Position paper

International consensus on allergy immunotherapy

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Allergen immunotherapy (AIT) has been used to treat allergic disease since the early 1900s. Despite numerous clinical trials and meta-analyses proving AIT efficacious, it remains underused and is estimated to be used in less than 10% of patients with allergic rhinitis or asthma worldwide. In addition, there are large differences between regions, which are not only due to socioeconomic status. There is practically no controversy about the use of AIT in the treatment of allergic rhinitis and allergic asthma, but for atopic dermatitis or food allergy, the indications for AIT are not well defined. The elaboration of a wider consensus is of utmost importance because AIT is the only treatment that can change the course of allergic disease by preventing the development of asthma and new allergen sensitizations and by inducing allergen-specific immune tolerance. Safer and more effective AIT strategies are being continuously developed both through elaboration of new allergen preparations and adjuvants and alternate routes of administration. A number of guidelines, consensus documents, or both are available on both the international and national levels. The international community of allergy specialists recognizes the need to develop a comprehensive consensus report to harmonize, disseminate, and implement the best AIT practice. Consequently, the International Collaboration in Asthma, Allergy and Immunology, formed by the European Academy of Allergy and Clinical Immunology; the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the World Allergy Organization, has decided to issue an international consensus on AIT. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *International consensus, allergy, immunotherapy, allergen vaccine, allergic rhinitis, asthma, food allergy, atopic dermatitis*

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Disclosure of potential conflict of interest: M. Jutel has received research support from the Polish National Science Centre and lecture fees from Allergopharma and Stallergenes. S. Bonini has provided expert testimony for the European Medicines Agency. A. W. Burks is on the FARE and World Allergy Organization boards; is on the Murdoch Children's Research Institute advisory board; has received consultancy fees from Gerson Lehrman Group, ActoGeniX, Genentech, Sanofi US, Valeant Pharmaceuticals North America; has provided unpaid consultation for Dynavax Technologies, Perrigo Company (PBN Nutritionals), and Perosphere; is employed by the University of North Carolina; has patents (US5558869, US55973121, US6441142, US6486311, US6835824, US7485708, and US7879977); has received payment for developing educational presentations from Current Views 2012; and has stock/stock options in Allertein and Mastcell Pharmaceuticals. M. Calderon has received consultancy fees from ALK-Abelló, STG, and Hal Allergy; has received lecture fees from ALK-Abelló STG, and Allergopharma; and has received travel support from ALK-Abelló, STG, Allergopharma, and Hal Allergy. W. Canonica has received consulting fees from ALK-Abelló, Allergy Therapeutics, Lofarma, and Stallergenes. L. Cox has received consulting fees from Greer, has received fees for participation in review activities from Circassia and Biomay, is on the American Board of Allergy and Immunology and American Academy of Allergy, Asthma & Immunology Boards, and has received lecture fees from Southeastern Allergy Asthma Immunology Association. P. Demoly has received consultancy fees from ALK-Abelló, Circassia, Stallergenes, Allergopharma, Thermo Fisher Scientific, DBV, Chiesi, and Pierre Febre Medicaments and has received lecture fees from Menarini, MSD, AstraZeneca, and GlaxoSmithKline. J. Kleine-Tebbe is on the ALK-Abelló, Novartis, Leti, and Bencard advisory boards; has received consultancy fees from Merck and Circassia; has received research support from Circassia; and has received lecture fees from Allergopharma, ALK-Abelló, Bencard, HAL Allergy, LETI, Lofarma, Novartis, and Stallergenes. A. Muraro has received consultancy fees from Meda, Nutricia, Allergopharma, and Novartis. G. Lack has stock/stock options in DBV Technologies. D. Larenas is on the CMICA board; has received consultancy fees from Meda, Pfizer, MIT, Boehringer Ingelheim, Novartis,

Abbreviations used
AD: Atopic dermatitis
AIT: Allergen immunotherapy
AR: Allergic rhinitis
EAACI: European Academy of Allergy and Clinical Immunology
HDM: House dust mite
LR: Local reaction
OIT: Oral immunotherapy
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
SR: Systemic reaction
WAO: World Allergy Organization

INTRODUCTION

Aim

The international consensus statement on allergen immunotherapy (AIT) is a concise document authored by a multinational group of experts reviewing the pertinent literature and summarizing the key statements for AIT. The document combines the best scientific evidence with expert opinion consensus and was developed to serve as the resource for health care professionals managing patients with allergic diseases. The document also provides a rationale for providing better access to AIT based on the public health and pharmacoeconomic analyses that can be used by policymakers. It is adaptable for all countries worldwide, allowing for modifications based on the regional availability of diagnostic and therapeutic interventions.

Methodology of the international consensus on AIT

The current board of the International Collaboration in Asthma, Allergy and Immunology and the participating organizations formed the working committee on the basis of regional representation, expertise in the field, and previous participation in the creation of AIT guidelines. The members of the committee proposed the most relevant areas and selected the documents for critical review; the major documents are listed in Table I.[1-30] Many task force reports and consensus documents of the European Academy of Allergy and Clinical Immunology (EAACI) AIT Interest Group, as well as key scientific papers, were also considered. Each member was responsible for the preparation of text. A draft was subsequently compiled and circulated (in January 2015) among the authors for comments and corrections. The governing boards of the participating organizations then approved the final draft. The nomenclature and terms used are summarized in Box 1.

Current status of AIT

AIT was introduced by Leonard Noon 103 years ago and is the only potential disease-modifying treatment for allergic subjects. Significant progress has been made in terms of proving its efficacy and safety both for respiratory allergy and venom hypersensitivity, and recent data look promising also for AIT as a disease-modifying treatment for food allergy and atopic dermatitis (AD). However, AIT remains underused mainly because of: (1) a lack of agreement in documented efficacy; (2) insufficient data on its cost-effectiveness; (3) differing proportion and educational level of physicians taking care of allergic subjects; (4) lack of awareness of AIT in the general population and non–allergy/immunology-trained population; (5) scattered availability of regimens, products for application, or both; and (6) varying selection of potential responders.[31]

Historically, AIT was administered by means of subcutaneous immunotherapy (SCIT), but in the past 25 years, there has been a substantial increase in the use of sublingual immunotherapy

and Glenmark; has received research support from Novartis, Pfizer, Meda, UCB, GlaxoSmithKline, AstraZeneca, Sunovion, Sanofi, MSD, Teva, and Commet; has received lecture fees from AstraZeneca, Glenmark, MSD, UCB, Meda, and Pfizer; has received payment for developing educational presentations from Glenmark; and has received travel support from MSD, UCB, AstraZeneca, Pfizer, Meda, Senosiain, Glenmark, ALK-Abelló, Novartis, and Chiesi. H. Nelson is on the advisory board for Merck and Circassia, is on the data monitoring board for AstraZeneca and Pearl Therapeutics, and has received research support from Circassia. O. Pfaar has received consultancy fees from Bencard (Germany), HAL-Allergy (The Netherlands), Novartis/LETI (Germany), MEDA (Germany), ALK-Abelló (Germany/Denmark), Allergopharma (Germany), Biotech Tools s.a. (Belgium), GfK Bridgehead (United Kingdom), NAVIGANT-consulting (United States), Sanofi (United States), Guidepoint Global Advisors (United States), Stallergenes (Germany/France), and Mobile Chamber Experts (MCX), a GA2LEN Partner (Germany); is employed by Universitätsmedizin Mannheim, Heidelberg University; has received research support from ALK-Abelló (Germany/Denmark), Allergopharma (Germany), Stallergenes (Germany/France), HAL-Allergy (Germany/The Netherlands), Artu Biologicals (The Netherlands), Allergy Therapeutics/Bencard (UK/Germany), Hartington (Spain), Lofarma (Italy), Novartis/Leti (Germany/Spain), GlaxoSmithKline (United Kingdom/Germany), Essex-Pharma (Germany), Cytos (Switzerland), Curalogic (Denmark), Roxall (Germany), Biomay (Austria), Thermo Fisher (Germany), Circassia (UK), E.U (FP-7-Health-2013-Innovation 1), Biotech Tools s.a. (Belgium), and MEDA-Pharma GmbH (Germany); has received lecture fees from ALK-Abelló (Germany/Denmark), Allergopharma (Germany), Stallergenes (Germany/France), HAL-Allergy (Germany/The Netherlands), Allergy Therapeutics/Bencard (United Kingdom/Germany), Hartington (Spain), Lofarma (Italy), Novartis/Leti (Germany/Spain), GlaxoSmithKline (United Kingdom/Germany), Roxall (Germany), Thermo Fisher (Germany), and MEDA-Pharma GmbH (Germany); is coeditor and author of textbook "Allergien bei Kindern und Jugendlichen" (Schattauer, Germany), author of different chapters of "Allergologie-Handbuch" (Schattauer, Germany), and author of 1 chapter in "Allergologie" (Springer, Germany); has received payment for developing educational presentations from GlaxoSmithKline (Germany), Bencard (Germany), and Novartis (Germany); has received travel support from HAL-Allergy (Netherlands/Germany) and Allergopharma (Germany); and is current chairman of IT IG of European Academy of Allergy and Clinical Immunology (EAACI), and current secretary of ENT-section of DGAKI. R. van Ree is on the EAACI board, has received consultancy fees from HAL Allergy BV, has received research support from the European Union, and has received lecture fees from Thermo Fisher Scientific. H. Sampson is an unpaid consultant on the DBV Scientific Advisory Board. G. Du Toit has received lecture fees from Thermo Fisher, owns 2% equity of the FoodMaestro app, and has received travel support from the EAACI as secretary of the paediatric section. R. Gerth van Wijk has received consultancy fees from MSD, HAL, Crucell, ALK-Abelló, and Novartis; has received research support from NWO, STW, Novartis, Biomay, and DBV; has received lecture fees from Allergopharma and Thermo Fisher; has received payment for manuscript preparation from Chiesi; and receives royalties from de Tijdstroom and Bohn, Stafleu, van Loghum. C. A. Akdis has received consultancy fees from Actellion, Aventis, Stallergenes, Allergopharma, and Circacia; is employed by the Swiss Institute of Allergy and Asthma Research, University of Zuurich; has received research support from Novartis, PREDICTA, Swiss National Science Foundation, MeDALL (Programme no. 261357), and the Christine-Kuhne Center for Allergy Research and Education. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication March 15, 2015; Revised April 20, 2015; Accepted for publication April 29, 2015.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.04.047

TABLE I. Comparison between established guidelines for AIT

	Year	Evidence model	No. of RCTs, SCIT/SLIT*	SCIT recommendation	SLIT recommendation
Specific guidelines on AIT†					
EAACI 1988 Workshop report[1]	1988	None	8/0	Demonstrated IgE-mediated disease: with symptoms related to exposure High-quality extracts, proper dose	None
WHO consensus[2]	1989	None	±8/0	Rhinoconjunctivitis, asthma, venom IT Use of standardized extracts is stressed	None
EAACI position paper, 1993[3]	1993	None	28/6	Only references available	None
Australasian guidelines on SCIT for asthma[4]	1997	None	0/0	SCIT is given as an alternative treatment option to add to pharmacotherapy in asthmatic patients	None
WHO position paper[5]	1998	None	11/0	ARC (with allergic asthma) If medication is not sufficient/ wanted	High-dose SLIT might be a viable alternative
EAACI local immunotherapy[6]	1998	None	x/4	x	Suggested in adults
EAACI SCIT[7]	2006	None	8/x	ARC, asthma, SRs to HV Standardized products with documented efficacy Single or few causative allergens	x
Canadian guideline[8]	2006	None	4/10	• Significant symptoms of IgE-mediated AR/asthma inadequately treated • Proved efficacy of extracts • Early treatment might prevent chronic disease	SLIT evaluated positively as "novel form" but no recommendation given
AAAAI/ACAAI practice parameters[9]	2007	Shekelle et al[10]	62/14	ARC, asthma, SRs to HV	SLIT as investigational in United States (no FDA approval yet)
WAO SLIT guidelines[11]	2009		60 RDBPC trials	NA	SLIT is indicated for treatment of different allergic conditions according to the general criteria of selecting patients for SIT; mild-to-moderate IgE-mediated disease, clinically relevant allergens, exhausting pharmacologic and nonpharmacologic therapeutic options, and unavoidable side effects of medication
Argentinean guidelines[12]	2010	None‡	No review	ARC, asthma IgE-mediated disease with detected causal allergens as cotreatment with medication	Same as in SCIT + extra indication for SLIT if SCIT is not tolerated/acceptable
AAAAI/ACAAI practice parameters[13]	2011	Shekelle et al[10]	65/9	ARC, asthma, SRs to HV AD if associated with aeroallergen sensitivity HV bothersome large LRs	SLIT as investigational in United States (no FDA approval yet)
British guidelines[14]	2011	SIGN	15/25	IgE-mediated seasonal pollen-induced rhinitis not responding to optimal pharmacotherapy Some HDM/animal dander allergy cases SRs to HV	SLIT for adults and children with AR after treatment failure with medication and avoidance

(Continued)

TABLE I. *(Continued)*

	Year	Evidence model	No. of RCTs, SCIT/SLIT*	SCIT recommendation	SLIT recommendation
Mexican guidelines[15]	2011	GRADE	55/18	ARC, asthma, SRs to HV Eventually in AD and some specific cases of urticaria with IgE-mediated mechanism	Recommend SLIT for adults and children with AR and asthma; suggest for some cases of AD, latex allergy, and large LRs to hymenoptera venom
Chinese expert consensus on AIT for AR[16]	2011	Consensus; article in Chinese			
Finnish update on current care guidelines: AIT[17]	2012	Article in Finnish; data from abstract		SCIT for ARC and asthma with pollens, HDM, animal dander, and insect venoms effective for both adults and children	Indicated for AR caused by grass pollen Oral tolerance induction in children older than 5 y with severe food allergy
Guiding principles of SCIT for AR in Japan[18]	2013	Modified Shekelle et al[10]	12/0 (+data from meta-analysis)	Indicated for AR in adults and children >5 years of age No specific list on indications, only contraindications	None
WAO SLIT guidelines[19]	2013	GRADE	77 RDBPC trials, of which 62 with grass or HDM extracts 4 new meta-analyses	NA	SLIT clinically effective for rhinitis and conjunctivitis in adults; asthma and rhinitis in children, although differences exist among allergens Long-term benefits of SLIT for at least 1 or 2 y after discontinuation for immunotherapy with grass pollen allergen tablets in adults
Polish position paper on SLIT[20]	2014	Consensus/ none (?)	x/17 (+data from meta-analysis)	x	AR, asthma Advantage of SCIT over SLIT in decreasing symptoms and lower respiratory tract inflammation SLIT might be the method for children, and SCIT might be the method for adults
Spanish allergists' consensus on IT in polysensitized patients[21]	2014	Consensus with Delphi method	0/0 review and opinion articles	Correct diagnosis of the allergen causing the symptoms is essential based on clinical history, SPT, and *in vitro* (preferentially molecular diagnosis) No more than 3 related extracts in 1 vial	x
German, Austrian, and Swiss allergists' and specialists' consensus on IT in patients with allergic airway diseases[22]	2014	Consensus with conference and Delphi method	Comprehensive evaluation and citation of RCTs (SCIT and SLIT)	ARC, asthma	ARC
Other guidelines in which immunotherapy is mentioned					
ARIA 2001[23]	2001	Shekelle et al[10]	0/12	SCIT is recommended for AR, allergic asthma, and insect hypersensitivity	High-dose nasal and high-dose sublingual swallow–specific immunotherapy might be indicated in the following groups: • some patients with rhinitis, conjunctivitis, and/or asthma caused by pollen and mite allergy • patients whose symptoms are not sufficiently controlled by conventional pharmacotherapy • patients who have SRs associated with injection immunotherapy • patients who are poorly compliant and refuse injections

(Continued)

TABLE I. *(Continued)*

	Year	Evidence model	No. of RCTs, SCIT/SLIT*	SCIT recommendation	SLIT recommendation
ARIA update 2008[24]	2008	Shekelle et al[10]	34/18 (+data from meta-analysis)/36	SCIT is effective in adults and children for pollen and mite allergy Burdened by the risks of side effects Cost-effective	SLIT recommended in adults with pollen allergy Can be used in patients with mite allergy Patients who have presented SRs during SCIT
ARIA update 2010[25]	2010	GRADE	24/63 (+data from meta-analysis)/0	Suggests the use of pollen and HDM SCIT for AR in adults and children and for concomitant AR and asthma	Suggests the use of pollen and HDM SLIT for AR in adults and of pollen SLIT in children Does not suggest HDM SLIT in children for treatment of AR Suggests SLIT in patients with AR plus asthma for asthma treatment
GA^{2}LEN/EAACI pocket guide for AIT[26]	2010	Based on WAO IT papers and ARIA 2001, 2008, and 2010	No new review	Indications are given for SLIT and SCIT together: ARC, mild asthma IgE-mediated disease with symptoms of sufficient severity and duration Availability of a standardized high-quality extract Adverse reactions differ between both routes (SCIT more systemic; SLIT more local)	
BSACI guidelines on Hymenoptera venom allergy[27]	2011	NICE accredited	6/0	Presence of IgE to venom SCIT for patients with history of severe (and moderate) SRs Not indicated for only LRs	SLIT for venom immunotherapy is mentioned as a future research area
Japanese guidelines on rhinitis[28]	2011	More descriptive No specific method	0/0	SCIT for patients from 6 years onward in whom therapy can be continued	Not mentioned
Guidelines for treatment of atopic eczema of the European Academy of Dermatology and Venereology[29]	2012	Appraisal of Guidelines Research and Evaluation and DELPHI procedure	0/0 (this is a review of guidelines and not RCTs)	Allergen IT (not stating SLIT or SCIT) to aeroallergens might be useful in selected cases of atopic eczema	
GINA 2014[30]	2014	Adapted from Shekelle et al[10]	1 review/3 reviews/1 RCT	Efficacy of AIT in asthma is limited Level of evidence given for this claim: potential benefits (SCIT or SLIT) must be weighed against the risk of adverse events and the inconvenience and cost of the prolonged course of therapy (D)	

AAAAI, American Academy of Allergy, Asthma & Immunology; *AC*, allergic conjunctivitis; *ACAAI*, American College of Allergy, Asthma and Immunology; *AIT*, allergen-specific immunotherapy; *ARC*, allergic rhinoconjunctivitis; *ARIA*, Allergic Rhinitis and its Impact on Asthma; *BSACI*, British Society for Allergy and Clinical Immunology; *FDA*, US Food and Drug Administration; *GINA*, Global Initiative for Asthma; *GRADE*, Grading of Recommendations Assessment, Development and Evaluation; *IT*, immunotherapy; *HV*, Hymenoptera venom; *NA*, not applicable; *NICE*, National institute for Health and Care excellence; *RCT*, randomized controlled trial; *RDBPC*, randomized, double-blind placebo-controlled; *SIGN*, Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/); *SPT*, skin prick test; *WHO*, World Health Organization.
*Number of randomized controlled trials on SLIT.
†Normal font indicates published in the original WAO SLIT position paper; boldface font indicates new guidelines published since 2009.
‡Table of evidence and recommendation taken from other guidelines based on Shekelle et al.[10]

(SLIT). In part, this has been driven by issues concerning the safety of SCIT: in the 1980s, a number of fatal adverse reactions were reported,[32] which led to restrictions on the use of SCIT in some parts of Europe and stimulated the exploration of safer routes of administration. Practical and logistic considerations have also favored the introduction of SLIT because many patients cannot easily commit time to for an injection regimen. Standardization of allergen extracts has also improved significantly. Several novel approaches are under investigation. They use either recombinant antigen technology to produce modified proteins and peptides or intradermal or epicutaneous application of immunodominant peptides or approaches to enhance the desirable immune response to allergens with decreased side effects by using adjuvants or by stimulating the innate immune system. Such approaches are under development, aiming to reduce the risk of anaphylaxis and hence allow more rapid updosing. Although this is a desirable objective, most of these approaches are still in the early phases of clinical trials. Assessment of cost-effectiveness has been difficult, mainly because of problems in assessing efficacy.

Increasingly, health care payers and regulators are asking for greater detail about the clinical benefit that can be achieved, and to that end, we need better systems for defining benefit not only in statistical terms but also in terms of what is relevant to individual patients. Harmonization of scoring systems is desirable, but it is more important to validate these in terms of patient-relevant

outcomes. A World Allergy Organization (WAO) Task Force proposed a 20% effect over placebo as a reasonable cutoff of clinical efficacy for clinical trials.[33] Recently, an EAACI Task Force recommended a homogeneous combined symptom and medication score as the primary outcome for AIT effectiveness, which provides a simple and standardized method that balances both symptoms and the need for antiallergic medication in an equally weighted manner.[34] On the other hand, reliable systems of allergen exposure are needed to assess AIT-induced allergen-specific tolerance. In this context environmental exposure chambers provide a very promising approach.[35]

METHODS OF AIT

Routes of administration

Subcutaneous injection has been the predominant method of administration. Over the last 2 decades, sublingual application of the extracts has increased and is now the dominant approach in several European countries.[36] Additional approaches to AIT under active investigation include epicutaneous and intralymphatic administration.[37,38]

Administration regimens

The conventional schedule for SCIT with unmodified allergen extracts consists of a dose build up by means of one-weekly injections, followed by maintenance dose injections at 4- or 8-week intervals. Fewer build-up injections are possible with modified allergenic extracts, such as allergoids or addition of adjuvants.

The build-up phase can be shortened by using cluster or rush schedules. During a cluster schedule, multiple injections (usually 2-3) are administered on nonconsecutive days. In a rush protocol multiple injections are administered on consecutive days, reaching maintenance typically in 1 to 3 days. A direct comparison showed no increase in systemic reactions (SRs) and a more rapid achievement of symptomatic improvement for the cluster schedule.[39] A rush protocol, on the other hand, even with use of premedication, is associated sometimes with an increase in SRs but can also be well tolerated.[32,40,41] In SLIT the build-up period is either shortened or not needed.

Treatment duration

The customary duration of AIT is 3 to 5 years. Prospective studies of SCIT with grass pollen extract for allergic rhinitis (AR)[42] and house dust mite (HDM) extract for asthmatic patients[43] suggest that 3 years of AIT produces prolonged remission of symptoms after discontinuation. A prospective study of SLIT with HDM extract in patients with AR demonstrated remissions lasting 7 and 8 years, respectively, with 3 or 4 years of active treatment.[44]

Special considerations

Polysensitized patients. The majority of patients with AR or allergic asthma seen by specialists are polysensitized. Not all of these sensitivities are clinically important. Moreover, AIT is equally effective in monosensitized and polysensitized patients if the relevant allergen is selected.[45]

Monoallergen immunotherapy versus allergen mixes. Virtually all of the published randomized controlled studies of both SCIT and SLIT are with single allergen extracts. These studies dominate the meta-analyses that indicate both SCIT and SLIT are effective treatments for AR and allergic asthma. There is conflicting evidence for the effectiveness of allergen mixes.[46-48]

Selection of allergens for AIT. Relevant allergens are major contributors to the safety and efficacy of the allergenic extracts used for AIT. Most of the available data address mites, selected pollens, and animal dander, whereas less is known about the efficacy and safety of mold or cockroach allergens. Selection of the relevant allergen is usually based on the combination of history with results of skin prick or *in vitro* tests. Component-resolved diagnosis might prove useful for excluding cross-reactive allergens.

Multiple AIT products. An alternative to allergen mixes for both SLIT and SCIT is the administration of multiple allergen extracts at different times during the day or different locations.[45]

SPECIFIC CLINICAL INDICATIONS FOR AIT

AR

Indications and efficacy. According to the Allergic Rhinitis and its Impact on Asthma guidelines,[25,49] AIT is indicated for the treatment of moderate-to-severe intermittent or persistent symptoms of AR, especially in those who do not respond well to pharmacotherapy. Allergen extracts are available for grass, tree, and weed (ie, ragweed) pollens; HDMs; mold; and animal dander. Standardized extracts should be used in clinical practice because the efficacy and safety of AIT depends strictly on extract quality.

Recent systematic reviews have consistently shown that AIT can achieve substantial clinical results by improving nasal and ocular symptoms and by reducing medication need.[11,20,50-52] AIT also improves quality of life, prevents progression of AR to asthma, and reduces new sensitizations.[53-55] Clinical efficacy persists after discontinuation of AIT.[44,56] All the outcomes of AIT in patients with AR lead to a clear pharmacoeconomic advantage over other therapies.[57]

Contraindications and side effects

SCIT requires that injections should be performed by trained personnel in clinical settings who are equipped to manage any possible systemic adverse reactions or anaphylaxis. SRs are quite rare when AIT is performed according to proper safety recommendations.[58-60] AIT is contraindicated in patients with medical conditions that increase the risk of treatment-related severe SRs, such as those with severe or poorly controlled asthma or significant cardiovascular diseases (eg, unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension) and should be administered with caution to patients receiving β-blockers or angiotensin-converting enzyme inhibitors.[13] Chronic nasal inflammatory responses and nasal polyps are not a contraindication for AIT.

Measuring clinical outcome. Symptom and medication scores are the recommended measure of efficacy for randomized controlled trials, particularly the combined symptom and medication score. For clinical practice, the visual analog scale or the newly developed rhinitis control tests might be more helpful. However, standardized and globally adopted measures of AIT efficacy in randomized controlled trials are still lacking.[34]

Treatment duration. The recommended duration of AIT for AR is 3 years both for SCIT and SLIT. Evidence from a long-term open controlled study suggests that a 3-year course of SLIT might not be sufficient for a long-term protection.[44]

Pediatric considerations. SLIT is shown to be safe and effective, even in children as young as 3 years of age.[11,20,52] A meta-analysis of SLIT in children reported significantly reduced symptoms and medication scores.[61] However, criteria for new well-designed and well-powered studies in children are

requested by the European Medicines Agency within the pediatric investigations plan, with an emphasis on long-term efficacy.

Allergic asthma

The pathologic process of airways inflammation in asthmatic patients is not invariably associated with atopy. Within the allergic asthma subgroup, the pathophysiology is very complex and includes several disease variants.[59] Various endotypes have been described that define intrinsically distinct pathogenetic mechanisms. Endotyping asthma could eventually lead to individualized management, including selection of asthmatic patients responding best to AIT.[62]

Current asthma therapies can effectively control symptoms and the ongoing inflammatory process but do not affect the underlying dysregulated immune response.[63] Thus they are very limited in controlling the progression of the disease.

Indications and efficacy. The current Allergic Rhinitis and its Impact on Asthma guidelines[25,49] give both SCIT and SLIT a conditional recommendation in patients with allergic asthma because of the moderate or low quality of evidence. According to the Global Initiative for Asthma report updated in 2014,[64] the efficacy of AIT in asthmatic patients is limited (level A evidence), and compared with pharmacologic and avoidance options, the benefit of both SCIT and SLIT must be weighed against the risk of side effects and the inconvenience and cost incurred by the prolonged course of treatment (level D evidence).

Few specifically designed studies evaluated AIT in asthmatic patients, and only 1 had a formal sample size calculation.[65] In addition, no consensus exists on the optimal end points, with pulmonary function or asthma exacerbations or control assessed as the primary outcome only sporadically. Several double-blind, placebo-controlled trials and meta-analysis (potentially hampered by the heterogeneity of the trials included) have confirmed that both SCIT and SLIT are of value in patients with allergic asthma associated with AR. An effectiveness and safety review conducted by the US Food and Drug Administration[66] showed moderate to high (somewhat weaker in children) evidence for the efficacy of both SCIT and SLIT in asthmatic patients, with weak evidence for assessing the superiority of either route. One Cochrane review[67] reported a significant reduction in symptom scores, medication use, and allergen-specific airway hyperreactivity and a limited reduction in nonspecific airway hyperreactivity. The effects on lung function were not consistent among trials. The most recent systematic review up to May 2013 concluded that SCIT significantly reduces asthma symptoms and medication use.[68] Because most of the published evidence for SLIT comes from studies primarily in patients with rhinitis, they are not adequately powered. A systematic review on SLIT reports strong evidence for improvement in asthma symptoms versus the comparator but only moderate evidence for a decrease in use of asthma medication.[69]

A potential steroid-sparing effect of AIT is of utmost importance to avoid the potential side effects of inhaled corticosteroids in asthmatic patients. For both SCIT and SLIT, a reduction of the inhaled corticosteroid dose needed to maintain asthma control was demonstrated.[65,70,71]

Ongoing phase 3 confirmatory double-blind, placebo-controlled trials with both SCIT and SLIT in patients with perennial HDM allergic asthma will provide more robust evidence (data from ClinicalTrials.gov, EU Clinical Trials Register, Japan Pharmaceutical Information Center: Clinical Trials Information).

Contraindications and side effects. Severe or uncontrolled asthma is the major independent risk factor for both nonfatal and fatal adverse reactions and thus a major contraindication for both SLIT and SCIT.[13,45,72] All patients undergoing AIT should be observed typically for at least 30 minutes after injection to ensure proper management of SRs.[13]

Measuring clinical outcomes. Most of the clinical trials evaluated clinically relevant parameters, such as symptom and medication scores (with an emphasis on the corticosteroid sparing effect) and lung function. According to the European Medicines Agency, clinical trials on AIT in asthmatic patients start as add-on therapy, which has to be considered in the evaluation of the primary end point (eg, evaluation in the context of a stepwise reduction in controller medication). Lung function, composite scores, number of exacerbations, and reduced need for controller medication could be considered primary end points.

Treatment duration. The duration of AIT is still a matter of debate. A recent study in asthmatic children showed that that 3 years of SCIT is an adequate duration for the treatment of asthma in patients with HDM allergy.[73]

Pediatric considerations. A systematic review evaluating the evidence regarding the efficacy and safety of SCIT and SLIT for the treatment of pediatric asthma and allergic rhinoconjunctivitis concluded that SCIT reduces symptoms and medication scores, whereas SLIT can improve asthma symptoms.[60] A meta-analysis of SLIT in children reported moderate effectiveness on asthma symptoms and medication intake.[74] New well-controlled studies are requested by the European Medicines Agency within the pediatric investigations plan.

AD

Indications and efficacy. There is still controversy about the potential role of AIT as a therapeutic intervention for patients with AD and aeroallergen sensitivity. Case reports and smaller cohort studies showed some positive effects of AIT on skin conditions. A large dose-finding phase II study in HDM-sensitized patients with AD[75] showed a significant SCORAD score decrease after 8 weeks, and the effect was maintained over 1 year, including lower glucocorticosteroid use. A recent meta-analysis proved moderate-level evidence of efficacy.[76] However, the largest prospective placebo-controlled study included in this meta-analysis showed efficacy only in severely affected patients (SCORAD score >50).[77] A recent systematic review with the Grading of Recommendations Assessment, Development and Evaluation system reported improvement in clinical symptoms.[78] Serious methodological shortcomings were noted, such as many dropouts, small study size; incomplete descriptions of randomization, blinding, and allocation concealment; and data analysis not by the intention-to-treat principle. The only SLIT study performed with HDM allergens in children with AD described a positive outcome only in those with mild-to-moderate disease.[79]

Contraindications and side effects. There is no contraindication for AIT in patients with respiratory allergic diseases (allergic rhinoconjunctivitis and mild allergic asthma) associated with AD. Eczema is not worsened during or after AIT.[29,80]

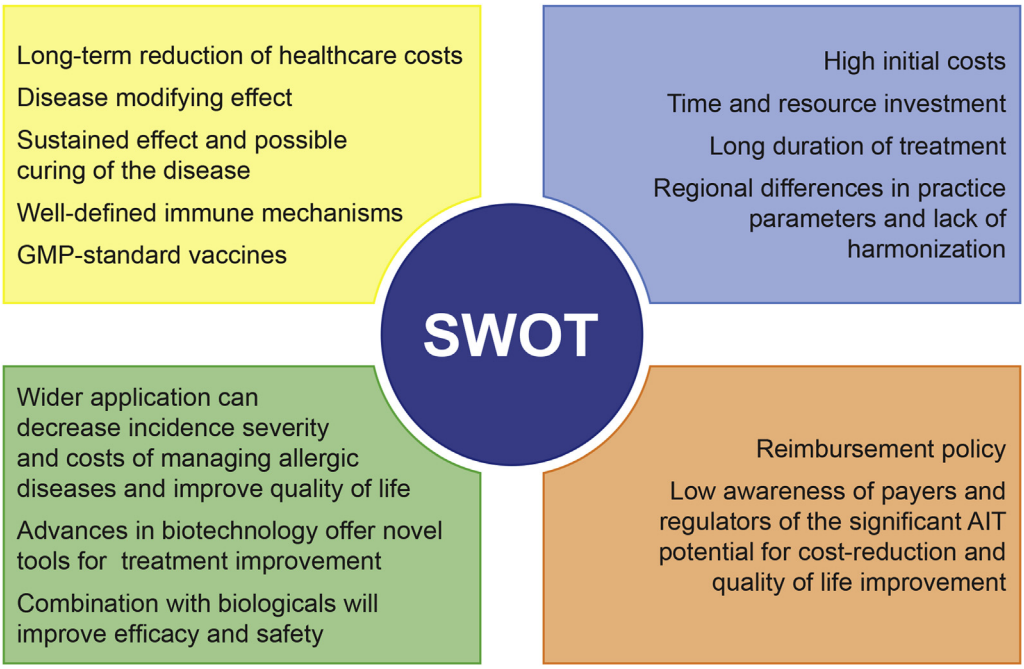

FIG 1. Strengths, weaknesses, opportunities, and threats (SWOT) analysis for AIT.

Food allergy

The first case of oral immunotherapy (OIT) to treat food allergy reported in *Lancet* in 1908[81] offers an accurate description of an episode of severe anaphylaxis on exposure of a child to egg. The demonstration that large amounts of egg can be tolerated after gradual desensitization followed by long-term maintenance with continued consumption of egg raises the question of how long OIT needs to continue.[81] These issues are more pertinent than ever, with a growing number of publications and research into immunotherapy for food allergy.

Early studies of SCIT to peanut were discontinued because of the high rate of anaphylactic reactions. More recently, studies using OIT or SLIT to peanut, milk, and egg have shown promise.[82-88] Recently, a first safety trial has been performed with a hypoallergenic mutant of fish parvalbumin in SCIT for the treatment of fish allergy.[89]

OIT using raw or heat-modified food appears to be more effective than SLIT.[90] A high proportion of patients were able to pass an oral food challenge after 1 to 4 years of OIT with a 20- to 100-fold increase in threshold reactivity and daily ingestion of high maintenance doses (300-4000 mg) of the food protein. However, the rate of SRs requiring epinephrine, which were observed in up to 25% of participants, especially those using raw food, is still too high for recommending OIT in daily practice. With SLIT, the doses are much lower (<10 mg/d), and the safety profile is better, but the threshold of reactivity reached at the end of the treatment is usually lower, affecting efficacy. Although increased food-specific IgG levels and decrease in basophil activation are observed during immunotherapy, there are currently no biomarkers to predict the response. Efficacy can only be demonstrated through sequential oral food challenges. A good response is associated with a longer AIT duration and a larger amount of food tolerated. Associated treatments, such as omalizumab, can reduce adverse reactions and improve efficacy.[91]

Food immunotherapy can induce desensitization that would require continuous therapy. Whether food immunotherapy can induce long-term tolerance in which therapy can be discontinued indefinitely is unknown. Two studies have shown sustained unresponsiveness to egg and peanut after OIT in only 28% and 50% of cases.[90,92,93] In another peanut OIT study,[94] only 3 of 7 patients successfully desensitized after 3 months of treatment withdrawal remained unresponsive for an additional 3 months. There is evidence that children who tolerate baked milk and egg can outgrow their food allergies independent of attempted therapeutic measures.[95,96] An improvement in quality of life has been suggested, but the risk-taking behavior encouraged by the false sense of security provided by treatment was not evaluated.

Because of the risk of adverse reactions, including anaphylaxis, EAACI guidelines do not recommend food AIT for routine clinical use (level III, grade D). The procedure should be performed only in highly specialized centers with expert staff and adequate equipment and in accordance with clinical protocols approved by local ethics committees.[96,97]

SAFETY OF AIT

Adverse reactions associated with AIT can be local or systemic. Local reactions (LRs) are fairly common with both SCIT (erythema, pruritus, and swelling at the injection site) and SLIT (oropharyngeal pruritus, swelling, or both), affecting up to 82% of patients receiving SCIT[13] and 75% of patients receiving SLIT.[98] Gastrointestinal symptoms associated with SLIT can be classified as LRs (if only associated with oromucosal symptoms) or SRs (if occurring with other systemic symptoms).

Most SLIT-related LRs occur shortly after treatment initiation and cease within days to a few weeks without any medical intervention. Although the overall dropout rate in double-blind,

Box 1. Nomenclature and terms

Anaphylaxis: Immediate systemic reaction, often occurring within minutes and occasionally as long as an hour or longer after exposure to an allergen.

Allergen immunotherapy (AIT): Procedure inducing tolerance to a specific allergen through repetitive administration of an allergen.

Allergic rhinitis (AR): Inflammation of the nasal mucosa induced on exposure to an allergen together with proof of immunologic sensitization to that allergen.

Allergic asthma: Typical symptoms of asthma (wheezing, cough, dyspnea, and chest tightness) induced on exposure to an allergen together with proof of immunologic sensitization to that allergen.

Build-up phase: Period of AIT in which increasing amounts of allergen are administered until a maintenance dose is reached.

Cluster immunotherapy: An accelerated build-up schedule that allows reaching the maintenance dose more rapidly.

Combined symptom and medication score (CSMS): Standardized method that balances both symptoms and the need for antiallergic medication in an equally weighted manner.

Homologous allergen groups: Allergen extracts prepared from different species, different genera, or different families and finished products that are derived from these allergen extracts for which clinical experience already exists and fulfill the criteria provided by the European Medicines Agency.

Local reaction (LR): Inflammatory response confined to the contact site.

Oral immunotherapy (OIT): Oral route of allergen administration to induce tolerance.

Oral food challenge (OFC): Provocation test used for the diagnosis of food allergy.

Pediatric investigation plan (PIP): Development plan aimed at ensuring that appropriate pediatric studies are performed to obtain the necessary quality, safety, and efficacy data to support the authorization of a medicine for use in children.

Systemic allergic reaction (SR): Triggered by AIT vaccine administration.

Subcutaneous immunotherapy (SCIT): Subcutaneous injectable route of allergen administration.

Sublingual immunotherapy (SLIT): Sublingual (drops or tablets) route of allergen administration.

Box 2. Key messages

- Better selection of responders based on an endotype-driven strategy is desired to increase both efficacy and safety.
- High-quality studies are needed to answer questions regarding optimal dosing strategies, disease-modifying potential, and cost-effectiveness over the standard of care.
- AIT achieves substantial clinical results in patients with AR by improving nasal and ocular symptoms and reducing medication need, improving quality of life, preventing progression of AR to asthma, and reducing new sensitizations.
- SLIT and SCIT can be used in patients with mild and moderate asthma associated with allergic rhinoconjunctivitis provided that asthma is controlled by pharmacotherapy.
- A measurable clinical benefit on asthma symptoms and a steroid-sparing effect is expected.
- AIT cannot be presently recommended as single therapy when asthma is the sole manifestation of respiratory allergy.
- Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or that make the resultant treatment a relative contraindication for AIT must be identified. Examples include severe asthma uncontrolled by pharmacotherapy and significant cardiovascular disease.
- There is no contraindication for AIT in patients with respiratory allergic diseases (allergic rhinoconjunctivitis and mild allergic asthma) associated with AD.
- AIT might have positive effects in selected sensitized patients with AD; the best evidence is available for HDM AIT.
- Patients with a positive IgE test response and corresponding history of eczema triggered by a clearly defined allergen are potential candidates for AIT in the setting of AD.
- For food allergy, an EAACI systematic review of the literature highlighted a large heterogeneity in the protocols used by different research groups in terms of preparation of food allergens, updosing, maintenance dose, and OFC procedure; therefore there is no single established protocol that has been shown to be both effective and safe in large multicenter studies.
- Currently, there is agreement that although immunotherapy to foods is an important area of research, it is not yet ready for clinical practice.
- Some risk factors for SCIT-induced severe SRs have been identified, but none have been clearly established for SLIT.
- Both SLIT and SCIT have acceptable safety profiles if administered under the appropriate circumstances. SLIT's more favorable safety profile allows for administration outside of a medically supervised setting, whereas SCIT is recommended only in a medically supervised setting with appropriate staff and equipment to identify and immediately treat anaphylaxis.
- Consistent use of the uniform classification systems for grading AIT-related (SLIT and SCIT) SRs and LRs both in clinical trials and surveillance studies will allow better comparisons and best practices for all AIT treatments.

placebo-controlled trials was similar to that with placebo,[99] dropouts because of adverse events were significantly greater in the SLIT group. A 3-grade classification system for SLIT LRs based on the patient's subjective accounting was developed by a WAO task force with the intent of improving and harmonizing the surveillance and reporting of SLIT safety.[100] Treatment discontinuation caused by LRs (grade 3 reaction) is one of the major determinants of the LR severity grade in this classification system. With this same aim, a previous WAO document proposed a grading system for SCIT.[101]

LRs were "deemed not bothersome at all or only slightly bothersome" by 82% of SCIT survey respondents, with only 4% indicating they would stop SCIT because of the LR.[102]

LRs are not predictive of subsequent SRs with either AIT route.[103,104] No study found that increased frequency of large SCIT LRs increases the risk for future SRs.[105]

Box 3. Unmet needs for AIT

- Better definition of homologous allergen groups
- Standardization of rare allergens
- Shorter duration of AIT
- Evaluation of the effect of booster therapy courses as for other vaccines
- Large multicenter studies with novel products both in SCIT and SLIT
- Large multicenter studies within the pediatric investigation program evaluating efficacy and safety in younger children and optimal age for treatment initiation
- Use for primary and secondary prevention
- Biomarkers to select responders and evaluate the efficacy objectively
- Improved safety profile
- Harmonization and validation of clinical outcomes
- Strong cost-effectiveness analysis adjusted to socioeconomic differences within and between countries
- Guidelines that consider socioeconomic differences and health policies between regions and countries
- Standardization of products between companies

SCIT-related SRs can range in severity from mild to life-threatening or fatal anaphylaxis. The incidence of SCIT SRs varies depending on the induction schedule, augmenting factors, premedication, and the degree of sensitization. In most surveys the rate of SRs with nonaccelerated SCIT induction is approximately 0.1% to 0.2% of injections and 2% to 5% of patients.[101,106] A 5-grade classification system based on reaction severity and the organ system or systems involved was developed in 2010 for reporting of AIT-related SRs (SCIT and SLIT).[104] In a 4-year AIT safety survey that included 23.3 million injection visits, the SR rate was consistently 0.1% of injection visits, with 97% of the SRs being classified as mild or moderate in severity.[106,107] The incidence of severe SRs was approximately 1 in one million injections, which is similar to previous surveys.[58] There was 1 confirmed SCIT-related fatality in this survey. In previous surveys there was an estimated rate of 3 to 4 SCIT-related fatalities per year, which translated to a fatality rate of 1 in 2 to 2.5 million SCIT injections.[105] Risk factors for SCIT-related SRs include symptomatic asthma, prior SCIT-related SRs, and a high degree of skin test reactivity.[13] Other potential risk factors for SCIT-related SRs, such as administration during the height of the pollen season, updosing schedule (cluster vs conventional), and treatment phase (maintenance vs updosing), have been suggested, but none have been clearly established.[106,108] Symptomatic or poorly controlled asthma was identified as a contributing factor in most fatal and near-fatal SCIT-related SRs.[106] It has been suggested that better safety measures, especially regarding asthma assessment before SCIT injections, might be a factor in the reduced fatality rates seen in the most recent AIT survey.[109]

Compared with SCIT, the SLIT-related SR rate is significantly lower, and severe SRs are relatively uncommon. In a comprehensive review of 104 SLIT studies published through October of 2005, the SLIT-related SR rate was 0.056% of doses administered (ie, 14 probable SLIT-related serious adverse events, which translated to 1.4 serious adverse events per 100,000 SLIT administered doses).[98] To date, there have been no confirmed reports of SLIT-related fatalities, but SRs of a severity to be categorized as anaphylaxis have been reported.[72] In a few of the anaphylaxis cases, the subjects had experienced an SR in an earlier SCIT treatment course, 2 of whom had SRs with their first SLIT dose.[110] No clear predictors for SLIT-related SRs have been established. Unlike SCIT, the incidence of SRs does not appear to be related to induction schedule, allergen dose, symptomatic asthma, or degree of sensitization. Because SLIT is administered in a setting without direct medical supervision, specific patient instructions should be provided regarding management of adverse reactions and the clinical scenarios when the administration of SLIT should be postponed (eg, asthma exacerbation, acute gastroenteritis, and stomatitis or esophagitis). SLIT for environmental pollen has been associated with the onset of eosinophilic esophagitis.[111] In addition, OIT for food allergy can trigger eosinophilic esophagitis.[112]

SLIT's more favorable safety profile allows for administration outside of a medically supervised setting, whereas SCIT's greater risks recommend administration only in a medically supervised setting with appropriate staff and equipment to identify and immediately treat anaphylaxis.[7,68] This recommendation is consistent with US-licensed allergenic extract package insert's black box warning.[113]

CONCLUSIONS AND UNMET NEEDS

The key messages of this position statement are summarized in Box 2. AIT is effective in reducing symptoms of allergic asthma and rhinitis and potentially modifies the underlying course of disease. Studies on AIT in the treatment of AD and food allergy could broaden the indications. However, AIT remains underused because of a lack of awareness, limited access to specialist care, the reimbursement policy, long duration, and concerns regarding safety and effectiveness (Fig 1). The major barrier for the further development of AIT, especially for the new technologies, is the capacity to perform 1 or more phase 3 confirmatory double-blind, placebo-controlled trials per allergen source. Several unmet needs have been identified (Box 3).

We thank Professor Stephan Vieths for critical reading of the manuscript.

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