert Cooke in 1935 demonstrated the passive transfer of suppressive activity for immediate ragweed IgE-sensitivity in the skin by use of serum obtained from patients who had undergone ragweed subcutaneous immunotherapy (45). Serum and nasal inhibitory activity for IgE after subcutaneous immunotherapy was subsequently shown to reside within serum IgG, IgG4 and IgA fractions (46-50). Studies have shown 10-100-fold increases in serum concentrations of IgG, particularly IgG4 (7, 51-54). Sublingual immunotherapy has also been shown to induce allergen-specific (55) IgG1, IgG4 and IgA antibodies (10, 48, 56-58) These increases in immunoreactive antibodies have been observed following immunotherapy to both seasonal pollens and perennial allergens such as HDM (59, 60). Serum specific IgG4 has been shown to increase in a time- and dose-dependent manner during grass pollen immunotherapy (58). Several studies have highlighted the inhibitory capacity of IgG4 for IgE-dependent events. IgG4 antibodies are bi-specific and have the capacity to exchange F(ab) arms by swapping heavy-light chain pairs between IgG4 molecules with diverse specificities (61). IgG may compete with IgE for allergen (62) thereby blocking allergen-IgE complex formation. This prevents crosslinking of high affinity IgE receptors (FcεR1) on basophils and mast cells inhibiting histamine release. Competition of IgG/IgG4 for IgE may also block binding of allergen-IgE complexes to low affinity receptors (Fc□RIIb) on B cells, thereby inhibiting IgE-

facilitated antigen presentation to T cells, a major driver of allergen-specific Th2 responses (16, 63-65).

Paradoxically, while immunoreactive IgG/IgG4 levels fell by 80-90% within one year of stopping allergen immunotherapy, IgG-associated serum IgE-inhibitory activity persisted for several years and accompanied long-term clinical efficacy (48). This suggests that despite lower levels, the IgG antibodies that persist after discontinuation of immunotherapy may have either higher avidity and/or affinity. The data raise the possibility that long-lived memory B cells induced by immunotherapy may persist as a result of low level environmental allergen stimulation, thereby contributing to long-term tolerance.

IgG antibodies have also been detected locally in nasal fluid as well as in serum following immunotherapy (52). Both specific IgG4 and associated inhibitory activity for IgE-facilitated antigen binding (IgE-FAB) were increased in the nasal fluid of patients undergoing sublingual immunotherapy compared to untreated participants (66). The IgG4-dependency of IgE-inhibitory activity has been shown by depletion experiments using an IgG4 affinity chromatography. The magnitude of IgE suppression was higher with nasal fluid than with serum thereby highlighting the potency of local IgG inhibitory antibodies (66).

Immunotherapy and effector cells.

The influence of immunotherapy on effector cells has been studied following nasal allergen provocation and during natural seasonal pollen exposure. Immunotherapy inhibits early and late phase responses after allergen challenge (56, 67). Suppression is accompanied by a reduction in early increases in local nasal histamine, TAME-Esterase and tryptase concentrations in nasal fluid. Inhibition of late responses is associated with a decrease in eosinophils (68) and Th2 cytokines including IL-4, 5, 9 and 13 (69). A reduction following immunotherapy is also noted in nasal fluid levels of the CC chemokine eotaxin that contributes to eosinophil recruitment. Decreases in Th2 cytokines in nasal fluid have also been recorded following both subcutaneous and sublingual immunotherapy (69, 70). A double-blind trial of subcutaneous grass pollen immunotherapy resulted in decreases in effector cells including CD117+ (c-kit+) mast cells, (71) basophils (73) and eosinophils (72) in the nasal mucosa compared to pre-treatment that was significant compared to placebo-treated participants (73, 74). These local changes detected in nasal biopsies were accompanied by improvements in seasonal symptoms and a decrease in requirements for rescue medication. A direct correlation was noted between IL-5 and nasal mucosal eosinophil numbers and also between eosinophils and the severity of seasonal symptoms. The data suggest that IL-5-maintained nasal mucosal eosinophilia is a driver of symptoms during the pollen season that is ameliorated by subcutaneous immunotherapy. In house dust mite-sensitive patients, sublingual immunotherapy with mite extract inhibited local mucosal vascular ICAM-1 expression and also decreased local eosinophilia (73). These data illustrate that both sublingual and subcutaneous immunotherapy result in decreases in recruitment and/or activation of effector cells at allergic tissue sites.

Immunotherapy and T lymphocyte responses

Decreases in Th2 cells

Suppression of allergen-induced late nasal responses during subcutaneous grass pollen immunotherapy has been associated with decreases in CD4+ T cells and local IL-4 mRNA+ T cells in the nasal mucosa (74). These findings are supported by the finding of decreases in Th2 cytokines in nasal lining fluid after nasal challenge (69). Recent techniques that include *ex-vivo* tetramer analysis (75-78) have allowed the phenotyping and identification of peripheral circulating allergen-specific T cells (85-88). This has permitted the identification of key T cell surface markers such as CD27, CRTH2, CD161 and CCR4 associated with type 2 pro-allergic responses. In patients with grass pollen allergy, tetramer-specific T cells that did not express CD27 mostly expressed the surface markers CRTH2 and CCR4. This was in contrast to non-allergic individuals whose T cells expressed low CRTH2 and CCR4 and high levels of CD27. Patients with alder pollen allergy expressed a high frequency of $CD27^-$ Th2 cells that decreased after subcutaneous immunotherapy. Similarly, in the

GRASS trial (44), both (11) subcutaneous and sublingual immunotherapy resulted in clinical improvement during 2 years that was paralleled by a decrease in peripheral tetramer positive CRTH2+CCR4+CD27-CD4+Th2 cells. These changes were paralleled by a decrease in local nasal Th2 cytokines, including IL-4, IL-5 and IL-13 levels in nasal fluid following nasal allergen provocation. Both circulating tetramer-positive Th2 cells and local nasal Th2 cytokines rebounded during year 3, along with a deterioration in seasonal symptoms, one year after discontinuation of immunotherapy. The failure of 2 years immunotherapy (in contrast to 3 years continuous treatment (9, 10) to induce durable tolerance may have been related to this re-emergence of antigen-specific Th2 immunity.

Increases in T regulatory cells (Tregs)

Immune tolerance during immunotherapy has been shown to be associated with the induction of allergen-specific Tregs (79-84). Treg cells can be grouped into two subsets, natural Tregs that express the transcription factor FOXP3 and inducible Tregs (iTregs) that produce regulatory cytokines such as IL-10, IL-35 and TGF-β (58, 79, 85).

- Natural T regulatory cells (nTregs)

nTregs were first described by Sakaguchi (86). In addition to the transcription factor FOXP3, nTregs have increased expression of the IL-2 receptor (CD25) and low expression of the IL-7 receptor (CD127). nTregs are thought to exert their suppressive capacity in a direct cell-cell contact-dependent manner (87, 88). Functional roles have been proposed for membrane CTLA-4, surface-bound TGF-β the glucocorticoid-induced TNF receptor (GITR) and PD-1. nTregs have also been shown to modulate allergen-specific T cell responses in healthy, non-atopic individuals (89). Subcutaneous immunotherapy was associated with local increases in $FOXP3^{+}CD25^{+}$ T cells (80) in the nasal mucosa compared to untreated control subjects. Following sublingual grass pollen immunotherapy, immunofluorescence studies on sublingual biopsies identified increases in FOXP3+CD3+ cells in the sublingual mucosa (83). Human *in vitro* studies of biopsies of human buccal mucosa and associated lingual tonsils and adenoids identify the oropharyngeal mucosa as an environment rich in pro-tolerogenic dendritic cells and regulatory T cells (90, 91). Altered nTreg function has been associated with epigenetic modification at the FOXP3 promoter region. In a randomized controlled study of dual sublingual immunotherapy in participants allergic to both house dust mite and grass pollen, methylated CpG sites within the Foxp3 locus of enriched peripheral memory Treg cells were decreased after 12 months treatment (92),

- T Follicular (Tfh/Tfr) cells

T follicular helper (Tfh) cells are characterised by surface CXCR5, the transcription factor B-cell lymphoma 6 protein (Bcl6) and increased expression of IL-4, IL-21 and IL-6. Tfh cells reside in the marginal zones of germinal follicles within regional lymph nodes, where they provide essential help for B cell maturation and class switching. In 2004, a distinct population of FOXP3+ CXCR5 expressing FoxP3+ Treg cells were identified, that possessed the ability to migrate into germinal centres and suppress T and B cell responses (93, 94). However, it was not until 2011 that this population of cells was recognised as a distinct subset of CD4+ T cells with regulatory capacity, namely T follicular regulatory (Tfr) cells. One study has shown that memory Tfh cells were significantly reduced after immunotherapy (95). Moreover, Tfr cells from immunotherapy-treated patients were shown to have higher capacity to produce IL-10 compared to Tfh cells. When CXCR5+ Tfh cells were enriched from immunotherapy-treated donors and cultured in the presence of TCR stimulation and IL-2 for 5 days, flow cytometric analysis revealed an increase in Tfr cells. These findings highlight the plasticity of Tfr cells and their likely role in suppressing Th2 responses and IgE antibody production during immunotherapy (95).

- Inducible Tregs (iTregs)

iTreg cells produce either IL-10 (Tr1) or TGF-β (Th3) and have been shown to modulate allergen-driven T cell proliferative responses and Th2 cytokine release (79). Studies of nasal biopsies obtained before and at 2 years after grass pollen immunotherapy identified a shift in favour of local iTreg responses in the nasal mucosa. There was an increase in IL-10-expressing T cells during the pollen

season that was associated with an increase in serum IgG4 (96). Seasonal increases in TGF-□$^+$ T cells in the nasal mucosa correlated with increases in peripheral circulating IgA concentrations (50).

The induction of peripheral IL-10$^+$ Tregs was reported following grass and birch pollen sublingual immunotherapy (55, 81). A time-course study during subcutaneous grass pollen immunotherapy demonstrated that peripheral blood mononuclear cells obtained as early as 2-4 weeks during early updosing, when co-cultured with grass pollen allergen for 6 days, produced high levels of IL-10 in supernatants (56). This early IL-10 signal was closely paralleled by suppression of the allergen-induced late phase response (Fig. 3). Increases in PBMC IL-10 production and suppression of the late response was followed sequentially by increases in serum IgG4 at 6-8 weeks that peaked at 16 weeks, along with a parallel suppression of immediate skin responses. Post-immunotherapy serum was shown to have IgG-associated IgE-blocking activity for both basophil activation (increased allergen stimulated basophil CD63) and IgE-FAB inhibition that paralleled increases in IgG4. The *in vivo* time course of PBMC IL-10 production and associated changes in serum blocking antibodies, allergen-induced skin responses and hypothetical changes in Th2 lymphocytes during up-dosing, and maintenance of grass pollen immunotherapy for 3 years and during immunotherapy withdrawal are illustrated in Fig.3.

B Regulatory cells (Bregs)

Bregs are a subset of B cells that produce IL-10 and have the capacity to inhibit T cell and dendritic cell-mediated inflammatory responses and to maintain natural immunological tolerance (97). Purified populations of IL-10 producing Bregs in bee venom tolerant individuals exhibited high surface expression of CD25 and CD71 and low expression of CD73. These cells had the capacity to suppress bee venom specific T cell proliferation (98). Moreover, the provenance of allergen-specific IgG4 antibodies following bee venom immunotherapy was shown to be from phospholipase A2-specific IL-10$^+$ Bregs. In addition to IL-10, B regs have been shown to exert their suppressive capacity by production of TGF-□ and IL-35 (97). It is likely that during immunotherapy with grass pollen or house dust mite allergens, that similar Breg responses may be elicited. Whether the same phenotype is expressed by B cells following immunotherapy with inhalant allergens remains to be determined.

Th1 immune deviation

Suppression of Th2 immunity during both subcutaneous and sublingual immunotherapy has also been associated with immune deviation and induction of Th1 cells (9, 99). *In situ* hybridisation studies of the nasal mucosa following successful subcutaneous immunotherapy demonstrated increases in interferon-gamma mRNA+ T cells after allergen challenge that correlated with decreases in nasal symptoms during the pollen season (9). Pollen immunotherapy was associated with decreases in the ratio of IL-5/Interferon gamma mRNA+ cells in the mucosa and increases in nasal interferon-gamma protein in nasal fluid during natural seasonal allergen exposure (51). Similarly, subcutaneous grass pollen immunotherapy resulted in increases in IL-12 mRNA+ macrophages in the skin that accompanied suppression of late cutaneous responses and correlated positively with local IFN-gamma+ T cells and inversely with IL-4-expressing T cells (100). Evidence for/against Th1 deviation in peripheral blood studies has been more controversial (101, 107). One study suggested that the shift from Th2 to Th1 responses may have been related to activation-induced cell death of allergen-responder Th2 cells (102). During birch pollen subcutaneous immunotherapy, a transient increase in Bet v 1-specific IL-10 secreting cells at 3 months was followed at 12 months by a reduction in the ratio of allergen-specific Bet v 1-specific IL-5/ Bet v 1-specific IFN-gamma secreting T cells (103, 104). Moreover, survival of Th1 cells has been reported following deletion of Th2 cells (105).

Immunotherapy and Innate Lymphoid cells

The influence of immunotherapy on ILC2 cells has been studied in peripheral blood, but not in target organs, partly due to difficulties in identifying these cells that do not express cell lineage markers accessible to immunohistochemical localisation in tissues. Following grass pollen subcutaneous immunotherapy there was a marked inhibition of seasonal increases in lineage negative

CRTH2+CD127+ ILC2 cells that correlated with the severity of self-reported symptoms during the pollen season (26). These results were highly significant when compared to the seasonal increases in ILC2s observed in matched untreated seasonal allergic rhinitis controls. These data were supported by inhibition of seasonal increases in CD117+ (ckit+) ILC2s and in the proportion of IL-13+ILC2s as determined by intracellular cytokine staining. In a study of immunotherapy in participants with seasonal asthma (27), there was no change in the number of ILC2s although this is likely explained by the measurements having been performed out of season when the participants were asymptomatic. To or knowledge, there have been no reports of the influence of immunotherapy on innate epithelial derived cytokines that are known to be closely involved in the regulation of both local Th2-mediated events and innate lymphoid cells.

Immunotherapy and dendritic cells

The buccal mucosa is constantly exposed to foreign proteins in foods and represents a distinct pro-tolerogenic environment. *Ex vivo* studies of biopsies of buccal mucosa from grass pollen allergic patients have shown that oral mucosal Langerhans cells bind the major grass pollen allergen *Phleum pratense 5* (*Phl p 5*) in a dose- and time-dependent manner that plateaus at 5 minutes and leads to a decelerated maturation of oral Langerhans cells, in parallel with an enhanced migratory capacity and increased production of tolerogenic cytokines that include IL-10 and TGF-□ (106)

In a randomised controlled trial of sublingual immunotherapy, despite local increases in FOXP3+ T reg cells in the sublingual mucosal biopsies there was no change in local monocyte-derived dendritic cells, although CD1a+Langerhans cells were not specifically examined (83). However, the influence of allergen immunotherapy on subtypes of dendritic cells in the circulation has been studied. Polymerase chain reaction studies of peripheral whole blood samples taken before and after 4 months sublingual grass pollen immunotherapy was used to characterise changes in dendritic cell phenotype. A significant increase in the number of dendritic cells with a DCreg phenotype was observed (32). The DCreg signature was reflected by an increase in mRNA expression for Stabilin-1 and C1Q, as predicted from the *in vitro* studies (32). Interestingly, this DCreg signature was observed only in those 'responders' to immunotherapy as reflected by a significant decrease in rhinoconjunctivitis symptoms (32). In support of these findings, one year's treatment with sublingual immunotherapy in mite-allergic children resulted in peripheral dendritic cells that showed a reduced capacity to produce IL-12 increased IL-10 secretion and a blunted maturation capacity (107).

Biomarkers

A greater understanding of underlying mechanisms of immunotherapy has raised potential approaches to develop biomarkers to predict/assess the clinical response to treatment and for identifying responders and non-responders. International guidelines highlight the need for quantitative and validated measurements (108). A European Academy of Allergy and Clinical Immunology Task Force reported a consensus statement on potential biomarkers of allergen immunotherapy (101). These were classified into seven domains (Table 1): (A) IgE (total IgE, specific IgE and sIgE/Total IgE ratio), (B) IgG-subclasses (sIgG1, sIgG4 including sIgE/IgG4 ratio), (C) Serum inhibitory activity for IgE (IgE-FAB), (D) Basophil activation, (E) Cytokines and Chemokines, (F) Cellular markers (T regulatory cells, B regulatory cells and dendritic cells) and (G) *In vivo* biomarkers which include provocation tests (108).

IgE (total IgE, specific IgE and sIgE/total IgE ratio)

Inclusion criteria for the initiation of immunotherapy rely on a history of symptoms upon exposure to allergen (1, 109, 110) and elevated serum allergen-specific IgE (sIgE) to the clinically relevant allergen as measured by the ImmunoCAP® system. Patient selection has been refined by the availability of recombinant allergen technology to identify specific IgE to the major allergen determinants and to recognise irrelevant cross-reacting allergens (111). An initial early increase in sIgE during both subcutaneous (58) and sublingual (112) pollen immunotherapy has been shown to be followed by blunting of seasonal increases in sIgE. In long-term studies of subcutaneous immunotherapy, a gradual decrease in sIgE over several years (43) was observed although there was no clear association between changes in sIgE and the magnitude of the clinical response (50,

96). Moreover, specific IgE measured against major allergens (i.e birch pollen allergen) can be a useful tool to detect irrelevant cross-reactive molecule such as profiling (PR10- Bet v2) which can lead to false positive skin prick test and potentially be used as predictor of immunotherapy failure. The ratio of specific IgE/Total serum IgE at baseline was reported to correlate with clinical response to immunotherapy (113,114), although others (52, 59, 115) have not replicated these findings.

IgG-subclasses (sIgG1, sIgG4 and sIgE/IgG4 ratio)

Immune reactive IgG1 and IgG4 antibodies can also be measured by ImmunoCAP (Fig.4a) and by allergen microarray (for example ImmunoSolid Allergen Chip Assay). Allergen-specific IgG subtypes, including sIgG1 and particularly sIgG4 have been shown to be elevated in the range of 10- to 100-fold compared to baseline values during immunotherapy, although with no consistent correlation with clinical response to treatment (79, 95, 105). ISAC can be performed using very small volumes of serum or nasal fluid. Rather than an indicator of efficacy, a large component of the observed elevations in serum immunoreactive allergen-specific IgG or IgG4 levels are likely to reflect allergen exposure and could potentially be used to monitor patients' adherence to immunotherapy regimens (108). A decrease in the sIgE/IgG4 ratio has been reported following subcutaneous immunotherapy and was associated with a reduction in late cutaneous skin reaction (101). However, this finding has not been reproduced in other studies (101).

Serum IgE inhibitory activity (IgE-FAB and ELIFAB)

IgG-associated IgE-inhibitory activity can be assessed by a flow-cytometry based assay (IgE-FAB) that has been validated according to the International Conference on Harmonisation (ICH) guidelines (116). This assay measures the ability of IgG-containing serum obtained after immunotherapy to inhibit the Fc□RII-dependent binding of allergen-IgE complexes to B cells, a surrogate for IgE-facilitated antigen presentation to T cells (Fig. 4b). Alternative approaches include the enzyme-linked immunosorbent-facilitated antigen binding assay (ELIFAB) (66). The IgE-FAB assay is reproducible but technically complex and currently confined to specialized laboratories (58). The ELIFAB assay is less complex and may also be used to assess functional IgG responses. The limited data available suggests a modest correlation between IgE-FAB and ELIFAB results and the clinical response to immunotherapy over and above that observed when simply measuring immunoreactive IgG levels (58, 66). This is likely related to IgE-FAB and ELIFAB providing a further functional measure of affinity and/or avidity of antibody binding.

Basophil activation

In flow cytometry-based assays using whole blood, basophil activation can be studied by monitoring expression of surface markers such as CD63 and CD203c. While CD63 expression measures degranulation of basophils (117), CD203c is a specific basophil marker that additionally measures IL-3-dependent activation of basophils. A novel functional assay that detects intracellular staining of phycoerythrin-conjugated diamine oxidase (DAO) has also been validated. DAO binds tightly to its substrate histamine, such that allergen stimulation results in a reduction in basophil intracellular DAO, proportional to the amount of intracellular histamine released. This reduction has been detected during both subcutaneous and sublingual immunotherapy (118, 119) (Fig.4 c and d).

Cytokines and Chemokines

Recent advances in miniaturised multiplex cytokine analysis using Meso Scale Discovery (MSD®) and Luminex® platforms have enabled the measurement of cytokines and chemokines in nasal fluid that increase in response to allergen provocation and are modified by immunotherapy (31, 32, 69).

Cellular and molecular markers

Cellular markers of potential use for assessing or predicting response to immunotherapy include phenotypic markers for T cells (Th2, Treg, Tfh/Tfr and Th1) and subpopulations of Bregs, all of which have been shown to be modified during immunotherapy, principally by flow cytometry. Whereas in clinical trials these markers have been able to distinguish between treatment groups and correlate overall with clinical outcomes of efficacy (69, 79, 84, 120, 121), they have been unable to distinguish

responders from non-responders or predict response in individual subjects. Furthermore, there is a need for optimal cell processing and transfer and storage of samples such that complex flow cytometry for multiple T and B cell associated markers is beyond the scope of routine clinical laboratories.

Dendritic cells (DCs), express distinct molecular markers according to their T cell differentiating capacity. Regulatory DCs (DCregs) preferentially express C1Q and Fc□RIII that favor preferential T regulatory cell development (32) whereas DC2s express CD141, GATA3, OX40L and RIPK4 that favor polarizing naïve T cells into Th2 cells (33). Expression of these markers in PBMCs were evaluated before and at 2 and 4 months after sublingual grass pollen immunotherapy. This qRT-PCR-based method correlated with clinical outcomes (33, 122). Remarkably, an optimal combination of five molecular markers that included three DC2 markers (CD141, GATA3, and RIPK4) and two DCregs markers (C1QA and FcγRIIIA) were able to distinguish clinical responders from non-responders with a sensitivity of 90.48% and a specificity of 61.9%. These interesting results demand further evaluation in clinical trials and ultimately in clinical practice.

***In vivo* biomarkers**

'*In vivo* biomarkers' refer to the use of allergen provocation tests to evaluate patients' allergen-specific reactivity before and after treatment. Provocation tests include skin prick tests, intradermal tests and nasal, conjunctival and bronchial provocation tests (101). The European Medicines Agency (EMA) elaborated on their relevance for proof of concept for novel approaches and for dose-finding in phase II clinical trials and as supportive secondary endpoints of efficacy during phase IIb/III trials of allergen immunotherapy (123).

Summary

In the presence of a clinical history of symptoms on exposure to relevant clinical allergens, a positive serum allergen-specific IgE (and/or positive skin prick test) is the single most relevant biomarker for selection of patients for allergen immunotherapy. However, neither the level of allergen-specific IgE, nor allergen-specific IgG/IgG4 concentrations are able to reliably predict or monitor the clinical response to immunotherapy. At present, the ratio of IgE/total IgE at baseline remains under evaluation as a possible predictor of response. Functional assays of IgG-associated inhibitory activity for IgE (IgE-FAB and ELIFAB) have better correlation with clinical response in clinical trials than immunoreactive IgG/G4 levels but do not predict efficacy in individual subjects. Serum-based assays have the advantage of ease of sample handling and storage and it seems likely that IgG/IgG4 levels may be more effective as a surrogate for compliance with treatment which could be of particular valuable for monitoring patients on sublingual immunotherapy. The various cellular assays reported are restricted to specialist centres. Basophil responsiveness assays and T/B cell phenotypic assays require flow cytometry and involve, respectively, either processing of fresh blood or complex cell separation and storage protocols. They are informative for proof of concept in clinical trials but are not feasible for routine clinical practice. Studies of dendritic cell phenotype by use of RT-PCR on whole blood or PBMCs have been shown to separate clinical responders and non-responders to grass pollen sublingual immunotherapy and further studies are needed to replicate these findings and assess their value in individual patients. Provocation testing in skin and target organs is valuable for proof of concept for novel allergen products and for dose-ranging studies but can only be supportive as secondary efficacy outcomes in clinical trials of immunotherapy.

Novel approaches for Immunotherapy

A better understanding of mechanisms should ideally translate into novel immunotherapy approaches (1, 124). The aim has been to improve efficacy over standard allergen extract-based extracts whilst permitting shorter, safer and more convenient strategies for patients. Alternative routes such as epicutaneous (125) and intralymphatic (126, 127) approaches have proved safer than conventional subcutaneous immunotherapy although there are no head-to-head trials to assess comparative efficacy. The intradermal route was ineffective for grass pollen allergen and may have exacerbated seasonal symptoms (128). Targeting immune deviation using the TLR4 agonist monophosphoryl lipid A in combination with subcutaneous grass pollen allergoid immunotherapy was

effective with four pre-seasonal injections without an increase in side-effects (129). The use of Bacterial DNA oligonucleotides rich in CpG sequences, covalently linked to the major ragweed allergen Ambosia a 1, was effective in a phase II trial, possibly by inducing T regs and/or immune deviation (130), although this approach failed at phase III (94). Targeting IgE or Type 2 cytokines (IL-4, IL-5) has been successful in reducing exacerbations in asthma, although without durable effects after discontinuation (131). Anti-IgE in combination with allergen immunotherapy was highly effective in reducing the risk of systemic allergic reactions (132). The combination of anti-IL-4 with subcutaneous allergen immunotherapy was effective in suppressing circulating Th2 cells and allergen-induced late responses but showed no advantage over allergen extract alone (133). Current novel approaches to reduce systemic adverse events include the use of engineered recombinant hypoallergenic molecules (111) and allergen peptide based approaches that specifically target T cell epitopes (134, 135) and B cell epitope based strategies to selectively promote allergen-specific IgG responses (136, 137). For the future, targeting the innate immune response using antibodies directed against the epithelial cytokines IL-33, IL-25 or TSLP in combination with allergen immunotherapy would be an attractive combination strategy to likely reduce inflammation, supress ILC2s and and promote a more tolerogenic dendritic cell phenotype.

Figure legends:

Figure 1: Figure 1: Mechanisms of Allergic inflammation. Summary of immunologic response to initial triggers of allergic sensitization and allergic inflammation following re-exposure to inhalant allergens (see text).

Figure 2: Mechanisms of AIT. During initial sensitization phase in allergic rhinitis, low allergen exposure at nasal mucosal surface results in activation of epithelial cells which then activate dendritic cells (DCs). DCs uptake and present antigens to naïve T cells to induce allergic helper T cell type 2 (Th2A) responses and Ig-E facilitated antigen presentation. Subsequent allergen re-exposure leads to mast cell and basophil degranulation, causing classic early phase reactions. Subsequent infiltration of other leukocytes leads to late phase allergic inflammation. High dose allergen exposure by immunotherapy restores DC function that produce IL-12, IL-27, IL-10 and promotes immune deviation from a Th2 to a Th1 response and induction of Treg and Breg cells (including other B cell subsets) that produce IgA, IgG and IgG4 blocking antibodies cells. The suppressive activities of Treg, Bregs and IgG-blocking activity is indicated by the red arrows.

Figure 3. the time-course effect of immunotherapy on surrogate clinical markers (early and late cutaneous responses) associated immunological events during induction and maintenance phases of immunotherapy (desensitisation) as well as their persistence following withdrawal of treatment (tolerance phase), are summarised in Fig.3.

Figure 4. Induction of IgG4 antibodies and associated IgE-inhibitory activity during immunotherapy. A) specific IgG4 levels, B) IgE-facilitated allergen binding to B cells, C) histamine release at single cell level using labelled Diamine Oxidase (Elevated intracellular DAO demonstrates inhibition of histamine release) and D) Histamine ELISA. Measurements were from untreated grass allergic individuals (SAR), subcutaneous (SCIT-) and sublingual (SLIT-)treated patients and those who had completed 3 years SLIT followed by discontinuation for up to 3 years (SLIT-TOL). Data are expressed as individual data, quintile box plots with contour. *P < .05 and ***P < .001, Mann-Whitney U test (16).

References

1. Burks AW, Calderon MA, Casale T, Cox L, Demoly P, Jutel M*, et al*. Update on allergy immunotherapy: American academy of allergy, asthma & Immunology/European academy of allergy and clinical Immunology/PRACTALL consensus report. J Allergy Clin Immunol. 2013 May;131(5):1288,96.e3.

2. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: Therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol. 1998 Oct;102(4 Pt 1):558-62.

3. Dhami S, Nurmatov U, Arasi S, Khan T, Asaria M, Zaman H*, et al*. Allergen immunotherapy for allergic rhinoconjunctivitis: A systematic review and meta-analysis. Allergy. 2017 Nov;72(11):1597-631.

4. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, van Wijk RG*, et al*. EAACI guidelines on allergen immunotherapy: Allergic rhinoconjunctivitis. Allergy. 2017 Sep 23.

5. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH*, et al*. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: A randomized clinical trial. JAMA. 2016 Apr 26;315(16):1715-25.

6. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W*, et al*. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med. 1999 Aug 12;341(7):468-75.

7. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. J Allergy Clin Immunol. 2005 Sep;116(3):608-13.

8. Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S*, et al*. Sublingual immunotherapy: World allergy organization position paper 2013 update. World Allergy Organ J. 2014 Mar 28;7(1):6,4551-7-6.

9. Durham SR, Ying S, Varney VA, Jacobson MR, Sudderick RM, Mackay IS*, et al*. Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4+ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma. J Allergy Clin Immunol. 1996 Jun;97(6):1356-65.

10. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK*, et al*. SQ-standardized sublingual grass immunotherapy: Confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol. 2012 Mar;129(3):717,725.e5.

11. Wu YC, James LK, Vander Heiden JA, Uduman M, Durham SR, Kleinstein SH*, et al*. Influence of seasonal exposure to grass pollen on local and peripheral blood IgE repertoires in patients with allergic rhinitis. J Allergy Clin Immunol. 2014 Sep;134(3):604-12.

12. Creticos PS, Peters SP, Adkinson NF,Jr, Naclerio RM, Hayes EC, Norman PS*, et al*. Peptide leukotriene release after antigen challenge in patients sensitive to ragweed. N Engl J Med. 1984 Jun 21;310(25):1626-30.

13. Naclerio RM, Proud D, Togias AG, Adkinson NF,Jr, Meyers DA, Kagey-Sobotka A*, et al*. Inflammatory mediators in late antigen-induced rhinitis. N Engl J Med. 1985 Jul 11;313(2):65-70.

14. Castells M, Schwartz LB. Tryptase levels in nasal-lavage fluid as an indicator of the immediate allergic response. J Allergy Clin Immunol. 1988 Sep;82(3 Pt 1):348-55.

15. Eifan AO, Orban NT, Jacobson MR, Durham SR. Severe persistent allergic rhinitis. inflammation but no histologic features of structural upper airway remodeling. Am J Respir Crit Care Med. 2015 Dec 15;192(12):1431-9.

16. Shamji MH, Layhadi JA, Scadding GW, Cheung DK, Calderon MA, Turka LA*, et al*. Basophil expression of diamine oxidase: A novel biomarker of allergen immunotherapy response. J Allergy Clin Immunol. 2015 Apr;135(4):913,21.e9.

17. Eifan AO, Durham SR. Pathogenesis of rhinitis. Clin Exp Allergy. 2016 Sep;46(9):1139-51.

18. Matsuoka T, Shamji MH, Durham SR. Allergen immunotherapy and tolerance. Allergol Int. 2013 Dec;62(4):403-13.

19. Gould HJ, Ramadani F. IgE responses in mouse and man and the persistence of IgE memory. Trends Immunol. 2015 Jan;36(1):40-8.

20. Wechsler ME, Fulkerson PC, Bochner BS, Gauvreau GM, Gleich GJ, Henkel T*, et al*. Novel targeted therapies for eosinophilic disorders. J Allergy Clin Immunol. 2012 Sep;130(3):563-71.

21. Sehra S, Yao W, Nguyen ET, Glosson-Byers NL, Akhtar N, Zhou B*, et al*. TH9 cells are required for tissue mast cell accumulation during allergic inflammation. J Allergy Clin Immunol. 2015 Aug;136(2):433,40.e1.

22. Durham SR, Ying S, Varney VA, Jacobson MR, Sudderick RM, Mackay IS*, et al*. Cytokine messenger RNA expression for IL-3, IL-4, IL-5, and granulocyte/macrophage-colony-stimulating factor in the nasal mucosa after local allergen provocation: Relationship to tissue eosinophilia. J Immunol. 1992 Apr 15;148(8):2390-4.

23. Spits H, Cupedo T. Innate lymphoid cells: Emerging insights in development, lineage relationships, and function. Annu Rev Immunol. 2012;30:647-75.

24. Artis D, Spits H. The biology of innate lymphoid cells. Nature. 2015 Jan 15;517(7534):293-301.

25. Doherty TA, Scott D, Walford HH, Khorram N, Lund S, Baum R*, et al*. Allergen challenge in allergic rhinitis rapidly induces increased peripheral blood type 2 innate lymphoid cells that express CD84. J Allergy Clin Immunol. 2014 Apr;133(4):1203-5.

26. Lao-Araya M, Steveling E, Scadding GW, Durham SR, Shamji MH. Seasonal increases in peripheral innate lymphoid type 2 cells are inhibited by subcutaneous grass pollen immunotherapy. J Allergy Clin Immunol. 2014 Nov;134(5):1193,5.e4.

27. Lombardi V, Beuraud C, Neukirch C, Moussu H, Morizur L, Horiot S*, et al*. Circulating innate lymphoid cells are differentially regulated in allergic and nonallergic subjects. J Allergy Clin Immunol. 2016 Jul;138(1):305-8.

28. Bal SM, Bernink JH, Nagasawa M, Groot J, Shikhagaie MM, Golebski K*, et al*. IL-1beta, IL-4 and IL-12 control the fate of group 2 innate lymphoid cells in human airway inflammation in the lungs. Nat Immunol. 2016 Jun;17(6):636-45.

29. Hams E, Locksley RM, McKenzie AN, Fallon PG. Cutting edge: IL-25 elicits innate lymphoid type 2 and type II NKT cells that regulate obesity in mice. J Immunol. 2013 Dec 1;191(11):5349-53.

30. Imai Y, Yasuda K, Sakaguchi Y, Haneda T, Mizutani H, Yoshimoto T*, et al*. Skin-specific expression of IL-33 activates group 2 innate lymphoid cells and elicits atopic dermatitis-like inflammation in mice. Proc Natl Acad Sci U S A. 2013 Aug 20;110(34):13921-6.

31. Kim BS, Siracusa MC, Saenz SA, Noti M, Monticelli LA, Sonnenberg GF*, et al*. TSLP elicits IL-33-independent innate lymphoid cell responses to promote skin inflammation. Sci Transl Med. 2013 Jan 30;5(170):170ra16.

32. Zimmer A, Bouley J, Le Mignon M, Pliquet E, Horiot S, Turfkruyer M*, et al*. A regulatory dendritic cell signature correlates with the clinical efficacy of allergen-specific sublingual immunotherapy. J Allergy Clin Immunol. 2012 Apr;129(4):1020-30.

33. Gueguen C, Bouley J, Moussu H, Luce S, Duchateau M, Chamot-Rooke J*, et al*. Changes in markers associated with dendritic cells driving the differentiation of either TH2 cells or regulatory T cells correlate with clinical benefit during allergen immunotherapy. J Allergy Clin Immunol. 2016 Feb;137(2):545-58.

34. Mjosberg J, Spits H. Human innate lymphoid cells. J Allergy Clin Immunol. 2016 Nov;138(5):1265-76.

35. Xue L, Salimi M, Panse I, Mjosberg JM, McKenzie AN, Spits H*, et al*. Prostaglandin D2 activates group 2 innate lymphoid cells through chemoattractant receptor-homologous molecule expressed on TH2 cells. J Allergy Clin Immunol. 2014 Apr;133(4):1184-94.

36. Kouser L, Kappen J, Walton RP, Shamji MH. Update on biomarkers to monitor clinical efficacy response during and post treatment in allergen immunotherapy. Curr Treat Options Allergy. 2017;4(1):43-53.

37. Pilette C, Jacobson MR, Ratajczak C, Detry B, Banfield G, VanSnick J*, et al*. Aberrant dendritic cell function conditions Th2-cell polarization in allergic rhinitis. Allergy. 2013 Mar;68(3):312-21.

38. Palomares O, O'Mahony L, Akdis CA. The many routes of dendritic cells to ensure immune regulation. J Allergy Clin Immunol. 2011 Jun;127(6):1541-2.

39. Palomares O, Akdis M, Martin-Fontecha M, Akdis CA. Mechanisms of immune regulation in allergic diseases: The role of regulatory T and B cells. Immunol Rev. 2017 Jul;278(1):219-36.

40. Dawicki W, Li C, Town J, Zhang X, Gordon JR. Therapeutic reversal of food allergen sensitivity by mature retinoic acid-differentiated dendritic cell induction of LAG3+CD49b-Foxp3- regulatory T cells. J Allergy Clin Immunol. 2017 May;139(5):1608,1620.e3.

41. van der Aar AM, Sibiryak DS, Bakdash G, van Capel TM, van der Kleij HP, Opstelten DJ*, et al*. Vitamin D3 targets epidermal and dermal dendritic cells for induction of distinct regulatory T cells. J Allergy Clin Immunol. 2011 Jun;127(6):1532,40.e7.

42. Semitekolou M, Morianos I, Banos A, Konstantopoulos D, Adamou-Tzani M, Sparwasser T*, et al*. Dendritic cells conditioned by activin A-induced regulatory T cells exhibit enhanced tolerogenic properties and protect against experimental asthma. J Allergy Clin Immunol. 2017 Jun 1.

43. Gleich GJ, Zimmermann EM, Henderson LL, Yunginger JW. Effect of immunotherapy on immunoglobulin E and immunoglobulin G antibodies to ragweed antigens: A six-year prospective study. J Allergy Clin Immunol. 1982 Oct;70(4):261-71.

44. Scadding GW, Calderon MA, Shamji MH, Eifan AO, Penagos M, Dumitru F*, et al*. Effect of 2 years of treatment with sublingual grass pollen immunotherapy on nasal response to allergen challenge at 3 years among patients with moderate to severe seasonal allergic rhinitis: The GRASS randomized clinical trial. JAMA. 2017 Feb 14;317(6):615-25.

45. Cooke RA, Barnard JH, Hebald S, Stull A. Serological evidence of immunity with coexisting sensitization in a type of human allergy (hay fever). J Exp Med. 1935 Nov 30;62(6):733-50.

46. Lichtenstein LM, Holtzman NA, Burnett LS. A quantitative in vitro study of the chromatographic distribution and immunoglobulin characteristics of human blocking antibody. J Immunol. 1968 Aug;101(2):317-24.

47. Platts-Mills TA, von Maur RK, Ishizaka K, Norman PS, Lichtenstein LM. IgA and IgG anti-ragweed antibodies in nasal secretions. quantitative measurements of antibodies and correlation with inhibition of histamine release. J Clin Invest. 1976 Apr;57(4):1041-50.

48. James LK, Shamji MH, Walker SM, Wilson DR, Wachholz PA, Francis JN*, et al*. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. J Allergy Clin Immunol. 2011 Feb;127(2):509,516.e1-5.

49. Renand A, Archila LD, McGinty J, Wambre E, Robinson D, Hales BJ*, et al*. Chronic cat allergen exposure induces a TH2 cell-dependent IgG4 response related to low sensitization. J Allergy Clin Immunol. 2015 Dec;136(6):1627,1635.e13.

50. Pilette C, Nouri-Aria KT, Jacobson MR, Wilcock LK, Detry B, Walker SM*, et al*. Grass pollen immunotherapy induces an allergen-specific IgA2 antibody response associated with mucosal TGF-beta expression. J Immunol. 2007 Apr 1;178(7):4658-66.

51. Wachholz PA, Soni NK, Till SJ, Durham SR. Inhibition of allergen-IgE binding to B cells by IgG antibodies after grass pollen immunotherapy. J Allergy Clin Immunol. 2003 Nov;112(5):915-22.

52. Reisinger J, Horak F, Pauli G, van Hage M, Cromwell O, Konig F*, et al*. Allergen-specific nasal IgG antibodies induced by vaccination with genetically modified allergens are associated with reduced nasal allergen sensitivity. J Allergy Clin Immunol. 2005 Aug;116(2):347-54.

53. Oefner CM, Winkler A, Hess C, Lorenz AK, Holecska V, Huxdorf M*, et al*. Tolerance induction with T cell-dependent protein antigens induces regulatory sialylated IgGs. J Allergy Clin Immunol. 2012 Jun;129(6):1647,55.e13.

54. Gleich GJ. The late phase of the immunoglobulin E-mediated reaction: A link between anaphylaxis and common allergic disease? J Allergy Clin Immunol. 1982 Sep;70(3):160-9.

55. Scadding GW, Calderon MA, Bellido V, Koed GK, Nielsen NC, Lund K*, et al*. Optimisation of grass pollen nasal allergen challenge for assessment of clinical and immunological outcomes. J Immunol Methods. 2012 Oct 31;384(1-2):25-32.

56. Francis JN, James LK, Paraskevopoulos G, Wong C, Calderon MA, Durham SR*, et al*. Grass pollen immunotherapy: IL-10 induction and suppression of late responses precedes IgG4 inhibitory antibody activity. J Allergy Clin Immunol. 2008 May;121(5):1120,1125.e2.

57. Shamji MH, Durham SR. Mechanisms of immunotherapy to aeroallergens. Clin Exp Allergy. 2011 Sep;41(9):1235-46.

58. Shamji MH, Ljorring C, Francis JN, Calderon MA, Larche M, Kimber I*, et al*. Functional rather than immunoreactive levels of IgG4 correlate closely with clinical response to grass pollen immunotherapy. Allergy. 2012 Feb;67(2):217-26.

59. Eifan AO, Akkoc T, Yildiz A, Keles S, Ozdemir C, Bahceciler NN*, et al*. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: An open randomized controlled trial. Clin Exp Allergy. 2010 Jun;40(6):922-32.

60. Demoly P, Kleine-Tebbe J, Rehm D. Clinical benefits of treatment with SQ house dust mite sublingual tablet in house dust mite allergic rhinitis. Allergy. 2017 Mar 8.

61. Aalberse RC, Schuurman J. IgG4 breaking the rules. Immunology. 2002 Jan;105(1):9-19.

62. Rispens T, Ooijevaar-de Heer P, Bende O, Aalberse RC. Mechanism of immunoglobulin G4 fab-arm exchange. J Am Chem Soc. 2011 Jul 6;133(26):10302-11.

63. van Neerven RJ, Wikborg T, Lund G, Jacobsen B, Brinch-Nielsen A, Arnved J*, et al*. Blocking antibodies induced by specific allergy vaccination prevent the activation of CD4+ T cells by inhibiting serum-IgE-facilitated allergen presentation. J Immunol. 1999 Sep 1;163(5):2944-52.

64. Wurtzen PA, Lund G, Lund K, Arvidsson M, Rak S, Ipsen H. A double-blind placebo-controlled birch allergy vaccination study II: Correlation between inhibition of IgE binding, histamine release and facilitated allergen presentation. Clin Exp Allergy. 2008 Aug;38(8):1290-301.

65. Burton OT, Tamayo JM, Stranks AJ, Koleoglou KJ, Oettgen HC. Allergen-specific IgG antibody signaling through FcgammaRIIb promotes food tolerance. J Allergy Clin Immunol. 2017 May 4.

66. Shamji MH, Francis JN, Wurtzen PA, Lund K, Durham SR, Till SJ. Cell-free detection of allergen-IgE cross-linking with immobilized phase CD23: Inhibition by blocking antibody responses after immunotherapy. J Allergy Clin Immunol. 2013 Oct;132(4):1003,5.e1-4.

67. Iliopoulos O, Proud D, Adkinson NF,Jr, Creticos PS, Norman PS, Kagey-Sobotka A*, et al*. Effects of immunotherapy on the early, late, and rechallenge nasal reaction to provocation with allergen: Changes in inflammatory mediators and cells. J Allergy Clin Immunol. 1991 Apr;87(4):855-66.

68. Furin MJ, Norman PS, Creticos PS, Proud D, Kagey-Sobotka A, Lichtenstein LM*, et al*. Immunotherapy decreases antigen-induced eosinophil cell migration into the nasal cavity. J Allergy Clin Immunol. 1991 Jul;88(1):27-32.

69. Scadding GW, Eifan AO, Lao-Araya M, Penagos M, Poon SY, Steveling E*, et al*. Effect of grass pollen immunotherapy on clinical and local immune response to nasal allergen challenge. Allergy. 2015 Jun;70(6):689-96.

70. Amadee R, Shamji MH, Harris KM, Qin T, Wambre E, Scadding GW*, et al*. Synchronous immune alterations mirror clinical response during allergen immunotherapy. . Journal of Allergy and Clinical Immunology. 2017;Favourably reviewed.:Revision under review.

71. Nouri-Aria KT, Pilette C, Jacobson MR, Watanabe H, Durham SR. IL-9 and c-kit+ mast cells in allergic rhinitis during seasonal allergen exposure: Effect of immunotherapy. J Allergy Clin Immunol. 2005 Jul;116(1):73-9.

72. Wilson DR, Nouri-Aria KT, Walker SM, Pajno GB, O'Brien F, Jacobson MR*, et al*. Grass pollen immunotherapy: Symptomatic improvement correlates with reductions in eosinophils and IL-5 mRNA expression in the nasal mucosa during the pollen season. J Allergy Clin Immunol. 2001 Jun;107(6):971-6.

73. Passalacqua G, Albano M, Fregonese L, Riccio A, Pronzato C, Mela GS*, et al*. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. Lancet. 1998 Feb 28;351(9103):629-32.

74. Tulic MK, Fiset PO, Christodoulopoulos P, Vaillancourt P, Desrosiers M, Lavigne F*, et al*. Amb a 1-immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response. J Allergy Clin Immunol. 2004 Feb;113(2):235-41.

75. Wambre E, Bajzik V, DeLong JH, O'Brien K, Nguyen QA, Speake C*, et al*. A phenotypically and functionally distinct human TH2 cell subpopulation is associated with allergic disorders. Sci Transl Med. 2017 Aug 2;9(401):10.1126/scitranslmed.aam9171.

76. Wambre E. Effect of allergen-specific immunotherapy on CD4+ T cells. Curr Opin Allergy Clin Immunol. 2015 Dec;15(6):581-7.

77. Wambre E, DeLong JH, James EA, Torres-Chinn N, Pfutzner W, Mobs C*, et al*. Specific immunotherapy modifies allergen-specific CD4(+) T-cell responses in an epitope-dependent manner. J Allergy Clin Immunol. 2014 Mar;133(3):872,9.e7.

78. Wambre E, DeLong JH, James EA, LaFond RE, Robinson D, Kwok WW. Differentiation stage determines pathologic and protective allergen-specific CD4+ T-cell outcomes during specific immunotherapy. J Allergy Clin Immunol. 2012 Feb;129(2):544,51, 551.e1-7.

79. Bohle B, Kinaciyan T, Gerstmayr M, Radakovics A, Jahn-Schmid B, Ebner C. Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation. J Allergy Clin Immunol. 2007 Sep;120(3):707-13.

80. Radulovic S, Jacobson MR, Durham SR, Nouri-Aria KT. Grass pollen immunotherapy induces Foxp3-expressing CD4+ CD25+ cells in the nasal mucosa. J Allergy Clin Immunol. 2008 Jun;121(6):1467,72, 1472.e1.

81. O'Hehir RE, Gardner LM, de Leon MP, Hales BJ, Biondo M, Douglass JA*, et al*. House dust mite sublingual immunotherapy: The role for transforming growth factor-beta and functional regulatory T cells. Am J Respir Crit Care Med. 2009 Nov 15;180(10):936-47.

82. Rolland JM, Gardner LM, O'Hehir RE. Functional regulatory T cells and allergen immunotherapy. Curr Opin Allergy Clin Immunol. 2010 Dec;10(6):559-66.

83. Scadding GW, Shamji MH, Jacobson MR, Lee DI, Wilson D, Lima MT*, et al*. Sublingual grass pollen immunotherapy is associated with increases in sublingual Foxp3-expressing cells and elevated allergen-specific immunoglobulin G4, immunoglobulin A and serum inhibitory activity for immunoglobulin E-facilitated allergen binding to B cells. Clin Exp Allergy. 2010 Apr;40(4):598-606.

84. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: Multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol. 2014 Mar;133(3):621-31.

85. Shamji MH, Ljorring C, Wurtzen PA. Predictive biomarkers of clinical efficacy of allergen-specific immunotherapy: How to proceed. Immunotherapy. 2013 Mar;5(3):203-6.

86. Sakaguchi S, Vignali DA, Rudensky AY, Niec RE, Waldmann H. The plasticity and stability of regulatory T cells. Nat Rev Immunol. 2013 Jun;13(6):461-7.

87. Sakaguchi S, Sakaguchi N. Regulatory T cells in immunologic self-tolerance and autoimmune disease. Int Rev Immunol. 2005 May-Aug;24(3-4):211-26.

88. Nakamura K, Kitani A, Strober W. Cell contact-dependent immunosuppression by CD4(+)CD25(+) regulatory T cells is mediated by cell surface-bound transforming growth factor beta. J Exp Med. 2001 Sep 3;194(5):629-44.

89. Ling EM, Smith T, Nguyen XD, Pridgeon C, Dallman M, Arbery J*, et al*. Relation of CD4+CD25+ regulatory T-cell suppression of allergen-driven T-cell activation to atopic status and expression of allergic disease. Lancet. 2004 Feb 21;363(9409):608-15.

90. Palomares O, Ruckert B, Jartti T, Kucuksezer UC, Puhakka T, Gomez E*, et al*. Induction and maintenance of allergen-specific FOXP3+ treg cells in human tonsils as potential first-line organs of oral tolerance. J Allergy Clin Immunol. 2012 Feb;129(2):510,20, 520.e1-9.

91. Kucuksezer UC, Palomares O, Ruckert B, Jartti T, Puhakka T, Nandy A*, et al*. Triggering of specific toll-like receptors and proinflammatory cytokines breaks allergen-specific T-cell tolerance in human tonsils and peripheral blood. J Allergy Clin Immunol. 2013 Mar;131(3):875-85.

92. Swamy RS, Reshamwala N, Hunter T, Vissamsetti S, Santos CB, Baroody FM*, et al*. Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy. J Allergy Clin Immunol. 2012 Jul;130(1):215,24.e7.

93. Varricchi G, Harker J, Borriello F, Marone G, Durham SR, Shamji MH. T follicular helper (tfh) cells in normal immune responses and in allergic disorders. Allergy. 2016 Aug;71(8):1086-94.

94. Sage PT, Sharpe AH. T follicular regulatory cells. Immunol Rev. 2016 May;271(1):246-59.

95. Schulten V, Tripple V, Seumois G, Qian Y, Scheuermann RH, Fu Z*, et al*. Allergen-specific immunotherapy modulates the balance of circulating tfh and tfr cells. J Allergy Clin Immunol. 2017 May 12.

96. Nouri-Aria KT, Wachholz PA, Francis JN, Jacobson MR, Walker SM, Wilcock LK*, et al*. Grass pollen immunotherapy induces mucosal and peripheral IL-10 responses and blocking IgG activity. J Immunol. 2004 Mar 1;172(5):3252-9.

97. Rosser EC, Mauri C. Regulatory B cells: Origin, phenotype, and function. Immunity. 2015 Apr 21;42(4):607-12.

98. van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Sollner S, Akdis DG*, et al*. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. J Allergy Clin Immunol. 2013 Apr;131(4):1204-12.

99. Ebner C, Siemann U, Bohle B, Willheim M, Wiedermann U, Schenk S*, et al*. Immunological changes during specific immunotherapy of grass pollen allergy: Reduced lymphoproliferative responses to allergen and shift from TH2 to TH1 in T-cell clones specific for phl p 1, a major grass pollen allergen. Clin Exp Allergy. 1997 Sep;27(9):1007-15.

100. Hamid QA, Schotman E, Jacobson MR, Walker SM, Durham SR. Increases in IL-12 messenger RNA+ cells accompany inhibition of allergen-induced late skin responses after successful grass pollen immunotherapy. J Allergy Clin Immunol. 1997 Feb;99(2):254-60.

101. Shamji MH, Kappen JH, Akdis M, Jensen-Jarolim E, Knol EF, Kleine-Tebbe J*, et al*. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: An EAACI position paper. Allergy. 2017 Aug;72(8):1156-73.

102. Guerra F, Carracedo J, Solana-Lara R, Sanchez-Guijo P, Ramirez R. TH2 lymphocytes from atopic patients treated with immunotherapy undergo rapid apoptosis after culture with specific allergens. J Allergy Clin Immunol. 2001 Apr;107(4):647-53.

103. Mobs C, Slotosch C, Loffler H, Jakob T, Hertl M, Pfutzner W. Birch pollen immunotherapy leads to differential induction of regulatory T cells and delayed helper T cell immune deviation. J Immunol. 2010 Feb 15;184(4):2194-203.

104. Mobs C, Ipsen H, Mayer L, Slotosch C, Petersen A, Wurtzen PA*, et al*. Birch pollen immunotherapy results in long-term loss of bet v 1-specific TH2 responses, transient TR1 activation, and synthesis of IgE-blocking antibodies. J Allergy Clin Immunol. 2012 Nov;130(5):1108,1116.e6.

105. Ciepiela O, Zawadzka-Krajewska A, Kotula I, van Overveld F, Kulus M, Demkow U. Sublingual immunotherapy for asthma: Affects T-cells but does not impact basophil activation. Pediatr Allergy Immunol Pulmonol. 2014 Mar 1;27(1):17-23.

106. Allam JP, Wurtzen PA, Reinartz M, Winter J, Vrtala S, Chen KW*, et al*. Phl p 5 resorption in human oral mucosa leads to dose-dependent and time-dependent allergen binding by oral mucosal langerhans cells, attenuates their maturation, and enhances their migratory and TGF-beta1 and IL-10-producing properties. J Allergy Clin Immunol. 2010 Sep;126(3):638,45.e1.

107. Angelini F, Pacciani V, Corrente S, Silenzi R, Di Pede A, Polito A*, et al*. Dendritic cells modification during sublingual immunotherapy in children with allergic symptoms to house dust mites. World J Pediatr. 2011 Feb;7(1):24-30.

108. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics. 2001;69(3):89-95.

109. Calderon MA, Casale T, Cox L, Akdis CA, Burks AW, Nelson HS*, et al*. Allergen immunotherapy: A new semantic framework from the european academy of allergy and clinical Immunology/American academy of allergy, asthma and Immunology/PRACTALL consensus report. Allergy. 2013 Jul;68(7):825-8.

110. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I*, et al*. Allergen immunotherapy: A practice parameter third update. J Allergy Clin Immunol. 2011 Jan;127(1 Suppl):S1-55.

111. Valenta R, Campana R, Focke-Tejkl M, Niederberger V. Vaccine development for allergen-specific immunotherapy based on recombinant allergens and synthetic allergen peptides: Lessons from the past and novel mechanisms of action for the future. J Allergy Clin Immunol. 2016 Feb;137(2):351-7.

112. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W*, et al*. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. J Allergy Clin Immunol. 2008 Feb;121(2):512,518.e2.

113. Di Lorenzo G, Mansueto P, Pacor ML, Rizzo M, Castello F, Martinelli N*, et al*. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy. J Allergy Clin Immunol. 2009 May;123(5):1103,10, 1110.e1-4.

114. Fujimura T, Yonekura S, Horiguchi S, Taniguchi Y, Saito A, Yasueda H*, et al*. Increase of regulatory T cells and the ratio of specific IgE to total IgE are candidates for response monitoring or prognostic biomarkers in 2-year sublingual immunotherapy (SLIT) for japanese cedar pollinosis. Clin Immunol. 2011 Apr;139(1):65-74.

115. Van Overtvelt L, Baron-Bodo V, Horiot S, Moussu H, Ricarte C, Horak F*, et al*. Changes in basophil activation during grass-pollen sublingual immunotherapy do not correlate with clinical efficacy. Allergy. 2011 Dec;66(12):1530-7.

116. Shamji MH, Wilcock LK, Wachholz PA, Dearman RJ, Kimber I, Wurtzen PA*, et al*. The IgE-facilitated allergen binding (FAB) assay: Validation of a novel flow-cytometric based method for the detection of inhibitory antibody responses. J Immunol Methods. 2006 Dec 20;317(1-2):71-9.

117. Knol EF, Mul FP, Jansen H, Calafat J, Roos D. Monitoring human basophil activation via CD63 monoclonal antibody 435. J Allergy Clin Immunol. 1991 Sep;88(3 Pt 1):328-38.

118. Ebo DG, Bridts CH, Mertens CH, Hagendorens MM, Stevens WJ, De Clerck LS. Analyzing histamine release by flow cytometry (HistaFlow): A novel instrument to study the degranulation patterns of basophils. J Immunol Methods. 2012 Jan 31;375(1-2):30-8.

119. Nullens S, Sabato V, Faber M, Leysen J, Bridts CH, De Clerck LS*, et al*. Basophilic histamine content and release during venom immunotherapy: Insights by flow cytometry. Cytometry B Clin Cytom. 2013 May;84(3):173-8.

120. Shamji MH, Achkova D, Layhadi JA, Perera-Webb A, Scadding GW, Khan SQ*, et al*. IL-35 producing regulatory T cells modulate grass pollen-specific Th2 responses and are induced following sublingual grass pollen immunotherapy. Clinical & Experimental Allergy. 2012;42:1816-1817.

121. Shamji M, Layhadi J, Perera-Web A, Scadding G, Durham SR. IL-35+ regulatory T cells suppress grass pollen-driven Th2 responses and are induced following grass pollen-specific sublingual immunotherapy. Journal of Allergy and Clinical Immunology. 2013;131(2):p.AB146.

122. O'Mahony L, Akdis CA, Eiwegger T. Innate mechanisms can predict successful allergy immunotherapy. J Allergy Clin Immunol. 2016 Feb;137(2):559-61.

123. Committee for Medicinal Products for Human Use. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. European Medicines Agency. 2008:1-13.

124. Hoffmann HJ, Valovirta E, Pfaar O, Moingeon P, Schmid JM, Skaarup SH*, et al*. Novel approaches and perspectives in allergen immunotherapy. Allergy. 2017 Jul;72(7):1022-34.

125. Senti G, von Moos S, Tay F, Graf N, Sonderegger T, Johansen P*, et al*. Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: A double-blind, placebo-controlled dose escalation study. J Allergy Clin Immunol. 2012 Jan;129(1):128-35.

126. Senti G, Prinz Vavricka BM, Erdmann I, Diaz MI, Markus R, McCormack SJ*, et al*. Intralymphatic allergen administration renders specific immunotherapy faster and safer: A randomized controlled trial. Proc Natl Acad Sci U S A. 2008 Nov 18;105(46):17908-12.

127. Hylander T, Latif L, Petersson-Westin U, Cardell LO. Intralymphatic allergen-specific immunotherapy: An effective and safe alternative treatment route for pollen-induced allergic rhinitis. J Allergy Clin Immunol. 2013 Feb;131(2):412-20.

128. Slovick A, Douiri A, Muir R, Guerra A, Tsioulos K, Hay E*, et al*. Intradermal grass pollen immunotherapy increases TH2 and IgE responses and worsens respiratory allergic symptoms. J Allergy Clin Immunol. 2017 Jun;139(6):1830,1839.e13.

129. DuBuske LM, Frew AJ, Horak F, Keith PK, Corrigan CJ, Aberer W*, et al*. Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. Allergy Asthma Proc. 2011 May-Jun;32(3):239-47.

130. Creticos PS, Schroeder JT, Hamilton RG, Balcer-Whaley SL, Khattignavong AP, Lindblad R*, et al*. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. N Engl J Med. 2006 Oct 5;355(14):1445-55.

131. Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: The next steps toward personalized care. J Allergy Clin Immunol. 2015 Feb;135(2):299,310; quiz 311.

132. Klunker S, Saggar LR, Seyfert-Margolis V, Asare AL, Casale TB, Durham SR*, et al*. Combination treatment with omalizumab and rush immunotherapy for ragweed-induced allergic rhinitis: Inhibition of IgE-facilitated allergen binding. J Allergy Clin Immunol. 2007 Sep;120(3):688-95.

133. Chaker AM, Shamji MH, Dumitru FA, Calderon MA, Scadding GW, Makatsori M*, et al*. Short-term subcutaneous grass pollen immunotherapy under the umbrella of anti-IL-4: A randomized controlled trial. J Allergy Clin Immunol. 2016 Feb;137(2):452,461.e9.

134. Patel D, Couroux P, Hickey P, Salapatek AM, Laidler P, Larche M*, et al*. Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: A randomized, placebo-controlled study. J Allergy Clin Immunol. 2013 Jan;131(1):103,9.e1-7.

135. Ellis AK, Frankish CW, O'Hehir RE, Armstrong K, Steacy L, Larche M*, et al*. Treatment with grass allergen peptides improves symptoms of grass pollen-induced allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2017 Aug;140(2):486-96.

136. Focke-Tejkl M, Weber M, Niespodziana K, Neubauer A, Huber H, Henning R*, et al*. Development and characterization of a recombinant, hypoallergenic, peptide-based vaccine for grass pollen allergy. J Allergy Clin Immunol. 2015 May;135(5):1207,7.e1-11.

137. Zieglmayer P, Focke-Tejkl M, Schmutz R, Lemell P, Zieglmayer R, Weber M*, et al*. Mechanisms, safety and efficacy of a B cell epitope-based vaccine for immunotherapy of grass pollen allergy. EBioMedicine. 2016 Sep;11:43-57.

138. Furuno T, Teshima R, Kitani S, Sawada J, Nakanishi M. Surface expression of CD63 antigen (AD1 antigen) in P815 mastocytoma cells by transfected IgE receptors. Biochem Biophys Res Commun. 1996 Feb 27;219(3):740-4.

139. Amano T, Furuno T, Hirashima N, Ohyama N, Nakanishi M. Dynamics of intracellular granules with CD63-GFP in rat basophilic leukemia cells. J Biochem. 2001 May;129(5):739-44.

140. Hennersdorf F, Florian S, Jakob A, Baumgartner K, Sonneck K, Nordheim A*, et al*. Identification of CD13, CD107a, and CD164 as novel basophil-activation markers and dissection of two response patterns in time kinetics of IgE-dependent upregulation. Cell Res. 2005 May;15(5):325-35.

141. Buhring HJ, Simmons PJ, Pudney M, Muller R, Jarrossay D, van Agthoven A*, et al*. The monoclonal antibody 97A6 defines a novel surface antigen expressed on human basophils and their multipotent and unipotent progenitors. Blood. 1999 Oct 1;94(7):2343-56.

142. Jutel M, Akdis M, Budak F, Aebischer-Casaulta C, Wrzyszcz M, Blaser K*, et al*. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. Eur J Immunol. 2003 May;33(5):1205-14.

143. Faith A, Richards DF, Verhoef A, Lamb JR, Lee TH, Hawrylowicz CM. Impaired secretion of interleukin-4 and interleukin-13 by allergen-specific T cells correlates with defective nuclear expression of NF-AT2 and jun B: Relevance to immunotherapy. Clin Exp Allergy. 2003 Sep;33(9):1209-15.

144. Fanta C, Bohle B, Hirt W, Siemann U, Horak F, Kraft D*, et al*. Systemic immunological changes induced by administration of grass pollen allergens via the oral mucosa during sublingual immunotherapy. Int Arch Allergy Immunol. 1999 Nov;120(3):218-24.

145. Cosmi L, Santarlasci V, Angeli R, Liotta F, Maggi L, Frosali F*, et al*. Sublingual immunotherapy with dermatophagoides monomeric allergoid down-regulates allergen-specific immunoglobulin E and increases both interferon-gamma- and interleukin-10-production. Clin Exp Allergy. 2006 Mar;36(3):261-72.

146. Akdis CA, Akdis M. Advances in allergen immunotherapy: Aiming for complete tolerance to allergens. Sci Transl Med. 2015 Mar 25;7(280):280ps6.

147. Stanic B, van de Veen W, Wirz OF, Ruckert B, Morita H, Sollner S*, et al*. IL-10-overexpressing B cells regulate innate and adaptive immune responses. J Allergy Clin Immunol. 2015 Mar;135(3):771,80.e8.

148. Agache I, Bilo M, Braunstahl GJ, Delgado L, Demoly P, Eigenmann P*, et al*. In vivo diagnosis of allergic diseases--allergen provocation tests. Allergy. 2015 Apr;70(4):355-65.

149. Scadding G, Hellings P, Alobid I, Bachert C, Fokkens W, van Wijk R*, et al*. Diag-nostic tools in rhinology EAACI position paper. Clin Transl Alle rgy. 2011;1:2.

150. Scadding GW, Eifan A, Penagos M, Dumitru A, Switzer A, McMahon O*, et al*. Local and systemic effects of cat allergen nasal provocation. Clin Exp Allergy. 2015 Mar;45(3):613-23.

151. Horak F, Zieglmayer P, Zieglmayer R, Lemell P, Devillier P, Montagut A*, et al*. Early onset of action of a 5-grass-pollen 300-IR sublingual immunotherapy tablet evaluated in an allergen challenge chamber. J Allergy Clin Immunol. 2009 Sep;124(3):471,7, 477.e1.

152. Nolte H, Maloney J, Nelson HS, Bernstein DI, Lu S, Li Z*, et al*. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. J Allergy Clin Immunol. 2015 Jun;135(6):1494,501.e6.

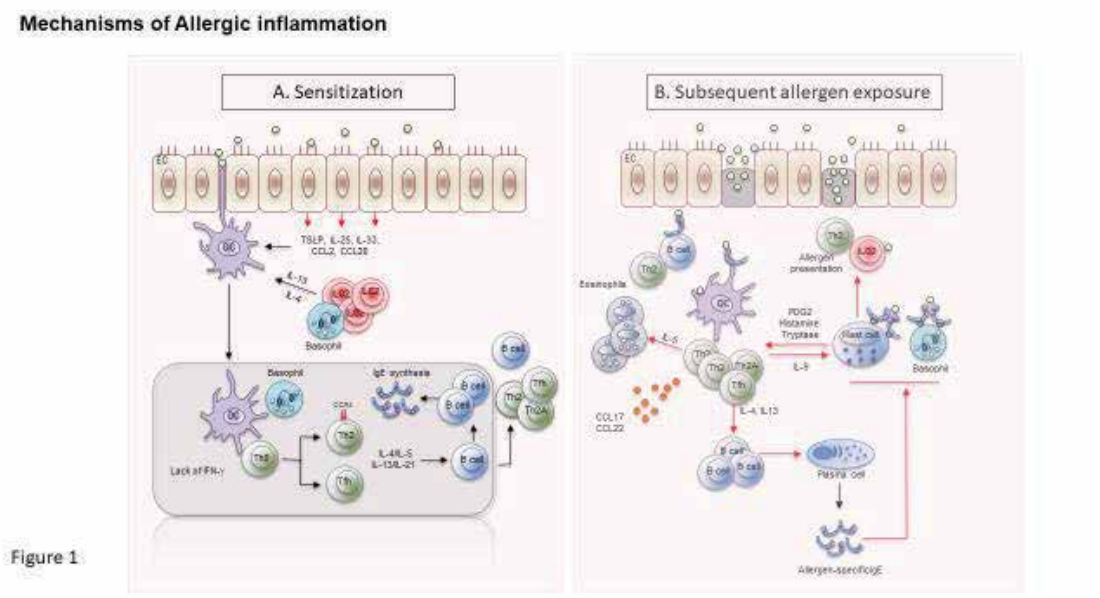
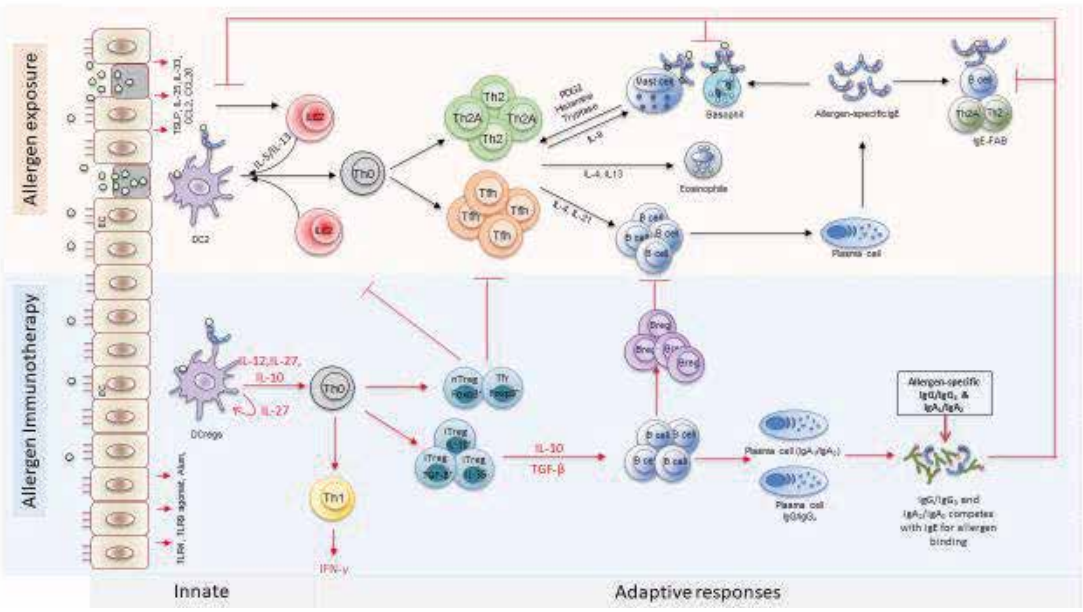


Figure 1


Allergen exposure
Allergen Immunotherapy
Innate
Adaptive responses
DC2
DCregs
Th0
Th1
Th2
Th2A
Tfh
Treg
Breg
B cell
Plasma cell
Basophil
Eosinophile
Allergen-specific IgE
IgE-FAB
IL-10
TGF-β
IFN-γ
Allergen-specific IgG1/IgG3 & IgA1/IgA2
IgG1/IgG3 and IgA1/IgA2 competes with IgE for allergen binding

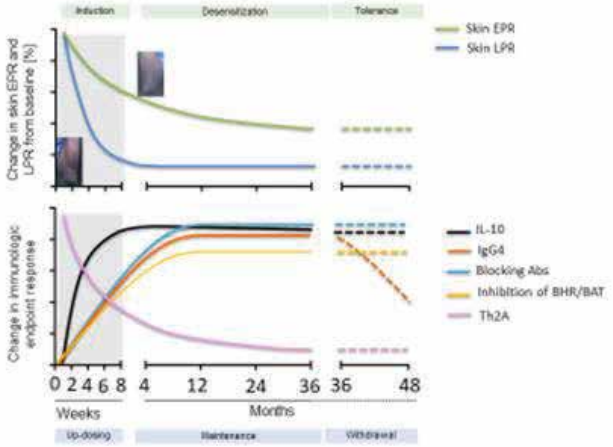

Induction
Desensitization
Tolerance
Skin EPR
Skin LPR
Change in skin EPR and LPR from baseline [%]
Change in immunologic endpoint response
IL-10
IgG4
Blocking Abs
Inhibition of BHR/BAT
Th2A
0 2 4 6 8
4 12 24 36
36 48
Weeks
Months
Up-dosing
Maintenance
Withdrawal

Figure 3

EAACI guidelines on allergen immunotherapy: Prevention of Allergy

Susanne Halken, Denmark

Accepted: 10 September 2017

DOI: 10.1111/pai.12807

REVIEW ARTICLE

WILEY

EAACI guidelines on allergen immunotherapy: Prevention of allergy

Susanne Halken[1] | Desiree Larenas-Linnemann[2] | Graham Roberts[3,4,5] | Moises A. Calderón[6] | Elisabeth Angier[7] | Oliver Pfaar[8,9] | Dermot Ryan[10,11] | Ioana Agache[12] | Ignacio J. Ansotegui[13] | Stefania Arasi[14,15] | George Du Toit[16] | Montserrat Fernandez-Rivas[17] | Roy Geerth van Wijk[18] | Marek Jutel[19,20] | Jörg Kleine-Tebbe[21] | Susanne Lau[15] | Paolo M. Matricardi[15] | Giovanni B. Pajno[14] | Nikolaos G. Papadopoulos[22,23] | Martin Penagos[6] | Alexandra F. Santos[16] | Gunter J. Sturm[24,25] | Frans Timmermans[26] | R. van Ree[27,28] | Eva-Maria Varga[29] | Ulrich Wahn[12] | Maria Kristiansen[30] | Sangeeta Dhami[31] | Aziz Sheikh[23] | Antonella Muraro[32]

[1]Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

[2]Investigational Unit, Hospital Medica Sur, Mexico City, Mexico

[3]The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport Isle of Wight, UK

[4]NIHR Biomedical Research Centre, University Hospital Southampton, NHS Foundation Trust, Southampton, UK

[5]Faculty of Medicine, University of Southampton, Southampton, UK

[6]Section of Allergy and Clinical Immunology, Imperial College London, National Heart and Lung Institute, Royal Brompton Hospital, London, UK

[7]Department of Immunology and Allergy, Northern General Hospital, Sheffield, UK

[8]Department of Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[9]Center for Rhinology and Allergology, Wiesbaden, Germany

[10]Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK

[11]Asthma UK Centre for Applied Research, The University of Edinburgh, Edinburgh, UK

[12]Department of Allergy and Clinical Immunology, Faculty of Medicine, Transylvania University Brasov, Brasov, Romania

[13]Department of Allergy & Immunology, Hospital Quironsalud Bizkaia, Erandio, Spain

[14]Department of Pediatrics, Allergy Unit, University of Messina, Messina, Italy

[15]Department for Pediatric Pneumology and Immunology, Charité Universitätsmedizin, Berlin, Germany

[16]Department of Paediatric Allergy, MRC & Asthma Centre in Allergic Mechanisms of Asthma, Division of Asthma, Allergy and Lung Biology, King's College London and Guy's & St Thomas' Hospital NHS Foundation Trust, London, UK

[17]Allergy Department, Hospital Clinico San Carlos, IdISSC, Madrid, Spain

[18]Department of Internal Medicine, Section of Allergology, Erasmus Medical Center, Rotterdam, The Netherlands

[19]Department of Clinical Immunology, Wroclaw Medical University, Wroclaw, Poland

[20]ALL-MED Medical Research Institute, Wroclaw, Poland

[21]Allergy & Asthma Center Westend, Berlin, Germany

[22]Institute of Human Development, University of Manchester, Manchester, UK

[23]Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece

Abbreviations: AD, atopic dermatitis (atopic eczema); AIT, allergen immunotherapy; AR, allergic rhinitis/allergic rhinoconjunctivitis; ARIA, allergic rhinitis and its impact of asthma; CBA, controlled before and after study; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; HDM, house dust mite; OAS, oral allergy syndrome; QoL, quality of life; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test; SR, systematic review; WAO, World Allergy Organization.

External expert panel: Steven R. Durham, Peter Eng, Hans Jørgen Malling, Antonio Nieto, Zolt Szepfalusi and Erkka Valovirta.

[24]Department of Dermatology and Venerology, Medical University of Graz, Graz, Austria

[25]Outpatient Allergy Clinic Reumannplaz, Vienna, Austria

[26]Nederlands Anafylaxis Netwerk – European Anaphylaxis Taskforce, Dordrecht, The Netherlands

[27]Department of Experimental Immunology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

[28]Department of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

[29]Department of Pediatric and Adolescent Medicine, Respiratory and Allergic Disease Division, Medical University of Graz, Graz, Austria

[30]Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[31]Evidence Based Health Care Ltd, Edinburgh, UK

[32]Food Allergy Referral Centre Veneto Region, Department of Woman and Child Health, Padua University Hospital

Correspondence
Antonella Muraro, Department of Women and Child Health, Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region, University of Padua, Padua, Italy.
Email: muraro@centroallergiealimentari.eu

Funding information
EAACI, This guideline project is funded only by EAACI and the "BM4SIT project (grant number 601763) in the Eurpopean Union's Seventh Framework Programme FP7". The remaining companies mentionen applies only for the authors outside this project

This Guideline published by the European Academy of Allergy and Clinical Immunology (EAACI) has drawn on data from a systematic review of the literature, more recent published studies and multi-stakeholder expert clinical opinion. This Guideline is aimed at healthcare professionals who are encouraged to take the recommendations into account in the context of delivering clinical care. This Guideline is not a substitute for professional clinical judgment, which professionals need to exercise in the context of delivering personalised healthcare.

Abstract

Allergic diseases are common and frequently coexist. Allergen immunotherapy (AIT) is a disease-modifying treatment for IgE-mediated allergic disease with effects beyond cessation of AIT that may include important preventive effects. The European Academy of Allergy and Clinical Immunology (EAACI) has developed a clinical practice guideline to provide evidence-based recommendations for AIT for the prevention of (i) development of allergic comorbidities in those with established allergic diseases, (ii) development of first allergic condition, and (iii) allergic sensitization. This guideline has been developed using the Appraisal of Guidelines for Research & Evaluation (AGREE II) framework, which involved a multidisciplinary expert working group, a systematic review of the underpinning evidence, and external peer-review of draft recommendations. Our key recommendation is that a 3-year course of subcutaneous or sublingual AIT can be recommended for children and adolescents with moderate-to-severe allergic rhinitis (AR) triggered by grass/birch pollen allergy to prevent asthma for up to 2 years post-AIT in addition to its sustained effect on AR symptoms and medication. Some trial data even suggest a preventive effect on asthma symptoms and medication more than 2 years post-AIT. We need more evidence concerning AIT for prevention in individuals with AR triggered by house dust mites or other allergens and for the prevention of allergic sensitization, the first allergic disease, or for the prevention of allergic comorbidities in those with other allergic conditions. Evidence for the preventive potential of AIT as disease-modifying treatment exists but there is an urgent need for more high-quality clinical trials.

KEYWORDS
AGREE II, allergen immunotherapy, allergic diseases, allergic rhinitis, allergy, asthma, atopic dermatitis/eczema, atopy, prevention, sensitization

1 | INTRODUCTION

Allergic diseases are among the commonest chronic diseases and encompass atopic eczema/dermatitis (AD), asthma, allergic rhinitis and allergic rhinoconjunctivitis (both from here onward referred to as AR), food allergy, and venom allergy.[1-5] They frequently start in early childhood and continue throughout adulthood. Allergies can cause a considerable burden to individuals leading to impaired quality of life.[6] At a societal level, they cause additional costs, particularly in terms of healthcare utilization, reduction in economic productivity, and impacting on activities of daily living. The latter may include loss of school days, work absence, presenteeism, and early retirement.[7,8] For allergic asthma and AR, many patients respond well to pharmacotherapy, whereas others do not or need treatment with more than 1 product.[9] However, there is good evidence for the clinical efficacy of allergen immunotherapy (AIT) for AR, allergic asthma, and moderate-to-severe venom allergy[10-12] with many patients responding to therapeutic AIT, leading to a sustained reduction in symptoms and requirement for symptomatic treatment.

AIT is considered a disease-modifying intervention in IgE-mediated allergic disease, with both a therapeutic, even beyond cessation of AIT,[10-12] and the potential for a preventive effect.[13-16] It has been

shown that children with AR have a 3-fold increased risk of developing asthma[17,18] and that childhood AD and AR are strongly associated with the incidence and persistence of adult atopic asthma and with allergic asthma persisting into adulthood.[19] Studies assessing the long-term effectiveness of AIT in children with AR indicate that AIT might reduce the risk of developing asthma.[20-23] AIT has the potential to induce immunologic changes that result in immune modification.[14] Therefore, AIT should be considered as a preventive strategy in the treatment for allergic diseases.

This guideline has been developed by the European Academy of Allergy and Clinical Immunology (EAACI) Taskforce on AIT for Allergy Prevention and forms part of the EAACI Guidelines on Allergen Immunotherapy. The aim is to provide evidence-based recommendations for the use of AIT for the prevention of (i) further allergic comorbidities in those with established allergic disease, (ii) first allergic disease, and (iii) development of allergic sensitization. This guideline does not cover prevention of symptoms, exacerbations, or progression of already-existing allergic disease as this is included in other guidelines in this series. Likewise, it does not cover weaning and dietetic strategies, which are considered in the "EAACI food allergy and anaphylaxis guidelines: Primary prevention of food allergy".[24] Definition of key terms is described in Box 1.

The primary audience for this guideline are clinical allergists (specialists and subspecialists). It may also provide guidance for other

Box 1 Key terms

Allergic asthma	Typical symptoms of asthma (wheezing, cough, dyspnea, chest tightness with evidence of reversibility) induced upon exposure to an allergen together with the proof of immunologic sensitization to that allergen
Allergic conjunctivitis	Inflammation of the conjunctiva characterized by watery, itchy, red eyes induced upon exposure to an allergen together with the proof of immunologic sensitization to that allergen
Allergic diseases	Atopic dermatitis (eczema) (AD), food allergy (FA), allergic asthma, allergic rhinitis/conjunctivitis (AR), and venom allergy at any age
Allergic rhinitis	Inflammation of the nasal mucosa resulting in at least 2 nasal symptoms: rhinorrhoea, blockage, sneezing or itching induced upon exposure to an allergen together with the proof of immunologic sensitization to that allergen
AIT (allergen immunotherapy)	Repeated allergen exposure at regular intervals to modulate immune response to reduce symptoms and need for medication for clinical allergies and to prevent the development of new allergies and asthma (adapted from European Medicines Agency [EMA]). This is also sometimes known as allergen-specific immunotherapy, desensitization, hyposensitization, and allergy vaccination[a] • Subcutaneous immunotherapy (SCIT): form of AIT where the allergen is administered as subcutaneous injections • Sublingual immunotherapy (SLIT): form of AIT where the allergen is administered under the tongue with formulation as drops or tablets
Healthy individuals	Individuals with or without IgE sensitization, but without any manifestations of current allergic disease
Prevention	Prevention of the development of a new sensitization or new allergic disease in healthy individuals without sensitizations, in healthy individuals with sensitizations, and in those who already have an allergic disease *Short-term prevention*: preventive effect assessed within a 2-y window post-AIT *Long-term prevention*: preventive effect maintained for two years and beyond AIT In this document, specific treatment effects such as effect on exacerbations and progression of the disease, including long-term effects, are not regarded as prevention.
Sensitization	Detectable specific IgE antibodies, either by means of SPT or determination of specific IgE antibody levels in a serum sample

[a]Dietary interventions in infants aimed at the prevention of food allergy are not covered in this guideline: They form part of the "EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy" https://www.ncbi.nlm.nih.gov/pubmed/24697491.[24]

healthcare professionals, for example, physicians, nurses, and pharmacists working across a range of primary, secondary, and tertiary care settings managing patients with allergic diseases and healthy individuals at risk of developing allergic diseases.

2 | METHODS

Development of the guideline has been informed by a formal systematic review and meta-analysis of AIT for the prevention of allergy[25] with SR principles being used to identify additional evidence, where necessary.

This guideline was produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach.[26,27] This structured method for guideline production is designed to ensure appropriate representation of the full range of stakeholders, an exhaustive search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations, and steps to ensure that the risk of bias is minimized at each step of the process. The process began in April 2015 with detailed face-to-face discussions agreeing on the process and the key clinical areas to address, followed by face-to-face and web conferences in which professional and lay representatives participated.

2.1 | Clarifying the scope and purpose of the guidelines

The scope of this EAACI guideline is multifaceted, providing recommendations that assist clinicians in the optimal use of AIT for the prevention of development of allergic disease in the management of individuals with, or at risk for, allergic disease, and identifying gaps for further research. The guideline builds on a SR conducted to summarize the evidence base in relation to these aims (Box 2).[25]

2.2 | Ensuring appropriate stakeholder involvement

Participants in the EAACI Taskforce on AIT for Prevention represented a range of countries, with various disciplinary and clinical backgrounds, including allergists, primary care physicians, allied health professionals, public health practitioners, representatives from patient interest organizations, and methodologists who took the lead in undertaking the underpinning SR. Clinical academics took the lead in formulating recommendations for clinical care. Additionally, producers of immunotherapy products were given the opportunity to review and comment on the draft guidelines as part of the peer-review and public comment process. The Taskforce members considered these comments and revised the guideline, where appropriate.

2.3 | Systematic reviews of the evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree on 1 key overarching question: "What is the effectiveness, safety, and cost-effectiveness of AIT for the prevention of allergic disease and sensitization in all populations?" This was then pursued through a formal SR of the evidence by independent methodologists as previously published.[25,28] We continued to track evidence published after our SR cutoff date October 31, 2015, and, where relevant, studies were considered by the Taskforce chairs and members.

2.4 | Formulating recommendations

We graded the strength and consistency of key findings from the SR and meta-analysis, using a random-effects model to take into account the heterogeneity of findings[25] to formulate evidence-based recommendations for clinical care, using an approach that was adapted from that proposed by the Oxford Centre for Evidence-Based Medicine (Oxford Centre for Evidence-based Medicine) (Box 3).[29] The adaptation involved providing an assessment of the risk of bias, based on the Cochrane risk of bias tool, of the underpinning evidence and highlighting other potentially relevant contextual information, formulating clear recommendations, and making clear the evidence base underpinning each recommendation. Where the systematic review did not cover the clinical area, we took a hierarchical approach reviewing other evidence until we could formulate a recommendation: (i) other systematic reviews on the subject to see whether these provided any clarity on the topic; (ii) RCTs within these systematic reviews; (iii) other RCTs known to Taskforce members; and (iv) a consensus-based approach within the Taskforce. This evidence was graded as described in Box 2 using the systematic review data and clearly labeled in the recommendation tables. In formulating the recommendations, not only possible beneficial effects, but also any possible disadvantages and harms were considered (Table 1).

2.5 | Identification of evidence gaps

The process of developing this guideline has identified a number of evidence gaps, which are prioritized in Table 2.

2.6 | Implementation of the guideline

The Taskforce members identified the resource implications, barriers, and facilitators to the implementation of each recommendation (Tables 3-5), advised on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organizational compliance with each recommendation (Table 6).

2.7 | Peer-review and public comment

A draft of this guideline was externally peer-reviewed by invited external experts in this field from a range of organizations, countries, and professional backgrounds: Stephen Durham, Peter Eng, Hans Jørgen Malling, Antonio Nieto, Zsolt Szepfalusi, and Erkka

Box 2 Summary of the aim and outcomes in the supporting systematic review[25]

Aim

To provide the evidence basis for formulating clinical practice guidelines for the use of AIT as preventive therapeutic intervention in allergy. This will be based on a rigorous evaluation of current SR evidence on the effectiveness, safety, and cost-effectiveness of AIT for the prevention of allergic sensitization(s) and allergic disease(s).

Outcomes of the SR

Primary

- The development of the first allergic manifestation in healthy individuals, or of a new allergic manifestation in those with a previous allergic condition (eg, development of asthma in patients with atopic eczema/dermatitis (AD) or AR, a) is lacking here assessed over the short-term (<2 y) or the longer-term (≥2 years) post-AIT.

Secondary

- The development of new allergic sensitization(s), spreading of allergic sensitization(s) from 1 allergen to other nonrelated allergen(s), spreading of allergic sensitization(s) at molecular level, from 1 allergenic molecule to other molecules.
- The development of previously nonexistent oral allergy syndrome (OAS).
- Safety as assessed by local and systemic reactions in accordance with the World Allergy Organization's (WAO) grading systems of local and systemic side effects.[77,78]
- Health economic analysis from the perspective of the health system/payer as reported in studies.

Box 3 Assigning levels of evidence and grade and strength of recommendations (adapted from Oxford Centre for Evidence-based Medicine—Levels of Evidence and Grades of Recommendations)[29]

Level of evidence	
Level I	Systematic reviews, meta-analyses, randomized controlled trials
Level II	Two groups, nonrandomized studies (eg, cohort, case-control)
Level III	One-group, nonrandomized studies (eg, before and after, pretest and post-test)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case series)
Level V	Case reports and expert opinion that include narrative literature, reviews, and consensus statements
Grades of recommendation	
Grade A	Consistent level I studies
Grade B	Consistent level II or III studies or extrapolations from level I studies
Grade C	Level IV studies or extrapolations from level II or III studies
Grade D	Level V evidence or troublingly inconsistent or inconclusive studies at any level
Strength of recommendations	
Strong	Evidence from studies at low risk of bias
Moderate	Evidence from studies at moderate risk of bias
Weak	Evidence from studies at high risk of bias

Recommendations are phrased according to the strength of recommendation: strong: "is recommended"; moderate: "can be recommended"; weak: "may be recommended in specific circumstances"; negative: "cannot be recommended"; or neutral: "cannot be recommended in favor or against".

Valovirta. Additionally, the draft guideline was made available on the EAACI website for a 3-week period in May 2017 for public review to allow a broader array of stakeholders to comment. All feedback was considered by the Taskforce members and, where appropriate, final revisions were made in light of the feedback received.

TABLE 1 Benefits and harms/disadvantages of AIT as preventive treatment in different populations

Population	Benefits	Harms/disadvantages
Healthy ± sensitization	Possible preventive effect remains to be documented	Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 y Frequency of visits to the clinic (SCIT) Risk for adverse events Costs[a]
Children with AD	Possible preventive effect remains to be documented	Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 y Frequency of visits to the clinic (SCIT) Risk of adverse events Costs[a]
Patients with AR	Documented beneficial effect on symptoms and reduction in medication on short- and long-term Possible preventive effect on development of asthma	Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 y Frequency of visits to the clinic (SCIT) Risk for adverse events Costs[a]

AIT, allergen immunotherapy; AD, atopic dermatitis/eczema; AR, allergic rhinitis/rhinoconjunctivitis.
[a]Costs should be evaluated in relation to potential direct and indirect costs related to the development of an eventual allergic disease and other comorbidities.

2.8 | Editorial independence and managing conflict of interests

The production of this guideline was funded and supported by EAACI. The funder did not have any influence on the guideline production process, on its contents, or on the decision to publish. Taskforce members' conflict of interests were declared at the start of the process and taken into account by the Taskforce Chairs as recommendations were formulated. Methodologists, who had no conflict of interests in this area, checked final decisions about strength of evidence for recommendations.

2.9 | Updating the guideline

EAACI plans to update this guideline using the AGREE II approach in 2022 unless there are important advances before then.

3 | AIT FOR PREVENTION: EVIDENCE AND CLINICAL RECOMMENDATIONS

3.1 | Overarching considerations

This guideline is based on a comprehensive SR evaluating the evidence according to predefined well-established methods.[25] As in other SRs, heterogeneity in the populations under study, methods employed, and outcomes studied made it challenging to interpret the evidence. Factors related to the population, such as atopic heredity, play a role in the risk of development of allergic disease. In addition, children with sensitization and/or early manifestations of atopic diseases—AD and food allergy—or later manifestations such as AR have a higher risk for development of other allergic manifestations such as asthma.[17,30] The age of the population is important as the phenotypic expression may change with age and some manifestations may even disappear spontaneously.[31] The results of individual studies are difficult to compare because studies have used different populations, outcome measures, diagnostic criteria (if any, eg, the exact definition of asthma, intermittent versus persistent asthma), methods, and cutoff values for measuring sensitization. Furthermore, the mode of administration and the products used for AIT differ as regards allergens, formulation, strength,[32,33] schedules, dose, route of administration, and duration of the intervention.[34] Additionally, many studies are small without sufficient power and adjustment for confounders. Where possible, these factors are taken into consideration in the risk of bias assessment in the SR on which this guideline is based.

The significant heterogeneity seen in meta-analysis can be explained by the differences in study design, study population, products, and schedules evaluated. Therefore, an individual product-based evaluation of the evidence for efficacy is strongly recommended before treatment with a specific product is initiated.[16,35] But caution is recommended as not all AIT products used currently provide sufficient data to support their efficacy in clinical practice. We might consider that a limited class effect can be assumed when the same clinical outcomes were used to evaluate clinical efficacy (and safety) of different products only if the same route of application, similar dosing schemes, and demonstrable comparable amounts of relevant allergens and potency were used. However, it should be noted that such comparability is also dependent on standardized and validated assays and that a limited class effect does not neglect the necessity for product-specific clinical studies.

Using AIT for the prevention of development of new allergic disease or sensitization requires use of products with a high level of safety, especially in healthy individuals. However, if AIT is indicated due to treatment of an already-existing allergic disease, and the preventive effect is regarded as an additional effect, then the safety profile should be considered in that context.

TABLE 2 Gaps in the evidence

Gaps	Plan to address	Priority
AIT for prevention of asthma in children with AR due to grass pollen—long-term effects	Long-term follow-up of RCTs Further evaluation of GAP trial	High
AIT for prevention of asthma in children with AR due to HDM	RCTs[a]	High
Optimal age for introduction of AIT for prevention	RCTs[a]	High
Optimal duration of AIT for prevention	RCTs[a]	High
Optimal product, administration form, dose, and schedule of AIT for prevention	RCTs[a] and high-quality real-life studies	High
Evaluation of influence of AIT for prevention on Qol in different age groups	Qol as outcome in RCTs[a]	High
AIT for prevention of AR/asthma in children and adults with AD/food allergy	RCTs[a]	Medium
Evaluation of health economics of AIT for prevention	Cost-effectiveness analysis of RCT	Medium
Evaluation of adherence in AIT for prevention in different age groups	Adherence measured in RCTs and real-life studies	Medium
Evaluation of acceptability of AIT for prevention in different age groups	RCTs[a]	Medium
AIT for the prevention of new allergic sensitizations		
Spreading from 1 allergen to related and unrelated allergen(s)	RCTs[a]	Medium
Spreading at molecular level, from 1 allergenic molecule to other molecules		
AIT for prevention of the oral allergy syndrome	RCTs[a]	Low
AIT for prevention of first allergic disease	RCTs[a]	Low

AIT, allergen immunotherapy; AD, atopic dermatitis/eczema; AR, allergic rhinitis/rhinoconjunctivitis; HDM, house dust mites; GAP, Grazax Asthma Prevention Trial[48].

[a]Apart from new RCTs, published clinical data can be reviewed, raw data can be reanalyzed, and blood samples can be analyzed further to provide new data.

Strategies to prevent the development of a new sensitization or of a new allergic disease by AIT may vary for different populations at different stages in life. Strategies need to be pursued for different scenarios, for example, for those planning pregnancy to take measures such as AIT to reduce the likelihood of their child becoming allergic, healthy infants, and young children with early manifestations such as AD, older children with manifest allergic disease such as AR, healthy adolescents/adults, and adolescents/adults with established allergic disease.

In order to recommend AIT for the prevention of allergic diseases, evidence is required that there is a relevant and substantial beneficial effect on clinical outcomes for the individual. Furthermore, safety aspects of the treatment and of the disease to be avoided, quality of life, and evaluation of health economics should be taken into consideration. Thus, an optimal balance between benefits, harms, costs, and other possible disadvantages should be achieved (Table 1).

3.2 | AIT in individuals with AR: short- and long-term prevention of development of new asthma

3.2.1 | Short-term prevention

The SR[25] identified six RCTs investigating the preventive effect up to 2 years post-AIT on the development of asthma in individuals with AR. These RCTs included 3 SCIT studies (1 of low,[36] 1 of moderate,[37] and 1 of high risk of bias[38]), 1 of moderate risk of bias on oral AIT[39] plus 1 of high[40] and 1 moderate risk of bias SLIT study.[32] Three of these[36,37,39] were small studies with a trend toward less development of asthma in the AIT group but no significant differences. The remaining 3 studies[38,40,41] showed a significant reduction in the development of asthma in the AIT groups as compared to the control groups. The SR and meta-analysis[25] demonstrated a significant preventive effect of AIT on the development of asthma up to 2 years post-AIT in patients with AR. Subgroup analyses showed that AIT with either SLIT or SCIT was beneficial for those aged <18 years but not ≥18 years and for pollen AIT. For HDM AIT, the groups were so small that there was a nonstatistically significant impact despite an OR of 0.20. There was a high degree of heterogeneity, and therefore, the meta-analysis should be interpreted with caution although 3 RCTs demonstrated a statistically significant preventive effect. Also, the results were supported by 2 large-scale, real-life, retrospective, nonrandomized CBAs,[42,43] based on German longitudinal prescription databases, both reporting a short-term preventive effect of AIT on the progression from AR to asthma.

3.2.2 | Long-term prevention

For the long-term preventive effect, that is, 2 or more years post-AIT, the SR[25] identified 2 high risk of bias SCIT RCTs[44,45] in patients with AR. Both showed a significantly lower risk for developing asthma in the SCIT groups as compared to the controls, up to 7 years post-AIT[38,44,46] and 2 years post-AIT.[45] A large recently published low risk

TABLE 3 AIT for prevention: recommendations for school-age children, adolescents, and adults with allergic rhinitis (AR) or asthma

Recommendations for individuals with manifest allergic disease(s), eg, allergic rhinitis	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In children and adolescents with AR and grass/birch pollen allergy, who are suboptimally controlled despite appropriate treatment with antihistamines/nasal corticosteroids, a 3-y course of AIT (SCIT or SLIT) can be recommended for the short-term (ie, <2 y post-AIT) prevention of the onset of asthma in addition to the sustained effect on AR symptoms and medication use.	I	A	Moderate recommendation: based on consistent significant results from 2 moderate[39,41] and 2 high risk of bias[38,40] RCTs and some CBA studies	The indication should be discussed with the patients/families including the asthma preventive effect as well as the effect on AR and risk of adverse effects, costs, and preferences	Möller,[38] Novembre,[41] Marogna,[40] Kristiansen[25]
In children and adolescents with AR and grass/birch pollen allergy, no recommendation can currently be made in favor of or against the use of AIT (SCIT or SLIT) for the long-term (≥2 years post-AIT) prevention of the onset of asthma as diagnosed by symptoms combined with demonstrated reversibility.	I	B	Weak recommendation: based on consistent results from 2 high risk of bias RCTs,[44,45] nonsignificant results from 1 low risk of bias RCT,[48] and the meta-analyses being not significant due to the latter study	In the Valovirta's (2017)[48] study, no effect on the primary asthma outcome using a restrictive definition of asthma based on demonstration of reversibility. More data are needed	Jacobsen,[44] Song,[45] Valovirta,[48] Kristiansen[25]
In children and adolescents with AR and grass/birch pollen allergy, the use of AIT (SCIT or SLIT) may be recommended for the long-term (≥2 y post-AIT) prevention of the onset of asthma symptoms and medication use.	I	B	Weak-moderate recommendation: based on consistent results from 2 high risk of bias RCTs[44,45] and secondary outcomes in 1 low risk of bias RCT[48]	In the Valovirta's (2017)[48] study, a significant preventive effect on the secondary outcomes asthma symptoms and medication was found. More data are needed	Jacobsen,[44] Song,[45] Valovirta[48]
In children and adolescents with AR and allergy to house dust mites or other allergens except for birch/grass pollen, no recommendation can currently be made in favor of or against the use of AIT (SCIT or SLIT) for the short-term (ie, <2 y post-AIT) or long-term (ie, ≥2 y post-AIT) prevention of the onset of asthma.	I	B	Weak recommendation: based on inconsistent results from 1 high[40] and 1 low risk of bias RCT[36]	Only HDM, Parietaria, and mix of these and grass/birch pollen investigated. More data are needed	Marogna,[40] Crimi,[37] Grembiale,[36] Kristiansen[25]

(Continues)

TABLE 3 (Continued)

Recommendations for individuals with manifest allergic disease(s), eg, allergic rhinitis	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In adults with AR and house dust mite or pollen allergy, no recommendation can currently be made in favor of or against the use of AIT (SCIT or SLIT) for the short-term (ie, <2 y post-AIT) or long-term (ie, ≥2 y post-AIT prevention of the onset of asthma	I	B	Weak recommendation: based on 1 small moderate risk of bias study[37]	Only SCIT with Parietaria Judaica investigated. More data are needed	Crimi[37]
In children or adults with AR and/or asthma, AIT cannot currently be recommended for the prevention of new sensitizations.	I	B	Weak recommendation: based on inconsistent results from 4 high,[40,45,58,67] 2 moderate,[57,66] and 3 low risk of bias[53,55,56] RCTs		Marogna,[58] Marogna,[40] Dominicus,[67] Song,[45] Pifferi,[57] Limb,[66] Garcia,[55] Szepfalusi,[56] Zolkipli,[53] Kristiansen[25]

of bias RCT (Grazax Asthma Prevention Trial)[47,48] explored the effect of a 3-year course of SLIT tablets on the prevention of asthma in 812 children with AR and grass pollen allergy. This study[48] failed to demonstrate the preventive effect of AIT on the development of asthma as defined by very strict a priori criteria including reversibility to beta-2-agonists (OR = 0.91; 95% CI [0.58 to 1.41])[47,48] 2 years post-AIT. However, the number of subjects with asthma symptoms or asthma medication usage (secondary efficacy parameter) was significantly lower in the SLIT group compared to the placebo group at the end of the 5-year trial period (OR 0.66; 95% CI 0.45 to 0.97; $P < .036$), during the 2-year post-AIT follow-up and during the entire 5-year trial period. Also, AR symptoms were significantly reduced during the entire 5-year trial period. In addition, it appeared that this preventive effect was strongest for the youngest children.[48] Two high risk of bias nonrandomized studies, namely 1 with grass pollen SCIT[22,23] and 1 with HDM SCIT[49] in children with AR, also suggested a long-term effect. As published in the SR,[25] the meta-analysis showed no overall evidence of reduction in the long-term (ie, at least 2 years post-AIT) risk of developing asthma, but there was a high degree of heterogeneity so the result should be interpreted with caution. Furthermore, the negative result was due to 1 RCT with very strict diagnostic criteria for primary outcome (GAP) in which there was an effect when asthma symptoms and/or medication was considered.[48] However, some suggest that there is a long-term preventive effect on the development of asthma symptoms and the use of asthma medication although further confirmatory studies are needed.

Thus, there is a question about which asthma outcome parameter is most relevant—a diagnosis based on demonstrated reversibility or on symptoms and medication use. There is an urgent need to define and standardize the optimal clinical asthma outcomes that should be used in future clinical trials.

3.3 | Indication for AIT for treatment and prevention in patients with AR

The RCTs included in the above evaluation of asthma prevention in subjects with AR[38,40,41,44,46–48] included patients with a history of AR and the need for medication combined with documented pollen allergy for at least 1 previous season. Yet, there is no description on AR severity (mild/moderate/severe) or stratification (intermittent/persistent) in these prevention trials, and thus, these subjects may have had a milder disease than those included in studies on efficacy of AIT. However, based on baseline descriptions of the populations in these studies,[38,40,41,44,46–48] it is reasonable to assume that most of the patients included had persistent symptoms.

As discussed in another manuscript on AIT for AR of this EAACI AIT Guideline series,[10,50] many patients with AR and pollen allergy benefit from AIT in reducing AR symptoms and need for medication. Thus, AIT is recommended for the treatment of patients with moderate-to-severe pollen-induced AR if not optimally controlled on antihistamines and nasal corticosteroids.[50]

None of the studies on prevention of development of asthma in AR included preschool children, and therefore, no recommendations

TABLE 4 AIT for prevention: recommendations for individuals with early-life atopic manifestations, eg, atopic dermatitis/eczema (AD) or food allergy

Recommendations for individuals with early atopic manifestations	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In children with AD, no recommendations can currently be made in favor of or against the use of AIT for the prevention of onset of later allergic manifestations	I	B	Weak recommendation: based on 1 small moderate risk of bias study[51]		Holt[51]
In individuals at all ages with other early atopic manifestations, eg, food allergy, no recommendations can currently be made in favor of or against the use of AIT for the prevention of onset of other allergic manifestations	V	D	Expert opinion. No studies		

can currently be made in favor of or against AIT for this age group for prevention.

Based on an objective and clinical evaluation of the current published evidence for AIT preventive effects and considering the potential harmful effects, disadvantages, and costs associated with the use of AIT, these seem to be outweighed by the beneficial effects for this group of patients (Table 1), ultimately resulting in a favorable risk benefit profile.

Thus, there is moderate-to-high-quality evidence indicating that AIT (SCIT or SLIT) can be recommended for short-term prevention up to 2 years post-AIT of asthma in children/adolescents with moderate/severe AR and pollen allergy who are suboptimally controlled despite appropriate pharmacotherapy, and there are data suggesting that this benefit persists after 2 years post-AIT as regards asthma symptoms and medication use (Table 3). AIT may even be considered in patients with milder AR, as AIT might modify the natural disease history, including the long-term effect in AR and the preventive effect regarding the development of asthma, qualities that could never be attributed to current pharmacotherapy.

The indication and initiation of AIT should always be preceded by a discussion with the patient/family considering the possible benefits, harms, disadvantages, costs, preferential route of AIT (SCIT vs SLIT) based on the individual patient's profile, preferences, and considerations for future AIT adherence. Using AIT for preventive purposes should include all normal safety recommendations as for the treatment of AR as indicated in the corresponding guideline on AIT for AR in this EAACI AIT Guideline series.[50]

3.4 | Which products and schedules for AIT asthma prevention in individuals with AR should be used?

The products, doses, and AIT schedules used in the AIT prevention trials vary. According to the subgroup analysis in the SR,[25] it appears that SCIT and SLIT are both effective and that a 3-year AIT course is preferable to a shorter course. The studies that have demonstrated a preventive effect used 3-year courses of continuous AIT.

The SR[25] did not compare different AIT products, SLIT drops versus tablets or pre-/coseasonal versus perennial AIT. However, according to the results from 2 lower-quality, real-life nonrandomized, controlled before-after AIT treatment studies based on large German longitudinal prescription databases,[42,43] it seems that SCIT[43] and grass pollen SLIT tablets[42] with natural allergen extracts have a preventive effect on the progression from AR to asthma and that AIT for 3 or more years tended to have a stronger preventive effect than AIT for less than 3 years. Further high-quality RCTs and real-life studies are recommended to objectively confirm this.

As the indication for AIT for the prevention of asthma is linked to the indication for treatment of AR, the products, schedules, and doses used should be proven effective for AR with the relevant allergen product. Therefore, only those products registered and with the indication for AR (eg, pollen allergy at present and maybe HDM in the future) should be considered for use in allergy prevention.

3.5 | AIT in individuals with AD: short- and long-term preventive effects

The SR[25] identified 1 moderate risk of bias RCT investigating the effects of 12 months of daily SLIT with a mixture of HDM, cat, and timothy grass allergens on the prevention of asthma and new sensitizations in children with AD and sensitization to 1 or more food allergens.[51] The investigators included the absence of a difference between active/placebo groups in early immunologic changes, that is, specific IgE/IgG antibodies and associated T_H-cell responses, as a stopping rule, as this was regarded an indication of whether the treatment was delivering sufficient allergen transmucosally to trigger immunologic recognition by the infant mucosal system. As these a priori immunologic changes were not met, recruitment was interrupted and the trial reduced to a pilot study status. After 48 months of follow-up, there were no differences in asthma prevalence between the 2 groups.[51]

Based on this study, we cannot currently make any recommendations in favor of or against AIT for the prevention of the development of a first allergic disease in individuals with AD at present (Table 4) and more studies are needed.

TABLE 5 AIT for prevention: recommendations for healthy individuals

Recommendations for healthy individuals of all ages	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In adult allergic patients, no recommendations can currently be made in favor of or against the use of AIT for the prevention of onset of allergic diseases in their offspring	IV-V	D	Weak recommendation: based on results from 1 high risk of bias study[52]		Bozek[52]
In healthy individuals with or without sensitization, AIT cannot currently be recommended for the prevention of onset of allergic diseases	I	A	Weak recommendation: based on 1 low[53] and 1 high risk of bias RCTs[54]	One RCT with infant and 1 with adult population	Zolkipli,[53] Yamanaka[54]
In healthy children, AIT cannot currently be recommended for the prevention of new sensitizations	I	B	Weak to moderate recommendation: based on results from 2 low risk of bias RCTs[53,56]	One RCT with infant and 1 with preschool population	Zolkipli,[53] Szepfalusi[56]
In healthy adults, no recommendations can currently be made in favor of or against the use of AIT for the prevention of new sensitizations	V	D	Expert opinion. No studies		

3.6 | AIT for prevention of allergy in the offspring of allergic individuals

This topic was not included in the protocol or in the SR. However, we found 1 recent case-control study of high risk of bias comparing 194 children of parents completing AIT at least 9 months before birth with 195 controls.[52] This study found that the odds ratios of developing any allergic disease and asthma was significantly lower in children with at least 1 allergic parent after AIT compared with those having allergic parents who did not receive AIT (odds ratio: 0.73, 95% confidence interval 0.59-0.86). The authors hypothesized that AIT in allergic parents might reduce the risk of allergies in their offspring, but this requires further investigation.

Based on the very scarce and very low-quality evidence, we cannot currently make any recommendations in favor of or against AIT for allergic adults for the prevention of allergic disease in their offspring (Table 5).

3.7 | AIT in healthy individuals: short- and long-term prevention of development of new allergic disease

Two RCTs, 1 of low[53] and 1 of high risk of bias,[54] investigated the possible effect of AIT in healthy individuals on the risk for the development of their first allergic disease. The large low risk of bias study[53] found no preventive effect of oral HDM AIT on AD, wheeze, and food allergy among infants with a family history of allergic diseases, whereas the small high risk of bias study[54] reported a reduced risk of developing pollinosis among asymptomatic adults sensitized to Japanese cedar pollen in the SLIT group. Data from these 2 trials[53,54] are not comparable. No data on a long-term preventive effect were identified. Based on these results from the SR,[25] there is currently no good evidence to recommend use of AIT for the prevention of a first allergic disease in healthy individuals (Table 5).

3.8 | AIT for the prevention of the development of new allergic sensitization

3.8.1 | Short-term effects

The SR identified 3 low risk of bias RCTs[53,55,56]: 1 moderate[57] and 2 high risk of bias[40,58] RCTs investigating the short-term effects of AIT on the risk of developing new sensitizations. One low risk of bias RCT[53] on oral HDM AIT for healthy infants at high risk of developing allergic disease found a significant reduction in sensitization to any common allergen (eg, HDM, grass pollen, cat, peanut, milk, and egg) in the active group compared with the placebo group at the end of the trial, but no difference in HDM sensitization.[53] The other 2 low risk of bias RCTs found no effect of SLIT in adult patients allergic to peach[55] post-AIT and after SLIT with grass pollen or HDM extract in monosensitized children.[56] Three additional RCTs of moderate to high risk of bias[40,57,58] found a significantly lower incidence of new sensitizations among children and adults with AR treated with SLIT[40,58] and SCIT[57] as compared to controls.

Thus, these RCTs of varying quality with varying allergens and formulations showed inconsistent results. Meta-analysis showed an overall reduction in the risk of allergic sensitization but the sensitivity analyses, excluding the 2 high risk of bias studies by Marogna,[40,58] failed to confirm this risk reduction.[25] Due to the high degree of heterogeneity, the results from the meta-analysis should be interpreted with caution.

The inconsistent evidence found in RCTs was also reflected in the included high risk of bias CBA studies with 3 finding a lower occurrence of new sensitizations among AIT-treated subjects compared with controls,[59–61] 1 reporting higher occurrence in the AIT group compared with controls[62] and 3 studies reporting no differences between groups.[63–65]

3.8.2 | Long-term effects

As regards the long-term (ie, at least 2 years post-AIT) effects on prevention of new sensitivities, the SR identified 1 moderate[66] and 1 high risk of bias RCT[67] showing no preventive effect of SCIT among children with moderate-to-severe asthma followed into adulthood[66] and SCIT in adults with AR 3 years post-AIT.[67] Another high risk of bias RCT[45] found that patients with AR treated with HDM SCIT less frequently developed new sensitizations compared with controls 2 years post-AIT.[45]

Thus, there is no good evidence for a reduction in the long-term risk of allergic sensitization.

The 7 high risk of bias CBAs investigating long-term preventive effects of AIT produced inconsistent results, 1 found no difference,[68] 4 showed reduced onset,[22,60,69–71] and 1 found a significantly higher occurrence of new sensitization among AIT-treated subjects compared with controls.[72]

The development of new sensitizations may impose a higher risk for the development of further symptomatic allergies, suggesting that it might be relevant to prevent the development of new sensitizations. However, this has not been investigated sufficiently. A subgroup analysis in the SR[25] showed a tendency toward an effect in children and adolescents after 3 years of AIT, supporting the rationale of the clinical effect.

Thus, there is currently no good evidence to recommend the use of AIT for either short- or long-term prevention of development of new sensitizations in healthy individuals, children with atopic predisposition (Table 5), children with AD/food allergy (Table 4), or children and adults with AR/asthma (Table 3). Some positive data, though, suggest that this may be a good focus for future high-quality trials.

3.9 | Safety

The safety issues are fully covered by the SR and guideline for AR in this AIT Guideline series.[10,50] SCIT is occasionally associated with allergic side effects and should therefore be administered in a specialist setting. Fatalities are very rare and have not been reported with the use of SLIT. In a recent meta-analysis about the efficacy of grass pollen SLIT tablet by Di Bona et al.,[73] 7 treatment-related adverse events

TABLE 6 Recommendations for individuals with allergic rhinitis: implementation

Prevention of development of asthma in patients with AR	Barriers to implementation	Facilitators to implementation	Audit criteria	Resource implications
In children and adolescents with AR and grass/birch pollen allergy who are suboptimally controlled despite appropriate treatment with antihistamines/nasal corticosteroids, a 3-y course of AIT (SCIT or SLIT) can be recommended for short-term (ie, < 2 y post-AIT) prevention of the onset of asthma in children with daily symptoms and need for medication	Lack of recognized policy in Europe about allergies and their treatment. Failure to recognize manifestations in primary care. Lack of knowledge among patients, caregivers, and primary care professionals about the benefits of AIT. Lack of communication specialists/primary care interface or specific referral criteria primary care. Lack of agreed clinical pathways Lack of access to AIT Unavailability of AIT No reimbursement Costs of travel and time of work for patients and caregivers Concerns about side effects and safety of especially SCIT Lack of health economics data	Government and European policy on allergy. Reimbursement of AIT Accessible education and training in allergy primary care. Agreed competencies in allergy for primary care and allied health workers for shared care protocols. Information among patients, caregivers, and healthcare professionals about the benefits of AIT. Integrated multidisciplinary working and service delivery. Timely advice and continuous guidance by specialists. Workforce remodeling. Agreed pathways of care with cross-boundary working	Proportion of potentially eligible patients referred from primary care for a specialist assessment. Proportion of potentially eligible patients formally considered for AIT	Identification of patients who may benefit from AIT. Thorough investigation of the patient including proper assessment of relevant allergies. AIT needs to be prescribed, made available, and administered to patients. Evaluation of effect and eventual AEs

requiring adrenaline were reported in the SLIT RCTs; however, no episode of anaphylaxis was reported. In recent real-life clinical studies of AIT, less severe systemic reactions were reported with SLIT than with SCIT, although the overall rate of adverse reactions is similar in SCIT and SCIT.[74,75] The safety profile for the present purpose is not regarded as being different from AIT for the treatment of AR. Due to its better safety profile, SLIT might be a better choice for prevention than SCIT.

4 | SUMMARY, GAPS IN THE EVIDENCE, FUTURE PERSPECTIVES, AND IMPLEMENTATION

This guideline on AIT for the prevention of allergy has been developed as part of the EAACI Guidelines on Allergen Immunotherapy Project. The recommendations in this guideline are based on a thorough SR performed by a group of experienced and independent methodologists and have been developed by a multidisciplinary EAACI Task Force representing a range of countries and disciplines and clinical backgrounds.

The guideline provides evidence-based recommendations for the use of AIT for the prevention of new allergic disease(s) and new allergic sensitization(s) in all populations. The guideline should assist all healthcare professionals as regards evaluation of AIT for the prevention of allergic disease/sensitization, and when to refer which individuals to further evaluation. The main results are summarized in Box 4.

The key limitation of this guideline is the heterogeneity and gaps in the underpinning literature. There are many areas for which there is no evidence or no high-quality evidence; these represent gaps in the current evidence (Table 2). Thus, for the preventive effect of AIT in healthy individuals or in children with early atopic manifestations such as AD or food allergy as well as for the possible long-term effect in children with AR, more high-quality data are needed. Also, we did not find studies related to spreading of allergic sensitization(s) at the molecular level, nor did we identify studies exploring the development of new OAS or health economic analyses of AIT used for prevention (Box 5).

In addition, there is a lack of evidence as regards patient selection (eg, optimal age and characteristics) for preventive AIT and for the optimal allergen preparation, mode, and duration of AIT administration; there is a need to define standardized relevant outcomes including asthma and quality of life (Qol) for future studies.

The current evidence does not allow to identify superiority between SCIT and SLIT; therefore, this choice depends on availability, patients'/family's preferences, safety, costs, routes, schedules, and patients' adherence to the AIT treatment. Only products and regimens proven effective for the treatment of AR should be used. Currently, only products with the indication for treatment of AR can be recommended for the prevention of asthma in children and adolescents with AR and pollen allergy.

Based on current evidence, AIT can be recommended for up to 2 years post-AIT prevention of development of asthma in children and adolescents with AR and pollen allergy primarily birch and grass. Some studies suggest a long-term asthma preventive effect as regards asthma symptoms and medication use, although it has to be further demonstrated if this effect can be extended to asthma as diagnosed by stricter diagnostic criteria. Such a disease-modifying effect after cessation of AIT is not achievable with pharmacotherapy. AIT should, in particular, be considered for those with moderate-severe AR as it has been shown to be effective in controlling this condition in addition to the preventive effect on the development of asthma.[10,50] Furthermore, some patients with less severe AR may prefer AIT to reduce medication use and avoid side effects of other treatments, to obtain long-term efficacy, and/or to obtain the asthma preventive effect.

Considerations should be taken when making recommendations for AIT as preventive treatment in allergy, as children and adolescents included in the prevention studies did not necessarily fulfill the criteria for proper endorsement of AIT for the treatment of AR as well as they did not necessarily meet the "Allergic Rhinitis and its Impact of Asthma" (ARIA)[9] criteria for moderate-severe AR.

At present, the indications for AIT for the prevention of allergic disease are the same as for the treatment of AR (ie, documented

Box 4 Summary

- A 3-y course of AIT (SCIT or SLIT) can be considered in children with moderate-to-severe AR and grass/birch pollen allergy, not sufficiently controlled with optimal pharmacotherapy, for:
  - Treatment of AR with a sustained effect on symptoms and use of medication beyond cessation of AIT.
  - Short-term (ie, up to 2 y post-treatment) prevention of the onset of asthma in addition to improving the control of AR. Moreover, some studies indicate that this asthma preventive effect is maintained over a longer period as evaluated by symptoms and medication use.
- Only AIT products with documented effect in patients with the relevant pollen allergy should be used and a product-specific evaluation of clinical efficacy and preventive effects is recommended.
- Before initiating AIT the possible benefits including the beneficial effects on controlling AR symptoms and the asthma preventive effect, disadvantages, potential harms, patients' preferences (SCIT or SLIT tablets/SLIT drops), patients' adherence to treatment and costs should be discussed with the patient/family on an individual basis.
- There is an urgent need for more high-quality clinical trials on prevention in AIT and more high-quality evidence.

Box 5 Key messages for primary care about referral to allergy services

- AIT has a role in delaying/preventing progression from seasonal AR/ARC to asthma.
  - Primary care teams should consider early referral of children with troublesome AR in spite of pharmacotherapy with antihistamine and/or nasal corticosteroids for a specialist assessment with a view to considering AIT to improve control of AR and also simultaneously delay/prevent asthma.
  - Patients should be considered as "individuals" during the assessment to prescribe AIT, and they all have to be aware of the potential benefits, risks, and costs of AIT.
- AIT may be indicated in those individuals with perennial AR on clinical grounds but not only for delaying/preventing progression to asthma (this preventive effect needs to have high-quality evidence).
- Recommendations cannot currently be made for AIT for prevention to (i) allergic parents who would be interested in receiving AIT to prevent allergy in their offspring; (ii) healthy infants/children; and (iii) infants/children with AD and/or food allergy.

IgE-mediated disease caused by the relevant allergens and not sufficiently controlled by antihistamines and nasal corticosteroids).[50] Contraindications are the same as for the treatment of AR.[50] The asthma preventive effect may in the future downgrade the level of severity of AR required before initiation of AIT in children and adolescents with AR and pollen allergy, especially grass pollen allergy. Therefore, AIT as a relevant treatment option for children and adolescents up to 18 years of age with less severe AR due to pollen allergy should be further investigated and discussed. Currently, there is no high-quality evidence to support AIT for prevention in HDM-allergic patients with AR, but further high-quality studies are warranted.

The products available, and registered for different indications, have varied over time and across countries. Therefore, at present, we cannot make homogeneous product-specific recommendations at a European level. In the context of the implementation of this guideline series, we plan to provide such recommendations based on each national country availability of the products,

For the implementation of this guideline (described in Table 6), there is a need to ensure that primary care healthcare professionals recognize AIT as a treatment option for some allergic diseases and have clear guidelines to aid patient selection for early referral to specialist care.[76] Patients and patient organizations need to be aware of AIT as a treatment option. Political awareness should be increased to ensure sufficient availability, knowledge, competences, skills, and resources in the healthcare system by demonstrating the economic benefits of AIT by proper assessment of its positive impact on economic productivity. In addition, methods to overcome problems with adherence should be further considered and evaluated. Finally, a plan for monitoring the audit criteria should be part of the dissemination and implementation plan, and as new evidence is published, these guidelines will be updated with appropriate revision of specific recommendations.

ACKNOWLEDGMENTS

We would like to acknowledge the support of EAACI and the EAACI Guidelines on Allergen Immunotherapy Group in developing this guideline. We would like to thank Kate Crowley for her assistance in preparing the guidelines; we thank Stefan Vieths, Andreas Bonertz, and Sergio Bonini for their advice; Stephen Durham, Peter Eng, Hans Jørgen Malling, Antonio Nieto, Zsolt Szepfalusi, and Erkka Valovirta for their expert review of the draft guidelines; all the EAACI members who commented about the draft guideline on the public website; EAACI and the "BM4SIT Project (Grant Number 601763) in the European Union's Seventh Framework Programme FP7" for funding this guideline.

AUTHORS' CONTRIBUTION

S Halken chaired the EAACI Guideline AIT for Allergy Prevention Taskforce. D Larenas-Linnemann, G Roberts, MA Calderón, M Penagos, S Bonini, G Du Toit, IJ Ansotegui, J Kleine-Tebbe, S Lau, P Maria Matricardi, G Pajno, NG Papadopoulos, O Pfaar, D Ryan, AF Santos, F Timmermans, U Wahn, M Kristiansen, S Dhami, A Sheikh, and A Muraro were all members of the Taskforce and were involved in conceptualizing the guideline, drafting of the guideline, and critically reviewed the guidelines draft and I Agache, S Arasi, M Fernandez-Rivas, M Jutel, GJ Sturm, EM Varga, R van Ree, R Gerth van Wijk, and Antonella Muraro were members of the Chairs Steering group who also critically discussed and reviewed the guideline draft. F Timmermans was also the patient group representative. All the authors satisfied the international Vancouver authorship criteria. This guideline is part of the EAACI Guidelines on Allergen Immunotherapy, chaired by Antonella Muraro and coordinated by Graham Roberts. All authors' job titles and role in the guideline development are in Table S1 in the online repository.

CONFLICTS OF INTEREST

S. Halken reports personal fees from ALK-Abelló, personal fees from different companies, for example, MEDA, Stallergenes, Allergopharma, and ALK-Abelló, outside the submitted work. D. Larenas-Linnemann reports personal fees from MSD, Grunenthal, Amstrong, and DBV; grants and personal fees from Astrazeneca, MEDA, GSK, Pfizer, Novartis, Boehringer-ingelheim, Sanofi, UCB;

grants from Chiesi and TEVA; other from Stallergenes and from ALK-Abelló, outside the submitted work; she is the Chair of the immunotherapy committee CMICA, member of the immunotherapy committee or interest groups of EAACI, WAO, SLAAI, and member and Program Chair of the Board of Directors CMICA 2018-2019. G. Roberts has a patent issued: "Use of sublingual immunotherapy to prevent the development of allergy in at risk infants"; and his university has received payments for the activities he has undertaken giving expert advice to ALK, and presenting at company symposia for ALK, Allergen Therapeutics, and Meda, and serving as a member of an Independent Data Monitoring Committee for Merck outside of this work. M. A. Calderón has received honorarium in advisory boards for ALK and Hal-Allergy and served as a speaker for ALK, Merck, Hal-Allergy, Allergopharma, and Stallergenes-Greer. E. Angier reports being Secretary of Primary Care Interest Group EAACI. Participated in ALK conference SOSA meeting 2015. Previous paid advisory board one each for MEDA 2012, Stallergenes, 2012, Schering Plough 2009, and one paid lecture by MEDA. I. Agache has nothing to disclose. I.J. Ansotegui has nothing to disclose. S. Arasi has nothing to disclose. George Du Toit reports income from grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH), Food Allergy & Research Education (FARE), MRC & Asthma UK Centre, UK Dept of Health through NIHR, National Peanut Board (NPB), and grants from UK Food Standards Agency (FSA); these grants part funded salary. Prof. Du Toit is scientific advisor for the Anaphylaxis Campaign, advisor to—and holds stock in—FoodMaestro and is site investigator for Aimmune-sponsored Peanut Desensitisation Trials and is scientific advisor to Aimmune. He was Chairperson of the EAACI Paediatric Section over the period when this document was formulated. Montserrat Fernandez-Rivas reports grants from European Union, grants from Instituto de Salud Carlos III, Ministerio de Ciencia, España, grants from Ministerio de Economia, España, personal fees from DBV, personal fees from Aimmune, Reacta Biotech, Schreiber foods, personal fees from ALK-Abelló, Merck, GSK, Allergy Therapeutics, nonfinancial support from EAACI, personal fees and nonfinancial support from Fundación SEAIC, other from Hospital Clínico San Carlos, and Universidad Complutense de Madrid. España, outside the submitted work; in addition, Dr. Fernandez-Rivas has a patent PT0042/2013 issued. R. Gerth van Wijk reports personal fees from ALK-Abelló, Circassia, and Allergopharma, during the conduct of this work. M. Jutel reports personal fees from ALK-Abello, Allergopharma, Stallergenes, Anergis, Allergy Therapeutics, Circassia, Leti, Biomay, HAL, during the conduct of the study; personal fees from Astra-Zeneca, GSK, Novartis, Teva, Vectura, UCB, Takeda, Roche, Janssen, Medimmune, Chiesi, outside the submitted work; J. Kleine-Tebbe reports personal fees for 1. Advisory Board membership (ALK-Abelló, Bencard, Leti, Novartis), personal fees for 2. Consultancy (Circassia, UK; MERCK, US), institutional grants from 3. Circassia, UK, LETI, Lofarma, Stallergenes, personal fees for 4. J. Kleine-Tebbe involved in lectures including service on speakers bureaus (Allergopharma, Allergy Therapeutics, ALK-Abelló, AstraZeneca, Bencard, HAL-Allergy, LETI, Lofarma, Novartis, Sanofi, Stallergenes-Greer, ThermoFisher) outside the submitted work. S. Lau reports grants from Allergopharma, personal fees from Merck, during the conduct of the study; grants from Symbiopharm Herborn, grants from Boehringer, outside the submitted work. P.M. Matricardi has nothing to disclose. G. Pajno reports grants from Stallergenes during the conduct of this work. N.G. Papadopoulos reports grants from Menarini, personal fees from Novartis, personal fees from Faes Farma, personal fees from BIOMAY, personal fees from HAL, personal fees from Nutricia Research, personal fees from Menarini, personal fees from Novartis, personal fees from MEDA, personal fees from Abbvie, personal fees from Novartis, personal fees from MEDA, personal fees from MSD, personal fees from MEDA, personal fees from Omega Pharma, personal fees from Danone, outside the submitted work. M. Penagos reports personal fees from Stallergenes and ALK, outside this work. O. Pfaar reports grants and personal fees from ALK-Abelló, Allergopharma, Stallergenes-Greer, HAL-Allergy Holding B.V./HAL-Allergie GmbH, Bencard Allergie GmbH/Allergy Therapeutics, Lofarma, Biotech Tools S.A., Laboratorios LETI/LETI Pharma, and Anergis S.A.; grants from Biomay, Nuvo, and Circassia; and personal fees from MEDA Pharma, Sanofi US Services, Mobile Chamber Experts (a GA^{2}LEN Partner), Novartis Pharma, and PohlBoskamp, outside this work. D. Ryan reports personal fees from MEDA, personal fees from Stallergenes, personal fees from Thermo Fisher, from null, outside the submitted work and 1. D. Ryan is Consultant Strategic Clinical Advisor, Optimum Patient Care; Director, Respiratory Effectiveness Group; Chair, Primary Care Interest Group, EAACI. A.F. Santos reports grants from Medical Research Council, grants from Immune Tolerance Network/NIAID, personal fees and other from Thermo Fisher Scientific, Nutricia, Infomed, outside the submitted work. G.J. Sturm reports grants from ALK-Abelló, personal fees from Novartis, personal fees from Bencard, personal fees from Stallergenes, outside the submitted work. F. Timmermans has nothing to disclose. R. van Ree reports consultancy and speaker fees for HAL-Allergy BV, consultancy for Citeq BV, and speaker fees for ThermoFisher Scientific. R. van Ree received funding from EU FP7, Dutch Science Foundation, and HESI-ILSI. E-M Varga reports lecture fees from ALK-Abelló, Stallergenes-Greer, Allergopharma, Bencard, MEDA, and Nutricia outside the submitted work. U. Wahn reports personal fees from Allergopharma, personal fees from ALK-Abelló, personal fees from Stallergenes-Greer, personal fees from Biomay, outside the submitted work. M. Kristiansen has nothing to disclose. S. Dhami reports grants from EAACI to carry out the review, during the conduct of this work. A. Sheikh reports grants from the EAACI during the conduct of this work. A. Muraro reports consultant fees from Meda-Mylan, other from Stallergenes-Greer, other from ALK, other from Nestlè, outside the submitted work.

ORCID

Susanne Halken http://orcid.org/0000-0003-0161-8278
Desiree Larenas-Linnemann http://orcid.org/0000-0002-5713-5331

Paolo M. Matricardi http://orcid.org/0000-0001-5485-0324
Antonella Muraro http://orcid.org/0000-0002-5026-5862

REFERENCES

1. Christiansen ES, Kjaer HF, Eller E, et al. The prevalence of atopic diseases and the patterns of sensitization in adolescence. *Pediatr Allergy Immunol*. 2016;27:847-853.
2. Henriksen L, Simonsen J, Haerskjold A, et al. Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. *J Allergy Clin Immunol*. 2015;136:360-366.
3. Tejedor Alonso MA, Moro MM, Mugica Garcia MV. Epidemiology of anaphylaxis. *Clin Exp Allergy*. 2015;45:1027-1039.
4. Patil VK, Kurukulaaratchy RJ, Venter C, et al. Changing prevalence of wheeze, rhinitis and allergic sensitisation in late childhood: findings from 2 Isle of Wight birth cohorts 12 years apart. *Clin Exp Allergy*. 2015;45:1430-1438.
5. Nwaru BI, Hickstein L, Panesar SS, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69:62-75.
6. Muraro A, Dubois AE, DunnGalvin A, et al. EAACI Food Allergy and Anaphylaxis Guidelines. Food allergy health-related quality of life measures. *Allergy*. 2014;69:845-853.
7. Zuberbier T, Lotvall J, Simoens S, Subramanian SV, Church MK. Economic burden of inadequate management of allergic diseases in the European Union: a GA(2) LEN review. *Allergy*. 2014;69:1275-1279.
8. Bahadori K, Doyle-Waters MM, Marra C, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med*. 2009;9:24.
9. Brozek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol*. 2017;140:950-958.
10. Dhami S, Nurmatov U, Arasi S, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. *Allergy*. 2017. https://doi.org/10.1111/all.13201. [Epub ahead of print].
11. Dhami S, Kakourou A, Asamoah F, et al. Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. *Allergy*. 2017. https://doi.org/10.1111/all.13208. [Epub ahead of print].
12. Dhami S, Zaman H, Varga EM, et al. Allergen immunotherapy for insect venom allergy: a systematic review and meta-analysis. *Allergy*. 2017;72:342-365.
13. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol*. 1998;102:558-562.
14. Jutel M, Agache I, Bonini S, et al. International Consensus on Allergen Immunotherapy II: mechanisms, standardization, and pharmacoeconomics. *J Allergy Clin Immunol*. 2016;137:358-368.
15. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol*. 2015;136:556-568.
16. Pfaar O, Bachert C, Bufe A, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (OGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). *Allergo J Int*. 2014;23:282-319.
17. Burgess JA, Walters EH, Byrnes GB, et al. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. *J Allergy Clin Immunol*. 2007;120:863-869.
18. Rochat MK, Illi S, Ege MJ, et al. Allergic rhinitis as a predictor for wheezing onset in school-aged children. *J Allergy Clin Immunol*. 2010;126:1170-1175.
19. Martin PE, Matheson MC, Gurrin L, et al. Childhood eczema and rhinitis predict atopic but not nonatopic adult asthma: a prospective cohort study over 4 decades. *J Allergy Clin Immunol*. 2011;127:1473-1479.
20. Jacobsen L, Nuchel PB, Wihl JA, Lowenstein H, Ipsen H. Immunotherapy with partially purified and standardized tree pollen extracts. IV. Results from long-term (6-year) follow-up. *Allergy*. 1997;52:914-920.
21. Nieto A, Wahn U, Bufe A, et al. Allergy and asthma prevention 2014. *Pediatr Allergy Immunol*. 2014;25:516-533.
22. Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy*. 2006;61:198-201.
23. Eng PA, Reinhold M, Gnehm HP. Long-term efficacy of preseasonal grass pollen immunotherapy in children. *Allergy*. 2002;57:306-312.
24. Muraro A, Halken S, Arshad SH, et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. *Allergy*. 2014;69:590-601.
25. Kristiansen M, Dhami S, Netuveli G, et al. Allergen immunotherapy for the prevention of allergy: a systematic review and meta-analysis. *Pediatr Allergy Immunol*. 2017;28:18-29.
26. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ*. 2010;182:E839-E842.
27. Collaboration Agree. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care*. 2003;12:18-23.
28. Dhami S, Nurmatov U, Halken S, et al. Allergen immunotherapy for the prevention of allergic disease: protocol for a systematic review. *Pediatr Allergy Immunol*. 2016;27:236-241.
29. Oxford Centre for Evidence-based medicine. Levels of Evidence and Grades of Recommendation. 2013. 31-3-2013. Ref Type: Online Source
30. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol*. 2002;109:419-425.
31. Nissen SP, Kjaer HF, Host A, Nielsen J, Halken S. The natural course of sensitization and allergic diseases from childhood to adulthood. *Pediatr Allergy Immunol*. 2013;24:549-555.
32. Larenas-Linnemann DE, Mosges R. Dosing of European sublingual immunotherapy maintenance solutions relative to monthly recommended dosing of subcutaneous immunotherapy. *Allergy Asthma Proc*. 2016;37:50-56.
33. Sander I, Fleischer C, Meurer U, Bruning T, Raulf-Heimsoth M. Allergen content of grass pollen preparations for skin prick testing and sublingual immunotherapy. *Allergy*. 2009;64:1486-1492.
34. Larenas-Linnemann D. Direct comparison of efficacy of sublingual immunotherapy tablets for rhinoconjunctivitis. *Ann Allergy Asthma Immunol*. 2016;116:274-286.
35. Bachert C, Larche M, Bonini S, et al. Allergen immunotherapy on the way to product-based evaluation-a WAO statement. *World Allergy Organ J*. 2015;8:29.
36. Grembiale RD, Camporota L, Naty S, Tranfa CM, Djukanovic R, Marsico SA. Effects of specific immunotherapy in allergic rhinitic individuals with bronchial hyperresponsiveness. *Am J Respir Crit Care Med*. 2000;162:2048-2052.
37. Crimi N, Li GF, Mangano G, et al. A randomized, controlled study of specific immunotherapy in monosensitized subjects with seasonal

rhinitis: effect on bronchial hyperresponsiveness, sputum inflammatory markers and development of asthma symptoms. *Ann Ital Med Int*. 2004;19:98-108.
38. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol*. 2002;109:251-256.
39. Moller C, Dreborg S, Lanner A, Bjorksten B. Oral immunotherapy of children with rhinoconjunctivitis due to birch pollen allergy. A double blind study. *Allergy*. 1986;41:271-279.
40. Marogna M, Tomassetti D, Bernasconi A, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol*. 2008;101:206-211.
41. Novembre E, Galli E, Landi F, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2004;114:851-857.
42. Zielen S, Devillier P, Heinrich J, Richter H, Wahn U. Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: a retrospective, real-world database analysis. *Allergy*. 2017. https://doi.org/10.1111/all.13213. [Epub ahead of print].
43. Schmitt J, Schwarz K, Stadler E, Wustenberg EG. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: results from a large retrospective cohort study. *J Allergy Clin Immunol*. 2015;136:1511-1516.
44. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. 2007;62:943-948.
45. Song W, Lin X, Chai R. Efficacy evaluation of standardized dust mite allergen specific immunotherapy to patients of allergic rhinitis. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2014;28:300-302.
46. Niggemann B, Jacobsen L, Dreborg S, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy*. 2006;61:855-859.
47. Valovirta E, Berstad AK, de Blic J, et al. Design and recruitment for the GAP trial, investigating the preventive effect on asthma development of an SQ-standardized grass allergy immunotherapy tablet in children with grass pollen-induced allergic rhinoconjunctivitis. *Clin Ther*. 2011;33:1537-1546.
48. Valovirta E, Petersen TH, Piotrowska T, et al. Results from the 5-year SQ grass SLIT-tablet asthma prevention (GAP) trial in children with grass pollen allergy. *J Allergy Clin Immunol*. 2017;pii: S0091-6749(17)31088-6. https://doi.org/10.1016/j.jaci.2017.06.014. [Epub ahead of print].
49. Peng H, Li CW, Lin ZB, Li TY. Long-term efficacy of specific immunotherapy on house dust mite-induced allergic rhinitis in China. *Otolaryngol Head Neck Surg*. 2013;149:40-46.
50. Roberts G, Pfaar O, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: allergic rhinitis. *Allergy*. 2017. https://doi.org/10.1111/all.13317. [Epub ahead of print].
51. Holt PG, Sly PD, Sampson HA, et al. Prophylactic use of sublingual allergen immunotherapy in high-risk children: a pilot study. *J Allergy Clin Immunol*. 2013;132:991-993.
52. Bozek A, Jarzab J, Bednarski P. The effect of allergen-specific immunotherapy on offspring. *Allergy Asthma Proc*. 2016;37:59-63.
53. Zolkipli Z, Roberts G, Cornelius V, et al. Randomized controlled trial of primary prevention of atopy using house dust mite allergen oral immunotherapy in early childhood. *J Allergy Clin Immunol*. 2015;136:1541-1547.
54. Yamanaka K, Shah SA, Sakaida H, et al. Immunological parameters in prophylactic sublingual immunotherapy in asymptomatic subjects sensitized to Japanese cedar pollen. *Allergol Int*. 2015;64:54-59.
55. Garcia BE, Gonzalez-Mancebo E, Barber D, et al. Sublingual immunotherapy in peach allergy: monitoring molecular sensitizations and reactivity to apple fruit and Platanus pollen. *J Investig Allergol Clin Immunol*. 2010;20:514-520.
56. Szepfalusi Z, Bannert C, Ronceray L, et al. Preventive sublingual immunotherapy in preschool children: first evidence for safety and protolerogenic effects. *Pediatr Allergy Immunol*. 2014;25:788-795.
57. Pifferi M, Baldini G, Marrazzini G, et al. Benefits of immunotherapy with a standardized Dermatophagoides pteronyssinus extract in asthmatic children: a three-year prospective study. *Allergy*. 2002;57:785-790.
58. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Randomized controlled open study of sublingual immunotherapy for respiratory allergy in real-life: clinical efficacy and more. *Allergy*. 2004;59:1205-1210.
59. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol*. 1997;99:450-453.
60. Inal A, Altintas DU, Yilmaz M, Karakoc GB, Kendirli SG, Sertdemir Y. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. *J Investig Allergol Clin Immunol*. 2007;17:85-91.
61. Reha CM, Ebru A. Specific immunotherapy is effective in the prevention of new sensitivities. *Allergol Immunopathol (Madr)*. 2007;35:44-51.
62. Asero R. Injection immunotherapy with different airborne allergens did not prevent de novo sensitization to ragweed and birch pollen north of Milan. *Int Arch Allergy Immunol*. 2004;133:49-54.
63. Harmanci K, Razi CH, Toyran M, Kanmaz G, Cengizlier MR. Evaluation of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. *Asian Pac J Allergy Immunol*. 2010;28:7-13.
64. Tella R, Bartra J, San MM, et al. Effects of specific immunotherapy on the development of new sensitisations in monosensitised patients. *Allergol Immunopathol (Madr)*. 2003;31:221-225.
65. Ohashi Y, Nakai Y. Immunotherapy for cure and prophylaxis of allergic rhinitis. *Clin Exp Allergy Rev*. 2009;9:6-10.
66. Limb SL, Brown KC, Wood RA, Eggleston PA, Hamilton RG, Adkinson NF Jr. Long-term immunologic effects of broad-spectrum aeroallergen immunotherapy. *Int Arch Allergy Immunol*. 2006;140:245-251.
67. Dominicus R. 3-years' long-term effect of subcutaneous immunotherapy (SCIT) with a high-dose hypoallergenic 6-grass pollen preparation in adults. *Eur Ann Allergy Clin Immunol*. 2012;44:135-140.
68. Di Rienzo V, Marcucci F, Puccinelli P, et al. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy*. 2003;33:206-210.
69. Purello-D'Ambrosio F, Gangemi S, Merendino RA, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy*. 2001;31:1295-1302.
70. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. *J Allergy Clin Immunol*. 2010;126:969-975.
71. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy*. 2001;31:1392-1397.
72. Gulen F, Zeyrek D, Can D, et al. Development of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. *Asian Pac J Allergy Immunol*. 2007;25:7-11.
73. Di Bona D, Plaia A, Leto-Barone MS, La PS, Di LG. Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinoconjunctivitis: a systematic review and meta-analysis. *JAMA Intern Med*. 2015;175:1301-1309.
74. Calderon MA, Vidal C, Del Rodriguez RP, et al. European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a real-life clinical assessment. *Allergy*. 2017;72:462-472.
75. Del Rodriguez RP, Vidal C, Just J, et al. The European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a paediatric assessment. *Pediatr Allergy Immunol*. 2017;28:60-70.

76. Ryan D, Gerth van Wijk R, Angier E, et al. EAACI guidelines on allergen immunotherapy: a situational analysis of current provision of allergen immunotherapy in primary care in Europe. *Allergy*. 2017. EPub ahead of print.
77. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *J Allergy Clin Immunol*. 2010;125:569-574.
78. Passalacqua G, Baena-Cagnani CE, Bousquet J, et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: speaking the same language. *J Allergy Clin Immunol*. 2013;132:93-98.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Halken S, Larenas-Linnemann D, Roberts G, et al. EAACI guidelines on allergen immunotherapy: Prevention of allergy. *Pediatr Allergy Immunol*. 2017;28:728–745. https://doi.org/10.1111/pai.12807

SPONSORSHIP

This section contains information that is promotion in nature, whilst relevant to the topic area, it is not part of the scientific/educational content.

DIAMOND

Merck

Calle Maria de Molina, 40, 2º PLANTA +34 917455603
coran.djillali@merckgroup.com
www.merckgroup.com

Merck is a leading science and technology company in healthcare, life science and performance materials. Around 53,000 employees work to further develop technologies that improve and enhance life – from biopharmaceutical therapies to treat cancer or multiple sclerosis, cutting-edge systems for scientific research and production, to liquid crystals for smartphones and LCD televisions. In 2017, Merck generated sales of €15.3 billion in 66 countries. Founded in 1668, Merck is the world's oldest pharmaceutical and chemical company. The founding family remains the majority owner of the publicly listed corporate group. Merck holds the global rights to the "Merck" name and brand. The only exceptions are the United States and Canada, where the company operates as EMD Serono, MilliporeSigma and EMD Performance Materials."

GOLD

Aimnmune Therapeutics

344-354 Gray's Inn Road WC1X 8BP
London, United Kingdom +44 20 86 29 02 40
www.aimmune.com

Aimmune is a clinical-stage biopharmaceutical company developing proprietary product candidates and advancing a therapeutic approach for the treatment of peanut and other food allergies. Our mission is to improve the lives of people with food allergies. We are developing desensitization treatments to help protect people with food allergies by potentially reducing the risk of allergic reactions, making accidental exposures to allergens less dangerous. We aim to address food allergies by providing a treatment option that goes beyond the current recommendations of avoiding exposure to food allergens and carrying adrenaline for administration in case of accidental exposure. Our work is grounded in our founding from within the food allergy community.

DBV Technologies

177-181 avenue Pierre Brossolette
92120 Montrouge, France
www.dbv-technologies.com

DBV Technologies is a clinical-stage biopharmaceutical company founded in 2002, developing immunotherapy product candidates utilizing a novel proprietary technology platform based on investigational epicutaneous immunotherapy, which aims at delivering biologically active compounds to the immune system through intact skin. The most advanced product candidates are currently being developed for the treatment of food allergies. Food allergies are an increasingly prevalent condition worldwide with no currently approved treatments. DBV Technologies has global headquarters in Montrouge, France and New York, NY.

DIATER

Avenida Gregorio Peces Barba 2
28919 Madrid, Spain +34 91 49 66 013
www.diater.com

We are a biopharmaceutical company, specialized in allergic, diseases that offers physicians a wide range of diagnosis and treatment products to significantly improve the quality of life of patients with allergies. Diater, founded in 1999, is a market leader that provides medical professionals with the tools required to meet any medical need in the field of immunotherapy with allergens and provide treatment tailored to each patient.

Immunotek S. L.

Calle Punto Mobi, 5
28805 Alcalá de Henares, Spain +34 64 79 17 492
www.inmunotek.com

Inmunotek is a pharmaceutical company based in Madrid (Spain), which investigates, develops, manufactures and commercializes products in the field of Allergy and Immunology for the diagnosis and treatment of allergic respiratory diseases in human and veterinary patients. From the outset, our goal has been to offer innovative and competitive products of the highest quality, useful for professionals and safe and effective for the treatment of patients. To this end we have put together a highly professional and motivated team; we have outstanding facilities and a broad product portfolio. Inmunotek complies with GMPs, and their products are approved by the Spanish Drug Agency and several international regulatory agencies.

SILVER

ALK

Bøge allé 6-8
2970 Hørsholm, Denmark +45 45 74 75 76
www.alk.net

ALK is a global specialty pharmaceutical company focused on allergy and allergic asthma. It markets allergy immunotherapy treatments and other products and services for people with allergy and allergy doctors. Headquartered in Hørsholm, Denmark, ALK employs around 2,300 people worldwide and is listed on Nasdaq Copenhagen.

Allergy Therapeutics plc.

Dominion Way
BN14 8SA Worthing, United Kingdom +44 19 03 84 47 20
www.allergytherapeutics.com

We are a visionary immunology business with specialist experience in the research and development of allergy treatments. We have a well-established commercial presence in Europe and are focused on the US market opportunity. We specialize in the diagnosis and treatment of allergy. Allergy vaccination is a successful treatment that deals with the underlying cause of allergies and not just the symptoms. We mainly sell our products in European countries and our pipeline of products in clinical development includes vaccines for grass, tree and house dust mite, as well as a peanut allergy vaccine in pre-clinical development. Adjuvant systems to boost performance of vaccines outside allergy are also under evaluation.

HAL Allergy

J. H.Oortweg 15-17
2333 CH Leiden, The Netherlands +31 88 95 90 00
www.hal-allergy.com

HAL Allergy Group is a modern leader and innovator in the field of biopharmaceuticals and located at the Bio Science Park in Leiden, The Netherlands. Our core business is the production of allergen extracts, both for therapeutic and diagnostic purposes as well as contract manufacturing with focus on biopharmaceutical products for preclinical and clinical studies. With office in major European countries, HAL Allergy is one of the European top players, particularly in the field of allergy. Established in 1959 we have long experience in developing and producing therapies against pollen, house dust mite, and insect venom allergy.

Leti

Gran Via de les Corts Catalanes, 184
08038 Barcelona, Spain +34 93 394 53 50

Laboratorios LETI is a company with a global presence of reference in specialized segments of health and wellness, a leader through innovation and development of prestige products and brands.
Specialists in diagnosing allergies and treating with immunotherapy.

Stallergenes Greer

6, rue Alexis de Tocqueville
92183 Antony Cedex, France +33 15 55 92 000
www.stallergenesgreer.com

STALLERGENES GREER is a fully integrated global biopharmaceutical company focused on allergen and allergy immunotherapy (AIT) products to treat patients suffering from allergies. We aspire to change the treatment paradigm of allergy therapies by delivering curative medicines and innovative tools for patients. With 5 manufacturing sites located in the U.S and Europe, we develop and commercialize products in more than 20 countries. AIT is an allergy treatment that treats the underlying cause of allergy.

NOTES

NOTES

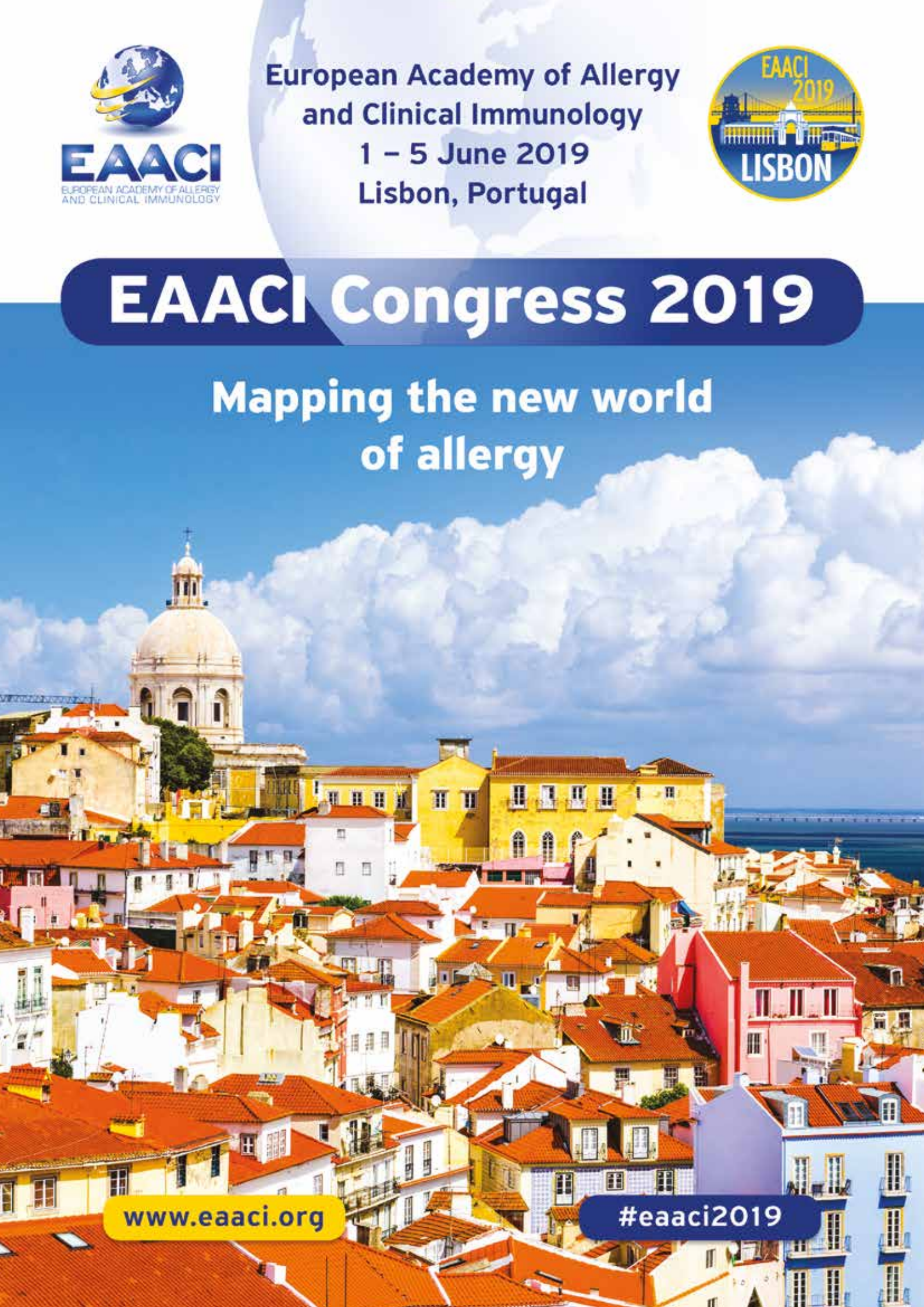
EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

European Academy of Allergy and Clinical Immunology
1 – 5 June 2019
Lisbon, Portugal

EAACI 2019 LISBON

EAACI Congress 2019

Mapping the new world of allergy



www.eaaci.org

#eaaci2019

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

FAAM 2018

18 - 20 October 2018
Copenhagen, Denmark

FAAM
Food Allergy and Anaphylaxis Meeting

5th Food Allergy and Anaphylaxis Meeting

www.eaaci.org/faam2018