International Consensus On (ICON) Allergy Immunotherapy (AIT)

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INTRODUCTION

Aim

The International consensus (ICON) 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 is developed to serve as the resource for health care professionals managing patients with allergic diseases. The document also provides rationale for providing better access to AIT based on the public health and pharmaco-economical analyses, which 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 ICON on AIT

The current board of iCAALL and the participating organizations formed the working committee on the basis of the regional representation, expertise in the field, and previous participation in the 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 1. Many task force reports and consensus documents of the 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.

Current status of AIT

AIT was introduced by Leonard Noon 103 years ago and is the only potential disease-modifying treatment for allergic individuals. Significant progress has been made in terms of proving its efficacy and safety both for respiratory allergy and for venom hypersensitivity and recent data look promising also for AIT as a disease-modifying treatment for food allergy and of atopic dermatitis. However, AIT remains underused mainly due to:

a) lack of agreement between documented efficacy,
b) insufficient data on its cost-effectiveness,

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.

AIT = allergen immunotherapy = procedure inducing tolerance to a specific allergen by repetitive administration of an allergen

AR = allergic rhinitis = inflammation of nasal mucosa induced upon exposure to an allergen together with the proof of immunological sensitization to that allergen

Allergic asthma = typical symptoms of asthma (wheezing, cough, dyspnea, chest tightness) induced upon exposure to an allergen together with the proof of immunological sensitization to that allergen

Build-up phase = period of AIT where increasing amounts of the allergen are given until a maintenance dose is reached

Cluster immunotherapy = an accelerated build-up schedule that allows reaching the maintenance dose more rapidly

CSMS = combined symptom and medication score = standardized method that balances both symptoms and the need for anti-allergic medication in an equally weighted manner

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

LR = local reaction – inflammatory response confined to the contact site

OIT = oral immunotherapy = oral route of allergen administration to induce tolerance

OFC = oral food challenge = provocation test used for the diagnosis of food allergy

PIP = pediatric investigation plan = 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

SR = systemic allergic reaction triggered by AIT vaccine administration

SCIT = Subcutaneous immunotherapy = subcutaneous, injectable route of allergen administration

SLIT = Sublingual immunotherapy = sublingual (drops or tablets) route of allergen administration

Table 1. Comparison between established guidelines for AIT

	Year	Evidence model	No. of RCTs SCIT /SLIT*	Recommendation SCIT	Recommendation SLIT
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, VIT. The use of standardized extracts is stressed	None
EAACI Position Paper1993 (3)	1993	None	28/6	Only references available	None
Australasian guidelines on SCIT for asthma(4)	1997	None	/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 may 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, Systemic reactions HV Standardized products with documented efficacy Single or few causative allergens	x

	Year	Evidence model	No. of RCTs SCIT /SLIT*	Recommendation SCIT	Recommendation SLIT
Canadian guidelines (8)	2006	None	4/10	• Significant symptoms of IgE-mediated AR/asthma inadequately treated • Proven efficacy of extracts • Early treatment may prevent chronic disease	SLIT evaluated positively as 'novel form', but no recommendation given
AAAAI/ACAAI Practice parameters (9)	2007	Shekelle (10)	62/14	ARC, asthma, Systemic reactions HV	SLIT as investigational in US (no FDA approval yet)
WAO SLIT guidelines (11)	2009		60 RDBPCs trials	NA	SLIT is indicated for treatment of different allergic conditions following the general criteria of selecting patients for SIT; mild to moderate IgE-mediated disease, clinically relevant allergens, exhausting pharmacological and nonpharmacological 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 co-treatment with medication.	Same as in SCIT + extra indication for SLIT if SCIT is not tolerated/ acceptable

	Year	Evidence model	No. of RCTs SCIT /SLIT*	Recommendation SCIT	Recommendation SLIT
AAAAI/ACAAI Practice parameters (13)	2011	Shekelle (10)	65/9	ARC, asthma, Systemic reactions HV AD if associated with aeroallergen sensitivity HV bothersome large local reactions	SLIT as investigational in US (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. Systemic reactions to HV	SLIT for adults and children with AR, after treatment failure with medication and avoidance.
Mexican guidelines (15)	2011	GRADE	55/18	ARC, asthma, Systemic reactions 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 atopic dermatitis, latex allergy, and large local reactions 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 is 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	12/0 (+data from metanalysis)	Indicated for AR in adults and children over 5 years. No specific list on indications, only contraindications.	None

	Year	Evidence model	No. of RCTs SCIT /SLIT*	Recommendation SCIT	Recommendation SLIT
WAO SLIT Guidelines (19)	2013	GRADE	77 RDBPC trials of which 62 with grass or HDM extracts 4 new meta-analyses	NA	SLIT is 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 years following discontinuation for immunotherapy with grass pollen allergen tablets in adults.
Polish position paper on SLIT (20)	2014	Consensus/none (?)	x/17 (+data from metanalysis)	x	AR, Asthma. Advantage of SCIT over SLIT in decreasing symptoms and lower respiratory tract inflammation. SLIT may be the method for children, SCIT 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 allergic airway diseases (22)	2014	Consensus with conference and Delphi method	comprehensive evaluation and citation of RCTs (SCIT, SLIT)	ARC, asthma	ARC

	Year	Evidence model	No. of RCTs SCIT /SLIT*	Recommendation SCIT	Recommendation SLIT
Other guidelines in which immunotherapy is mentioned					
ARIA 2001 (23)	2001	Shekelle (10)	/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 who are not sufficiently controlled by conventional pharmacotherapy • patients who have systemic reactions associated with injection immunotherapy • patients who are poorly compliant and refuse injections.
ARIA Update 2008 (24)	2008	Shekelle (10)	34/18 (+data from metanalysis)/36	SCIT is effective in adults and children for pollen and mite allergy. Burdened by the risks of side effects. It is cost-effective.	SLIT is recommended in adults with pollen allergy. May be used in patients with mite allergy. Patients who have presented systemic reactions during SCIT.

	Year	Evidence model	No. of RCTs SCIT /SLIT*	Recommendation SCIT	Recommendation SLIT
ARIA Update 2010 (25)	2010	GRADE	24/63 (+data from metanalysis)/	Suggests the use of pollen and HDM SCIT for allergic rhinitis in adults and children. And for concomitant AR and asthma.	Suggests the use of pollen and HDM SLIT for allergic rhinitis 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+Asthma for asthma treatment.
GA² 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 extracts. 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 Hx of severe (and moderate) systemic reactions. Not indicated for only local reactions	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

	Year	Evidence model	No. of RCTs SCIT /SLIT*	Recommendation SCIT	Recommendation SLIT
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 not RCTs)	Allergen IT (not stating SLIT or SCIT) to aeroallergens may be useful in selected cases of atopic eczema.	
GINA 2014 (30)	2014	Adapted Shekelle(10)	1 review/3 reviews/1 RCT	The efficacy of allergen immunotherapy in asthma is limited. Level of evidence given for this claim: A 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)	

* number of randomized controlled trials on SLIT the guidelines are based on
** normal font: published in the original WAO SLIT position paper; **bold font**: new guidelines published since 2009
† Table of evidence and recommendation taken from other guidelines based on Shekelle (10).
AC = allergic conjunctivitis; AIT, allergen specific immunotherapy; AR, allergic rhinitis; FDA, US Food and Drug Administration; HDM, house dust mite; IT, immunotherapy; NICE = National institute for Health and Care excellence, RCT, randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/); SLIT, sublingual immunotherapy.

c) differing proportion and educational level of physicians taking care of allergic subjects,
d) lack of awareness of AIT in general population and non-allergy/ immunology trained population
e) scattered availability of regimens and/or products for application,
f) varying selection of potential responders (1).

Historically, AIT was given by subcutaneous injection (SCIT), but in the past 25 years there has been a substantial increase in the use of sublingual immunotherapy (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 (2), 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 since many patients cannot easily commit time to attend for injections. Standardization of allergen extracts has also improved significantly. Several novel approaches are under investigation. They utilise the recombinant antigen technology to produce modified proteins and peptides, the intradermal or epicutaneous applicaton of immunodominant peptides or approaches to enhance the desirable immune response to the allergens with decreased side effects using adjuvants or by stimulating the innate immune system are under development aiming to reduce the risk of anaphylaxis and hence allow more rapid up-dosing. While 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, healthcare payers and regulators are asking for greater detail of what clinical benefit can be achieved, and to that end; we need better systems for defining benefit, not just in statistical terms, but 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 WAO Task Force proposed a 20% effect over placebo as a reasonable cut off of clinical efficacy for clinical trials (3). Recently, an EAACI Task Force recommended a homogeneous combined symptom and medication score (CSMS) as the primary outcome for AIT effectiveness, which provides as a simple and standardized method that balances both symptoms and the need for anti-allergic medication in an equally weighted manner (4). On the other hand, reliable systems of allergen exposure are needed to assess the AIT induced allergen-specific tolerance. In this context the environmental exposure chambers provides a very promising approach (5).

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 (6). Additional approaches to that AIT under active investigation include epicutaneous and intra-lymphatic administration (7, 8).

Administration regimens

The conventional schedule for SCIT employing unmodified allergen extracts consists of a dose build-up by injections once weekly followed by maintenance dose injections at four or eigth week intervals. Fewer build-up injections are possible, using modified allergenic extracts such as allergoids or addition of adjuvants.

The build-up phase can be shortened by employing cluster or rush schedules. During a cluster schedule, multiple injections (usually 2-3) are given on non-consecutive days. In a rush protocol, multiple injections are given on consecutive days, reaching maintenance typically in 1-3 days. A direct comparison showed no increase in systemic reactions and a more rapid achievement of symptomatic improvement for the cluster schedule (9). Rush, on the other hand, even with use of premedication, is associated sometimes with an increase in systemic reactions, but can also be well-tolerated (2, 10, 11). In SLIT the build-up period is either shortened or not needed.

Duration of treatment

The customary duration of AIT is 3-5 years. Prospective studies of SCIT with grass pollen extract for allergic rhinitis (AR) (12) and house dust mite (HDM) extract for patients with asthma (13) suggest that three 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 three or four years of active treatment (14).

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 mono- and polysensitized patients if the relevant allergen is selected (18).

- **Mono-allergen 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 (15, 16, 17).
- **Selection of allergens used for AIT**. Relevant allergens are major contributors to the safety and efficacy of allergenic extracts used for AIT. Most of the available data addresses mites, selected pollens and animal dander, while less is known for the efficacy and safety of mold or cockroach allergens. The selection of the relevant allergen is usually based on the combination of history with the result of the skin prick test or the in vitro testing. 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 (18).

SPECIFIC CLINICAL INDICATIONS FOR AIT

Allergic Rhinitis

- **Indications and efficacy.** According to the ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines (19, 20) 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 (i.e. ragweed) pollens; house dust mites; mold and animal dander. Standardized extracts should be used in clinical practice since the efficacy and safety of AIT strictly depended on the quality of the extracts.

  Recent systematic reviews have consistently shown that AIT can achieve substantial clinical results by improving nasal and ocular symptoms and by reducing medication need (21-25). AIT also improves the quality of life, prevents the progression of AR to asthma and reduces new sensitizations (26-28). Clinical efficacy persists after

discontinuation of AIT (29, 30). All the outcomes of AIT in AR lead to a clear pharmacoeconomic advantage over other therapies (31).

- **Contraindications and side-effects.** SCIT requires that injections should be performed by trained personal in clinical settings that are equipped to manage any possible systemic adverse reactions or anaphylaxis. Systemic reactions are quite rare when AIT is performed following proper recommendations on safety (32-34). AIT is contraindicated in patients with medical conditions that increase the patient's risk of treatment-related severe systemic reactions, such as those with severe or poorly controlled asthma or significant cardiovascular diseases (e.g., unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension) and should be administered with caution to patients receiving beta-blockers or ACE-inhibitors (47). 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 RCTs, in particular the CSMS. For clinical practice the visual analogue scale (VAS) or the newly developed rhinitis control tests may be more helpful. However, standardized and globally adopted measures of AIT efficacy in randomised controlled trials (RCTs) are still lacking (4).
- **Duration of treatment.** The recommended duration of AIT for AR is 3 years, both in SCIT and SLIT. Evidence from a long-term open controlled study suggest that 3-year course of SLIT might be not sufficient for a long-term protection (35).
- **Pediatric considerations.** SLIT is shown to be safe and effective even in children as young as 3 years of age (23-25). A meta-analysis of SLIT in children reported significantly reduced symptoms and medication scores (36). However, criteria for new well-designed and well-powered studies in children are requested by EMA within the pediatric investigations plan (PIP), with emphasis on long-term efficacy.

Allergic Asthma

The pathological process of the airways inflammation in asthma is not invariably associated with atopy. Within the allergic asthma subgroup the pathophysiology is very complex and includes several disease variants (33). Various endotypes have been described, which define intrinsically

distinct pathogenetic mechanisms. Endotyping asthma could eventually lead to an individualized management, including the selection of asthmatics responding best to AIT (37).

Current asthma therapies can effectively control symptoms and the ongoing inflammatory process but do not affect the underlying dysregulated immune response (38). Thus, they are very limited in controlling the progression of the disease.

- **Indications and efficacy**. The current ARIA guidelines (19, 20) give both SCIT and SLIT a conditional recommendation in allergic asthma due to moderate or low quality of evidence. According to the Global Innitiative for Asthma (GINA) report updated in 2014 (39) the efficacy of AIT in asthma is limited (level A evidence) and compared to pharmacological 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 treatment (level D evidence).

  Few specifically designed studies evaluated AIT in asthma, and only one had a formal sample size calculation (40). In addition, no consensus exists on the optimal endpoints with pulmonary function or asthma exacerbations or asthma control assessed as 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 allergic asthma associated with AR. An effectiveness and safety review conducted by the FDA (41) showed moderate-to high (somewhat weaker in children) evidence for efficacy of both SCIT and SLIT in asthma, with weak evidence for assessing the superiority of either route. One Cochrane review (42) reported a significant reduction in symptom scores, medication usage and allergen-specific airway hyperreactivity (AHR), and a limited reduction in non-specific AHR. 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 usage (43). As most of the published evidence for SLIT comes from studies primarily in rhinitis patients, they are not adequately powered. A systematic review on SLIT reports strong evidence for improvement in asthma symptom versus the comparator, but only moderate evidence for decrease of medication use for asthma (44).

A potential steroid-sparing effect of AIT is of utmost importance to avoid potential side effects of inhaled corticosteroids (ICS) in asthma. For both SCIT and SLIT a reduction of ICS dose needed to maintain asthma control was demonstrated (40, 45, 46).

Ongoing phase 3 confirmatory double-blind placebo-controlled (DBPC) trials with both SCIT and SLIT in 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 (18, 47, 48). All patients undergoing AIT should be observed typically for at least 30 minutes after injection to ensure proper management of systemic reactions (47).
- **Measuring clinical outcomes**. Most of the clinical trials evaluated clinically relevant parameters such as symptom and medication score (with an emphasis on the corticosteroid sparing effect) and lung function. According to the European Medicine Agency, clinical trials on AIT in asthma start as add on therapy, which has to be considered in the evaluation of the primary endpoint (e.g. evaluation in the context of a stepwise reduction of controller medication). Lung function, composite scores, number of exacerbations or reduced need for controller medication could be considered as primary endpoints.
- **Duration of treatment**. 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 HDM-allergic subjects (49).
- **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, while SLIT can improve asthma symptoms (34). A meta-analysis of SLIT in children reported a moderate effectiveness on asthma symptoms and medication intake (50). New well-controlled studies are requested by EMA within the pediatric investigations plan (PIP).

Atopic Dermatitis

- **Indications and efficacy**. There is still controversy about the potential role of AIT as a therapeutic intervention for patients with atopic dermatitis (AD) and aeroallergen sensitivity. Case reports and smaller cohort studies showed some positive effects of AIT on the skin condition. A large dose finding phase II study in HDM-sensitized AD patients (51) showed a significant SCORAD decrease after 8 weeks and the effect was maintained over one year including lower glucocorticosteroid use. A recent meta-analysis proved moderate-level evidence of efficacy (52). However, the largest prospective placebo-controlled study included in this meta-analysis showed efficacy only in severely affected patients (SCORAD >50) (53). A recent systematic review using the GRADE system reported improvement in clinical symptoms (54). Serious methodological shortcomings were noted, such as many dropouts, small study, incomplete descriptions of randomization, blinding, allocation concealment, and data analysis not by intention to treat principle. The only SLIT study, performed with HDM allergens in children with AD described a positive outcome only in patients with mild to moderate AD (55).
- **Contraindications and side effects**. There is no contraindication for AIT in patients with respiratory allergic diseases (allergic rhinoconjunctivitis, mild allergic asthma) associated with AD. Eczema is not worsening during or after AIT (56, 57).

Food allergy

The first case of oral immunotherapy (OIT) to treat food allergy reported in the Lancet in 1908 (58) offers an accurate description of an episode of severe anaphylaxis upon exposure of the child to egg. The demonstration that large amounts of egg can be tolerated after gradual desensitisation followed by long term maintenance with continued consumption of egg raises the question on how long OIT needs to continue (58). 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 due to the high rate of anaphylactic reactions. More recently, studies using OIT or SLIT to peanut, milk and egg have shown promise (59-65). Recently, a first safety trial has

been performed using a hypo-allergenic mutant of fish parvalbumin in SCIT for the treatment of fish allergy (66).

OIT using raw food or heat modified food appears to be more effective then SLIT (67). A high proportion of patients were able to pass an oral food challenge (OFC) after 1-4 years of OIT with a 20 to 100–fold increase in threshold reactivity and high maintenance doses (300-4000 mg) of the food protein are ingested on a daily basis. However, the rate of systemic reactions (SR) requiring epinephrine observed with up to 25% of participants especially using raw food is still too high for recommending OIT in daily practice. In SLIT, the doses are much lower (<10 mg/day), the safety profile is better, but the threshold of reactivity reached at the end of the treatment is usually lower, impacting on efficacy. Although increased food specific IgG 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 (OFCs). A good response is associated with a longer AIT duration and a larger amount of food tolerated. Associated treatments, such as omalizumab, may reduce adverse reactions and improve efficacy (68).

Food immunotherapy man 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 (67, 69, 70). In another peanut OIT study (71), only 3 out of 7 patients that were 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 may outgrow their food allergies independent of attempted therapeutic measures (72, 73). An improvement in quality of life has been suggested but the risk-taking behaviour encouraged by the false-sense of security provided by the treatment was not evaluated.

Due to 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 specialised centres, with expert staff and adequate equipment and in accordance with clinical protocols approved by local ethics committees (73, 74).

SAFETY OF AIT

Adverse reactions associated with AIT can be local or systemic. Local reactions (LR) are fairly common with both SCIT (erythema, pruritus and swelling at the injection site) and SLIT (oro-pharyngeal pruritus and/or swelling), affecting up to 82% of SCIT (47) and 75% of SLIT patients (75). Gastrointestinal symptoms associated with SLIT can be classified as local (if only associated with oromucosal symptoms) or SR (if occuring with other systemic symptoms).

Most SLIT 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, placebo-controlled trials was similar to placebo (76), drop-outs due to adverse events were significantly greater in the SLIT group. A 3-grade classification system for SLIT LR based on the patient's subjective accounting was developed by a WAO taskforce with the intent of improving and harmonizing the surveillance and reporting of the safety of SLIT (77). Treatment discontinuation due the LR (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 (78).

LR 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 (79).

LR are not predictive of subsequent systemic reactions with either AIT route (80, 81). No study found that increased frequency of large SCIT LR increases the risk for future systemic reactions (82).

SCIT SR can range in severity from mild to life-threatening or fatal anaphylaxis. The incidence of SCIT SR varies depending on the induction schedule, augmenting factors, premedication, and the degree of sensitisation. In most surveys, the rate of SR with non-accelerated SCIT induction is approximately 0.1 to 0.2% of injections and 2 to 5% of patients (78, 83). A 5-grade classification system, based on reaction severity and the organ system(s) involved was developed in 2010 for reporting of AIT SR (SCIT and SLIT) (81). 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 SR being classified as mild or moderate in severity (83, 84). The incidence of severe SR was approximately 1 in one million injections, which is similar to previous surveys (85). There

was one 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 into a fatality rate of 1 in 2 to 2.5 million of SCIT injections (82). Risk factors for SCIT SR include symptomatic asthma, prior SCIT SR, and high degree of skin test reactivity (47). Other potential risks factors for SCIT SR, such as administration during height of pollen season, updosing schedule (cluster vs. conventional), and treatment phase (maintenance vs. updosing), have been suggested but none have been clearly established (83, 86). Symptomatic or poorly controlled asthma was identified as a contributing factor in most fatal and near-fatal SCIT SR (83). It has been suggested that better safety measures, especially regarding asthma assessment before SCIT injections, may be a factor in the reduced fatality rate in the most recent AIT survey (87).

Compared with SCIT, the SLIT SR rate is significantly lower and severe SR are relatively uncommon. In a comprehensive review of 104 SLIT studies published through October of 2005, the SLIT SR rate was 0.056% of doses administered, 14 probable SLIT-related serious adverse events, which translated into 1.4 SAE per 100,000 SLIT administered doses (75). To date, there have been no confirmed reports of SLIT-related fatalities but SR of a severity to be categorized as anaphylaxis have been reported (48). In a few of the anaphylaxis cases, the subjects had experienced a SR in an earlier SCIT treatment course, two of whom had SR with their first SLIT dose (88). No clear predictors for SLIT SR have been established. Unlike SCIT, the incidence of SR does not appear to be related to induction schedule, allergen dose, symptomatic asthma or degree of sensitisation. Since 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 (asthma exacerbation, acute gastroenteritis, stomatitis or esophagitis, etc.). SLIT for environmental pollen has been associated with the onset of eosinophilic esophagitis (EE) (89). In addition, OIT for food allergy may trigger EE (90).

SLIT's more favourable 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 (43, 91). This recommendation is consistent with United States licensed allergenic extract package insert's black box warning (92).

Box 2: Unmet needs for AIT

- better defining of homologous allergen groups
- standardization of rare allergens
- shorter duration of AIT
- evaluate 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 primarly 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 socio-economical differences within and between conutires
- guidelines that consider the socio-economical differences and health policies between regions and countries
- standardization of products between companies

CONCLUSIONS AND UNMET NEEDS

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 underutilized due to lack of awareness, limited access to specialist care, 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 one or more phase 3 confirmatory DBPC trials per allergen source. Several unmet needs have been identified (Box 2).

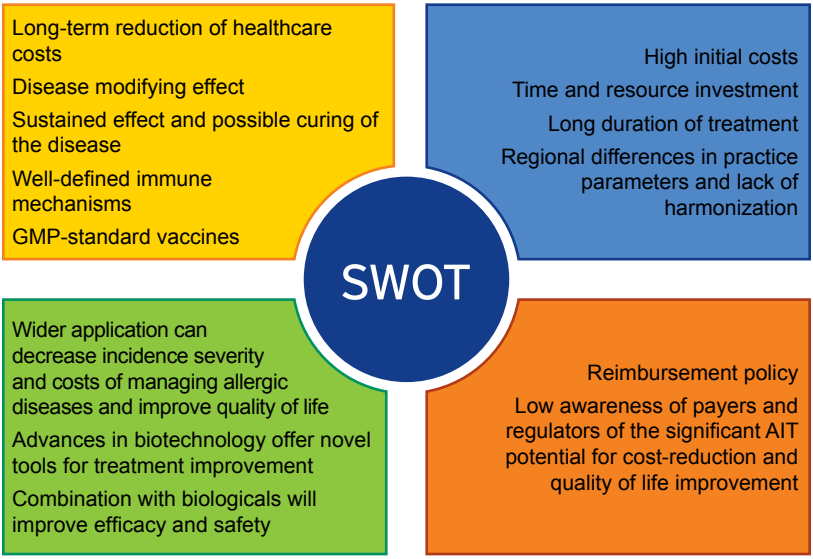

Figure 1. Strengths, weaknesses, opportunities, and threats (SWOT) analysis for AIT.

Box 3: 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, the disease-modifying potential and cost-effectiveness over the standard of care
- AIT achieves substantial clinical results in AR by improving nasal and ocular symptoms and reducing medication need, improving the quality of life, preventing the progression of AR to asthma and reducing new sensitizations
- SLIT and SCIT can be used in 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

Box 3: Key messages (continued)

- 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 the resultant treatment a relative contraindications for AIT. 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, mild allergic asthma) associated with AD.
- AIT may have positive effects in selected, sensitized patients with AD; the best evidence is available for house dust mite AIT
- Patients with a positive IgE tests and corresponding history of eczema triggered by a clearly defined allergen are potential candidates for AIT in 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, up-dosing, maintenance dose and OFC procedure; there is therefore no single established protocol that has been shown to be both effective and safe in large multicenter studies.
- Currently there is agreement that while immunotherapy to foods is an important area of research, it is not yet ready for clinical practice
- Some risk factors for SCIT induced severe SR 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 favourable 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 (SLIT and SCIT) systemic and local reactions both in clinical trials and surveillance studies will allow better comparisons and best practices for all AIT treatments.

References

1. Calderón M, Cardona V, Demoly P. EAACI 100 Years of Immunotherapy Experts Panel.One hundred years of allergen immunotherapy European Academy of Allergy and Clinical Immunology celebration: review of unanswered questions. *Allergy* 2012;**67**:462-476.
2. Committee on Safety of Medicine – CMS update. Desensitizing vaccines. *BMJ* 1986;**293**:9484.
3. Canonica GW, Baena Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ et al. Recommendations for standardized clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of the World Allergy Organization (WAO) taskforce. *Allergy* 2007;**62**:317-324.
4. 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**:854-867.
5. Rösner-Friese K, Kaul S, Vieths S, Pfaar O. Environmental exposure chambers in allergen immunotherapy trials: Current status and clinical validation needs. *J Allergy Clin Immunol* 2015;**135**:636-643.
6. Bauer CS, Rank MA. Comparative efficacy and safety of subcutaneous versus sublingual immunotherapy. *J Allergy Clin Immunol* 2014;**134**:765-765.
7. Casale TB, Stokes JR. Immunotherapy: What lies beyond. *J Allergy Clin Immunol* 2014;**133**:612-619.
8. von Moos S, Johansen P, Tay F, Graf N, Kündig TM, Senti G. Comparing safety of abrasion and tape-stripping as skin preparation in allergen-specific epicutaneous immunotherapy. *J Allergy Clin Immunol* 2014;**134**:965-967.
9. Tabar AI, Echechipia S, Garcia BE, Olaquibel JM, Lizaso MT, Gomez B et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with Dermatophagoides pteronyssinus. *J Allergy Clin Immunol* 2005;**116**:109-118.
10. Temiño VM, Wu P, Konig J, Fahrenholz JM. Safety of multiple aeroallergen rush immunotherapy using a modified schedule. *Allergy Asthma Proc* 2013;**34**:255-260.
11. Rieker-Schwienbacher J, Nell MJ, Diamant Z, van Ree R, Distler A, Boot JD et al. Open-label parallel dose tolerability study of three subcutaneous immunotherapy regimens in house dust mite allergic patients. *Clin Transl Allergy* 2013;**3**:16.
12. 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;**341**:468-475.
13. Des Roches A, Paradis L, Knani J, Hejjaoui A, Dhivert H, Chanez P et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. V. Duration of the efficacy of immunotherapy after its cessation. *Allergy* 1996;**51**:430-433.
14. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacque G. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-yearprospective study. *J Allergy Clin Immunol* 2010;**126**:969-975.
15. Calderon MA, Cox LS. Monoallergen sublingual immunotherapy versus multiallergen subcutaneous immunotherapy for allergic respiratory diseases: A debate during the AAAAI 2013 Annual Meeting in San Antonio, Texas. *J Allergy Clin Immunol Pract* 2014;**2**:136-143.

16. Nelson HS. Multiallergen immunotherapy for allergic rhinitis and asthma. *J Allergy Clin Immunol* 2009;**123**:763-769.
17. 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.
18. Calderón MA, Cox L, Casale TB, Moingeon P, Demoly P. Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: looking at the published evidence. *J Allergy Clin Immunol* 2012;**129**:929-934.
19. Bousquet J, Schunemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C et al. Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol* 2012;**130**:1049-1062.
20. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;**126**:466-476.
21. 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;**131**:1288-1296.e3.
22. Malling HJ, Bousquet J. Subcutaneous immunotherapy for allergic rhinoconjunctivitis, allergic asthma, and prevention of allergic diseases. *Clin Allergy Immunol* 2008;**21**:343-358.
23. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005;**60**:4-12.
24. Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 2009;**64**:1-59.
25. 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;**7**:6.
26. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A 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.
27. Des Roches A, Paradis L, Menardo JL, Bouges S, Daurés 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.
28. Purello-D'Ambrosio F, Gangemi S, Merendino RA, Isola S, Puccinelli P, Parmiani S 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.
29. 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.
30. Tahamiler R, Saritzali G, Canakcioglu S. Long-term efficacy of sublingual immunotherapy in patients with perennial rhinitis. *Laryngoscope* 2007;**117**:965-969.

31. Berto P, Frati F, Incorvaia C. Economic studies of immunotherapy: a review. *Curr Opin Allergy Clin Immunol* 2008;**8**:585-589.
32. Amin H, Liss G, Bernstein D. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 2006;**117**:169-175.
33. Schiappoli M, Ridolo E, Senna G, Alesina R, Antonicelli L, Asero R et al. A prospective Italian survey on the safety of subcutaneous immunotherapy for respiratory allergy. *Clin Exp Allergy* 2009;**39**:1569-1574.
34. Passalacqua G, Guerra L, Compalati E, Canonica GW. The safety of allergen specific sublingual immunotherapy. *Curr Drug Saf* 2007;**2**:117-123.
35. 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.
36. Kim JM, Lin SY, Suarez-Cuervo C, Chelladurai Y, Ramanathan M, Segal JB et al. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. *Pediatrics* 2013;**131**:1155-1167.
37. Agache I, Akdis C, Jutel M, Virchow JC. Untangling asthma phenotypes and endotypes. *Allergy* 2012;**67**:835-846.
38. Jutel M, Van de Veen W, Agache I, Azkur KA, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy and novel ways for vaccine development. *Allergol Int* 2013;**62**:425-433.
39. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2014. Available from: http://www.ginasthma.org/.
40. Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP 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.e7.
41. Lin SY, Erekosima N, Suarez-Cuervo C, Ramanathan M, Kim JM, Ward D, et al. Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review. Comparative Effectiveness Review No. 111. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2007-10061-I.) AHRQ Publication No. 13-EHC061-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2013
42. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* (8):CD001186.
43. Erekosima N, Suarez-Cuervo C, Ramanathan M, Kim JM, Chelladurai Y, Segal JB et al. Effectiveness of subcutaneous immunotherapy for allergic rhinoconjunctivitis and asthma: A Systematic Review. *Laryngoscope* 2014;**124**:616-627.
44. Lin SY, Erekosima N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA* 2013;**309**:1278-1288.
45. de Blay F, Kuna P, Prieto L, Ginko T, Seitzberg D, Riis B et al. SQ HDM SLIT-tablet (ALK) in treatment of asthma - Post hoc results from a randomised trial. *Respir Med* 2014;**108**:1430-1437.
46. Marogna M, Braidi C, Bruno ME, Colombo C, Colombo F, Massolo A et al. The contribution of sublingual immunotherapy to the achievement of control in birch-re-

lated mild persistent asthma: a real-life randomised trial. *Allergol Immunopathol (Madr)* 2013;**41**:216-224.
47. 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; **127**:S1-55.
48. 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.
49. Stelmach I, Sobocinska A, Majak P, Smejda K, Jerzynska 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.
50. Penagos M, Passalacqua G, Compalati E, Baena-Cagnani CE, Orozco S, Pedroza et al. 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.
51. Werfel T, Breuer K, Rueff F, Przybilla B, Worm M, Grewe M et al. Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. *Allergy* 2006;**61**:202-205.
52. Bae JM, Choi YY, Park CO, Chung KY, Lee KH. Efficacy of allergen-specific immunotherapy for atopic dermatitis: a systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol* 2013;**132**:110-117.
53. Novak N, Bieber T, Hoffmann M, Fölster-Holst R, Homey B, Werfel T et al. Efficacy and safety of subcutaneous allergen-specific immunotherapy with depigmented polymerized mite extract in atopic dermatitis. *J Allergy Clin Immunol* 2012;**130**:925-931.
54. Gendelman SR, Lang DM. Specific immunotherapy in the treatment of atopic dermatitis: a systematic review using the GRADE system. *Ann Allergy Asthma Immunol* 2013;**111**:555-561.
55. Pajno GB, Caminiti L, Vita D, Barberio G, Salzano G, Lombardo F et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2007;**120**:164-170.
56. Darsow U. Allergen-specific immunotherapy for atopic eczema: updated. *Curr Opin Allergy Clin Immunol* 2012;**12**:665-669.
57. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol* 2012;**26**:1176-1193.
58. Schofield AT. A case of egg poisoning. *Lancet* 1908:716.
59. Nurmatov U, Venderbosch I, Devereux G, Simons FE, Sheikh A. Allergen-specific oral immunotherapy for peanut allergy. *Cochrane Database Syst Rev* 2012;**9**:CD009014.
60. Buchanan AD, Green TD, Jones SM, Scurlock AM, Christie L, Althage KA et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J Allergy Clin Immunol* 2007;**119**:199-205.
61. 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**:640-6 e1.

62. 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;**129**:448-55, 55 e1-5.
63. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet* 2014;**383**:1297-1304.
64. Anagnostou K, Clark A. Peanut immunotherapy. *Clin Transl Allergy* 2014;**4**:30.
65. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol* 2015;**135**:1275-1282.e1-6.
66. Zuidmeer-Jongejan L, Fernandez-Rivas M, Poulsen LK, Neubauer A, Asturias J, Blom L et al. FAST: towards safe and effective subcutaneous immunotherapy of persistentlife-threatening food allergies. *Clin Transl Allergy* 2012;**2**:5.
67. 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.
68. Nadeau KC, Kohli A, Iyengar S, DeKruyff RH, Umetsu DT. Oral immunotherapy and anti-IgE antibody-adjunctive treatment for food allergy. *Immunol Allergy Clin North Am* 2012;**32**:111-133.
69. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol* 2014;**133**:468-475.
70. 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;**133**:500-510.
71. Nowak-Wegrzyn A, Bloom KA, Sicherer SH, Shreffler WG, Noone S, Wanich N et al. Tolerance to extensively heated milk in children with cow's milk allergy. *J Allergy Clin Immunol* 2008;**122**:342-347, 7 e1-2.
72. Kim JS, Nowak-Wegrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. *J Allergy Clin Immunol* 2011;**128**:125-31 e2.
73. de Silva D, Geromi M, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K et al. Acute and long-term management of food allergy: systematic review. *Allergy* 2014;**69**:159-167.
74. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014;**69**:1008-1025.
75. Cox LS, Linnemann DL, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006;**117**: 1021-1035.
76. Makatsori M, Scadding GW, Lombardo C, Bisoffi G, Ridolo E, Durham SR et al. Dropouts in sublingual allergen immunotherapy trials - a systematic review. *Allergy* 2014;**69**:571-580.
77. Passalacqua G, Baena-Cagnani CE, Bousquet J, Canonica GW, Casale TB, Cox L et al. Grading local side effects of sublingual immunotherapy for respiratory allergy:

speaking the same language. *J Allergy Clin Immunol* 2013;**132**:93-98.
78. 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, 574 e561-574 e567.
79. Coop CA, Tankersley MS. Patient perceptions regarding local reactions from allergen immunotherapy injections. *Ann Allergy Asthma Immunol* 2008;**101**: 96-100.
80. 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.
81. Tankersley MS, Butler KK, Butler WK, Goetz DW. Local reactions during allergen immunotherapy do not require dose adjustment. *J Allergy Clin Immunol* 2000; **106**:840-843.
82. Roy SR, Sigmon JR, Olivier J, Moffitt JE, Brown DA, Marshall GD. Increased frequency of large local reactions among systemic reactors during subcutaneous allergen immunotherapy. *Ann Allergy Asthma Immunol* 2007;**99**:82-86.
83. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI Surveillance Study of Subcutaneous Immunotherapy, Years 2008-2012: An Update on Fatal and Nonfatal Systemic Allergic Reactions. *J Allergy Clin Immunol Pract* 2014; **2**:161-167 e163.
84. Bernstein DI, Epstein T, Murphy-Berendts K, Liss GM. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI collaborative study. *Ann Allergy Asthma Immunol* 2010;**104**:530-535.
85. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 2006;**117**:169-175.
86. Tinkelman DG, Cole WQ, 3rd, Tunno J. Immunotherapy: a one-year prospective study to evaluate risk factors of systemic reactions. *J Allergy Clin Immunol* 1995;**95**:8-14.
87. Cox L, Aaronson D, Casale TB, Honsinger R, Weber R. Allergy Immunotherapy Safety: Location Matters! *J Allergy Clin Immunol Pract* 2013;**1**:455-454.
88. de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. *Allergy* 2009;**64**:963-964.
89. Miehlke S, Alpan O, Schröder S, Straumann A. Induction of eosinophilic esophagitis by sublingual pollen immunotherapy. *Case Rep Gastroenterol* 2013;**7**:363-368.
90. 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.
91. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Standards for practical allergen-specific immunotherapy. *Allergy* 2006;**61 Suppl 82**:1-20.
92. LLC H-SL. ALLERGENIC EXTRACTS IN BULK VIAL http://www.hsallergy.com/products_ordering/product_inserts.aspx. 2009, date accessed 5/11/13.

International Consensus On (ICON) Allergy Immunotherapy (AIT) II

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INTRODUCTION

This paper represents the second part of the international consensus (ICON) document on allergen immunotherapy (AIT), an effort of the International Collaboration in Asthma, Allergy and Immunology (iCAALL) that includes EAACI, AAAAI, ACAAI, and WAO. There are other papers that outline international or national guidelines, positions, or consensus statements on the current knowledge on AIT. In this document, we offer a critical appraisal of major evidence on AIT mechanisms, recommendations on allergen standardization, regulatory issues, pharmacoeconomics, and barriers to and facilitators of future developments in AIT. The governing boards of the participating organizations approved the final draft.

MECHANISMS OF IMMUNOTHERAPY

Allergen-specific immune response involves a series of complex mechanisms. These include the structural features and dose of the allergen, route and timing of its exposure, existence of innate immune response stimulants within the allergen and micromilieu, and the genetic susceptibility of the host (1, 2). Effective AIT sequentially activitates multiple mechanisms (Fig. 1), ideally resulting in multifaceted clinical improvement. Depending on the AIT protocol, desensitization to allergen, allergen-specific immune tolerance, and suppression of allergic inflammation appear within hours. This is followed by allergen-specific Treg and Breg cell generation and regulation of allergen-specific IgE and IgG4, and establishment of immune tolerance (Fig. 1A). AIT in particular targets type II immunity cells, including Th2 cells, type 2 innate lymphoid cells (ILC2), and type 2 cytotoxic T cells. The third produce IL-4, IL-5, and IL-13, which induce mast cell, basophil, and eosinophil activation; as well as IgE antibody production (3, 4) (Fig. 1 B).

Early desensitization

The literature indicates the administration of AIT leads to very early decreases in the susceptibility of mast cells and basophils to degranulation, in spite of the presence of elevated allergen-specific immunoglobulin (Ig) E (5). This effect appears to be similar to the one observed when these two immune cell types are rapidly desensitized in anaphylactic reactions to drugs (6). Several mechanisms have been proposed to explain why mast cells and basophils become unresponsive to environmental proteins, even in the presence of specific IgE. A number of studies have investigated the

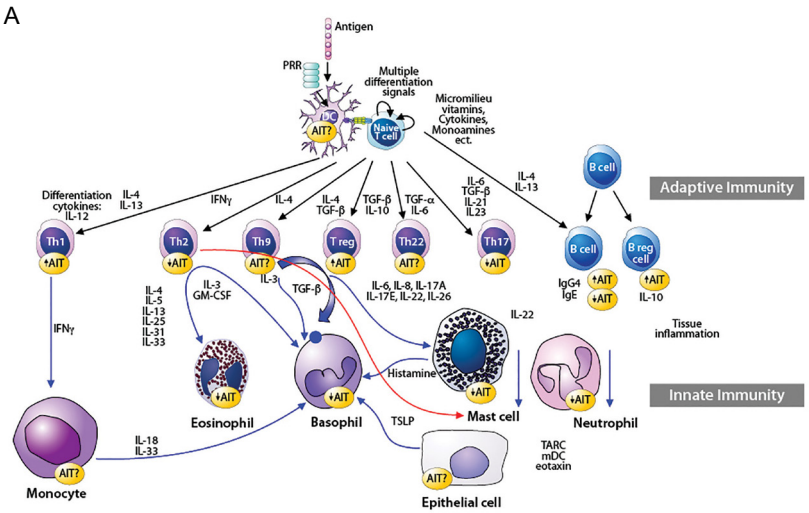

Figure 1. Cellular and molecular changes during AIT. A) The differentiation of naïve T cells after allergen presentation in the presence of innate immune response substances that trigger pattern recognition receptors (PRR) and vitamins, monoamins that control the cellular differentiation as well as co-exposed substances with the antigen and status of the cells and cytokines in the microenvironment, naïve T cells can differentiate into T-helper (Th)1, Th2, Th9, Th17, and Th22 types of T cells. Based on their respective cytokine profiles, responses to chemokines, and interactions with other cells, these T-cell subsets can contribute to general inflammation. The increase in Th1 and Treg cells play a role in counterbalancing other effector cells. The balance between allergen-specific effector T cells (particularly Th2) cells and IL-10- producing Treg cells is decisive for the development or suppression of allergic inflammation. Treg cells and their cytokines suppress Th2-type immune responses and contribute to the control of allergic diseases in several major ways. Similarly the induction of IL-10-producing B reg cells play an essential role in suppressed of IgE and induced of IgG4. B) The suppression of peripheral innate lymphoid cells (ILC) especially type 2 may contribute to Th2 suppression and immunological tolerance induced by AIT.

involvement of basophils in the very early induction of allergen tolerance and the so-called desensitization effect of venom immunotherapy (VIT) (7-9). Rapid upregulation of histamine type 2 receptors within the first 6 hours of the build-up phase of VIT was observed, which suppressed high affinity IgE receptor (FcεRI)-induced activation and mediator release of basophils (7), and histamine receptor 2 has strong immune regulatory

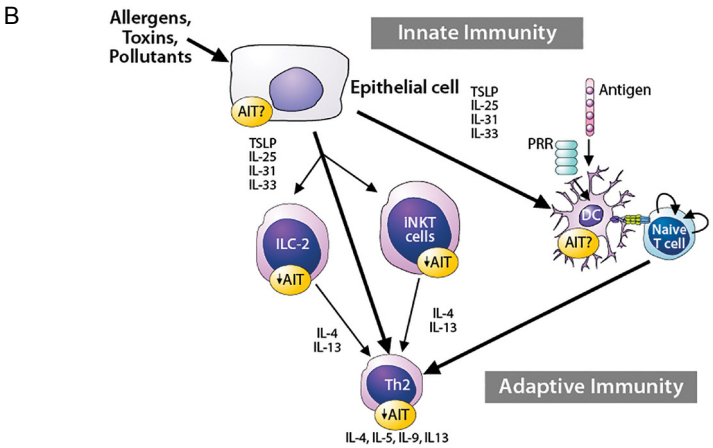

Figure 1. continued

activities on T cells, dendritic cells and basophils (10). Overall, mast cells and basophils express many targets for future enhancement of the efficacy of AIT as well as the development of novel biomarkers (11, 12).

T cell tolerance

Allergen immunotherapy (AIT) induces a major change in allergen-specific T cell subsets. The proportion of IL-4-secreting T helper (Th) 2 cells decreases; meanwhile, IL-10-secreting inducible T regulatory (Treg) cells specific for the same allergenic epitope increase in number and achieve function similar to the immune status observed in non-allergic healthy individuals. This appears to be one of the milestones in the development of peripheral tolerance to allergens (1, 13). A significant correlation exists between improvement of symptoms and the increase in inducible Treg cell numbers during immunotherapy (14, 15). Inducible Treg cells are composed of two sets: FOXP3 positive(Forkhead box protein 3) adaptive Treg cells and FOXP3 negative but IL-10-producing type 1 regulatory (Tr1) cells (16). Studies investigating the role of different types of Treg cells during AIT have shown overlapping effects of different Treg cell subsets for the induction of T cell tolerance (17, 18). Secretion of IL-10 and TGF-beta and expression of cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) protein on T cell surfaces are also important for the suppressor activity of inducible Tregs. Additionally, the runt homology domain transcription factors (RUNX) 1 and 3 both have an effect on TGF-beta-mediated FOXP3 expression of inducible Treg cells in humans.

Various mechanisms may underlie AIT's induction of an allergen-specific Treg cell response (19, 20). It has been recently suggested that the target organ and site of immune tolerance induction during SLIT may be the tonsils (21). This could hold true even in patients with tonsillectomy because the procedure removes only the pharyngeal tonsils, while preserving the lingual and palatine tonsils. Plasmacytoid dendritic cells (pDC) with a high percentage of Treg cells were co-localized in human palatine and lingual tonsils. The ability of pDCs of human tonsil cells to generate $CD4^+CD25^+CD127^-FOXP3^+$ functional Treg cells further supports the concept of tolerogenic function of DC (20). Similar to mechanisms of AIT, in high-dose antigen exposure of beekeepers, IL-10-secreting Treg cells inhibited proliferation of PLA-specific effector T cells seven days after the beginning of bee venom season (22). Blocking CTLA-4, PD-1 and IL-10 receptors inhibited this suppressive effect. Mouse models to mimic these effects are being developed and prolonged desensitization schedules have been proposed to study immune tolerance-inducing activities (23).

Another important recent study investigated the mechanisms underlying the way in which allergen tolerance can be broken in healthy individuals. The authors indicate stimulation of allergen-specific T cells with certain toll-like receptors (TLR) and proinflammatory cytokines can induce *in vitro* $CD4^+$ T cell proliferation in peripheral lymphocytes. In this context, stimulation with IL-1β, IL-6, TLR-4, TLR-8 of myeloid DC breaks allergen-specific $CD4^+$ T cell tolerance (24). Viral infections may play a role in immune tolerance-breaking roles by using the above mentioned or other molecular mechanisms. The infection of the respiratory epithelium with rhinovirus can antagonize tolerance to inhaled antigen through combined induction of TSLP, IL-33, and OX40 ligand (25).

B cell tolerance

The phenotypical expression of B regulatory cells (Breg) plays a role in allergic disease. Distinct from IL-10-secreting DCs, IL-10-secreting allergen-specific Breg cells were shown to exist in bee venom tolerant beekeepers and bee venom allergic individuals who had undergone VIT (26) They were characterized as $CD73^-CD25^+CD71^+$ B cells, with a suppressive function on antigen-specific $CD4^+$ T cells and the capacity specifically to produce IgG4. This work is supported by data showing that single IL-10 overexpression in human B cells is sufficient to induce a regulatory role of B cells (27). In addition to the direct role of Breg cells, Treg-derived IL-10

stimulates B cells to undergo class switching towards the production of IgG4 antibodies in the presence of IL-4, whereas IL-4 alone induces IgE production (28). Human B cells can regulate $CD4^+$ T-cell plasticity to create flexibility in the effector T-cell response (29). As a tolerogenic antibody, allergen-specific IgG4 competes with allergen-specific IgE with the same specificity for allergen binding, thus preventing the release of mediators from mast cells and basophils. There is further possible formation of IgE-allergen-IgG4 complexes that bind to both the FcγRIIb and FcεRI inhibiting the IgE receptor (30). IgG4 antibodies of different specificities can exchange their immunoglobulin heavy chain through a process referred to as Fab arm exchange. This process leads to the formation of bi-specific, functionally monovalent IgG4 antibodies that are unable to crosslink allergens (31). Furthermore, IgG4 is unable to fix complement and has limited affinity for activating Fcγ receptors (32). AIT is known to induce a transient increase in serum IgE levels in the early course of treatment, despite its protective clinical efficacy. The ratio of allergen-specific IgE to functional IgG4 antibody may be useful in monitoring AIT, as the IgE blocking activity of IgG4 appears to correlate with clinical AIT outcome (33, 34).

Regulation of innate lymphoid cells

Type II ILCs play a role in allergic responses via the secretion of IL-5 and IL-13, and ILC2s may be studied in human peripheral blood (3, 4). ILC2s may have a role in the development of adaptive type 2 responses to local, but not systemic, antigen exposure (35). ILC2s can also be demonstrated in induced sputum in children (36). AIT has been shown to regulate innate lymphoid cells, and seasonal increases in peripheral ILC2 are inhibited by subcutaneous grass pollen immunotherapy (37). Circulating ILC2 responses are increased in asthma but not in allergic rhinitis (38).

STANDARDIZATION OF ALLERGEN EXTRACTS

Allergen standardization (AS) is a prerequisite to providing reagents for the diagnosis of and allergen-specific intervention in atopic diseases. Established methods for AS measure potency, ensure consistency in composition, and demonstrate stability. Molecular technologies have accelerated the characterization of allergen preparations providing optimal reagents for advanced AS (39).

Box 1: Effective AIT triggers multiple mechanisms, which are sequentially activated (Fig. 2)

AIT induced immune tolerance controls

- acute phase of the allergic reaction
- chronic events leading to inflammation and remodeling

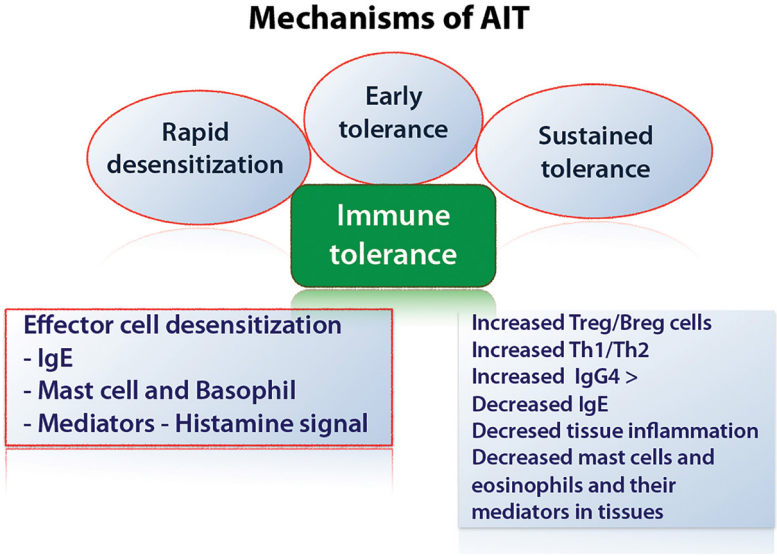

Figure 2. Rapid desensitisation: very early decreases in the susceptibility of mast cells and basophils to degranulation is observed. Mediators of anaphylaxis (histamine and leukotrienes) are released during AIT without inducing a systemic anaphylactic response. Several mechanisms have been proposed such as up-regulation of histamine type 2 receptors and decreased effector cell function as reflected by a decrease in allergen-stimulated surface expression of CD63. Early changes in basophil sensitivity predicts symptom relief with AIT. Immune tolerance involves the gradual increase in T and B regulatory cells and tolerogenic antibodies. Long term tolerance induced by AIT involves changes in memory T and B cell compartment, the Th1/Th2 shift, function of the effector and structural cells

Allergen standardization and regulatory framework

European manufacturers use "In-house Reference Preparations" (IHRP) and create their own allergen extract units accordingly (40). The European Medicines Agency (EMA) recently adopted a guideline on production and quality of allergen products (http://www.gmp-compliance.org/guidemgr/files/GUIDELINE ON ALLERGEN PRODUCTS PRODUCTION AND QUALITY ISSUES.PDF). Homologous allergens are now based on sequence identity among allergenic proteins rather than taxonomic relationships between allergen sources. This guideline complements existing documents for development and marketing authorization of products for AIT in Europe. The Food and Drug Administration (FDA) provides guidance for United States of America (USA) manufacturers. Vaccines standardized for potency in the USA include Hymenoptera venoms (five species), cat hair and pelt, dust mites (*Dermatophagoides farinae* and *pteronyssinus*), and pollen from eight grass species and short ragweed. For each standardized extract, reference materials from the Center of Biologics Evaluation and Research (CBER) are used to determine potency, forming the basis of IHRP calibration.

Biological allergen standardization (*in-vivo*)

The Nordic method, commonly used in Europe, considers 10,000 BU/mL (biologically standardized units) as equivalent to an allergen dose that elicits a wheal equal (in mm2) to that elicited by 10 mg/ml histamine-dihydrochloride. *In vivo* testing consists of titrated skin prick tests with 5-fold allergen dilutions averaged in at least 20 moderately to highly sensitized allergic subjects. The ID50EAL (intradermal dilution for 50 mm sum of erythema determines the bioequivalent allergy units) method is used in the United States (41). The dilution of extract that on average produces a 50 mm induration (sum of lengths and width) (D50) is assigned an arbitrary potency of 10 000 BAU/mL (bioequivalent allergen unit). Extracts with a mean D50 of 14, which falls between the 13th and 15th 3-fold serial dilution of the reference extract, are arbitrarily assigned the value of 100,000 BAU/ml. An extract with a mean D50 falling between the 11th and 13th dilutions is labeled 10,000 BAU/ml.

Biochemical and immunological standardization (*in-vitro*)

Various qualitative and quantitative biochemical methods provide information on extract composition (42). Newer methods, e.g., mass spectrometry can be expensive and technically challenging, but can offer

extremely powerful approaches to analysis of allergenic proteins, including detection of isoforms. Total potency is measured by IgE-binding inhibition or effector (i.e. basophil) cell assays. Manufacturers usually combine different methods for AS and establish various in-process control measures for robust and reproducible allergen extract production.

CREATE project and follow-up

A WHO/IUIS initiated and EU-funded (FP5) project for the Development of Certified Reference Materials for Allergenic Products and Validation of Methods for their Quantification (CREATE) established comprehensive information on purified or recombinant forms of important major allergens (Bet v 1, Phl p 1, Phl p 5, Ole e 1, Der p 1, Der p 2, Der f 1, and Der f 2) and explored immunoassays for their quantification (43, 44). A follow-up project, supported by the Biological Standardization Program (BSP) of the European Directorate for the Quality of Medicines (EDQM), performed a proficiency trial (BSP090) for ELISAs of Bet v 1 and Phl p 5a (45-47). After approval by the European Pharmacopoeia Commission (EPC) these assays will become mandatory for allergen manufacturers in IHRP calibration. In 2012, both major allergens were introduced by the EPC as biological reference materials, http://crs.edqm.eu/db/4DCGI/View=Y0001565 and http://crs.edqm.eu/db/4DCGI/View=Y0001566, and the future will likely bring important additions.

PHARMACOECONOMICS AND COST-EFFECTIVENESS OF IMMUNOTHERAPY

The costs of allergic diseases are substantial, and AIT is a treatment modality that may alter the natural course of disease. In the long run of health economics, immunotherapy has the potential to result in cost-savings due to decreased loss of workdays and lower drug costs, although it is not to be expected that the costs will be fully offset by savings in anti-allergic medications during the first years of therapy. Economic studies have been published on the cost-effectiveness of immunotherapy, primarily from Europe and the USA.

Costs of AIT and standard treatment (ST)

Retrospective analyses have shown that subcutaneous immunotherapy (SCIT) affects health care expenditure (48-50). In comparing costs, pre-

and post-SCIT treatment among 3048 Medicaid-enrolled children with allergic rhinitis, SCIT produced a 12% reduction (48). An 18-month period of SCIT resulted in associated costs that were reduced by 33% as compared to those incurred by pediatric controls (49). A prospective observational *Parietaria* SCIT study revealed a cost reduction of 48% in the third year of treatment, and of 80% 3 years after AIT concluded (51). A ragweed immunotherapy trial of 2 years in asthma patients showed 30% reduction in medical costs in the immunotherapy group versus placebo but these savings did not offset the increased costs due to immunotherapy (52). A one-year SLIT observational study showed a reduction in the costs of symptomatic drugs for 22% for patients with rhinitis and 34% for patients with rhinitis and asthma. When the costs of SLIT were included, the costs in the SLIT group were 73% higher (53). Another SLIT HDM study in asthmatics compared 2-year treatment with SLIT plus ST with ST only, followed by 3 years ST only. The savings in the fifth year amounted to 23% (54).

Cost-effectiveness (CEA) and cost-utility analyses (CUA).

Economic analyses of both benefits of treatment and its financial cost are important in addressing the question of whether one outweighs the other. CEA studies express the costs in a monetary units and effects in a physical unit (symptom-free days, occurrence of asthma exacerbations, and so on). CUA evaluates the effects of treatment in terms of health related quality of life (i.e., quality-adjusted life years; QALY). An incremental cost-effectiveness ratio (ICER), defined as costs divided by benefits, can be calculated to estimate the costs of a certain gain. A gain of 1 QALY at a threshold of £ 20,000-30.000 is considered acceptable: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/191504/NICE_guide_to_the_methods_of_technology_appraisal.pdf.

Several CEA studies have demonstrated that SCIT and SLIT are economically advantageous (55-58). A German study based on data from the literature in a decision tree model reached break-even within a duration of 6-8 years and net savings at 10 years (55). A French study, also based on a decision tree model, used the number of improved patients and the number of asthma cases avoided as determination of outcome. The incremental costs-effectiveness ratios (ICERS) were lower for SCIT (583 Euro and 597 Euro for dust-mite and pollen allergy) than those for SLIT (3938 Euro and 824 Euro) (57).

The cost-effectiveness of SCIT was confirmed by 2 CUAs and those of SLIT by 4 CUAs derived from randomized clinical trials with sublingual grass pollen tablets (52, 54, 59-61). Another CUA based on a post-hoc analysis of two SLIT studies indicated that an ICER below the threshold of £ 20.000 could be achieved in patients with medium or high outcomes in their symptom scores (62). One CUA evaluated treatment with different grass pollen products (Oralair™, Grazax™, Alutard™ depot). From the German health care perspective (cost-utility ratio vs symptomatic treatment; incremental costs, QALYs, and willingness-to-pay) the analysis resulted in dominance of Oralair™ (63).

Recently, a cost-effectiveness model was constructed based on MD data from the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) via meta-analyses and indirect comparison meta-analyses. Up to year 6, ICERS (cost per QALY) ranged from £28,650 (year 6) to £57,883 (year 3) for SCIT compared with standard treatment (ST), and from £27,269 to £83,560 for SLIT compared with ST. Thus, with increasing time, both SCIT and SLIT were found to be approaching cost-effectiveness thresholds of £20,000–30,000 (64).

In conclusion, the majority of pharmacoeconomics studies support the viewpoint that AIT gives value for the money, with cost-effectiveness within 6 years of treatment initiation. However, heterogeneity in methodology limits the interpretation of the studies. Data are obtained from small studies, retrospective databases, prospective observational studies, randomised trials, and literature searches. It is difficult to extrapolate the results from one healthcare setting to another and there is considerable variation in cost-effectiveness across countries (65). In addition, trials do not reflect real-life context, with non-compliance as a strong bias for the economic analyses. Finally, many pharmacoeconomics studies have been sponsored by or associated with manufacturers. Large prospective and independent cost-effectiveness studies using a study design that provides a more realistic model are required. Moreover, there is a lack of economic data in other areas of the world outside Europe or United States.

REGULATORY ISSUES

Although Noon and colleagues introduced AIT more than a century ago, a high degree of heterogeneity among countries on the regulatory aspects of this therapeutic option remains (66). In Europe, the majority of products

Table 1. Obtaining an MA in EU countries

National authorization	
The allergen product is only approved for marketing in the respective European country in which the application has been submitted.	The approval may be expanded to other European member states in a 'mutual recognition' procedure if the identical dossiers are submitted to these countries (62)
EU-wide registration	
The application is submitted to the EMA who nominates two EU countries as rapporteur and co-rapporteur for review and evaluation (33,62). The application contains a development plan documenting the quality, safety, and clinical efficacy of allergen products as outlined in the EMA-guidance (CHMP/EWP/18504/2006; 2008) (64) and a pediatric investigational plan (PIP) (58).	The central authorization allows MA in all EU member states The central procedure must be followed for recombinant allergen vaccines and other products based on biotechnological processes (62

for AIT have been marketed for decades as named-patient products (NPP), primarily responsible for meeting requirements of Good Manufacturing Practice (GMP) (67). Thus, NPP for AIT are commercially available and GMP-compliant, even if they are "named-patient", a term that refers to their prescription for a specific allergic individual (42).

For these NPPs, information on clinical efficacy is not necessarily based on the documentation required by regulatory agencies for providing marketing authorization (MA), while numbers of adverse reactions are mainly assessed via voluntary reports by producers, allergists, and patients.

In the last decade, the Directive 2001/20/EC and the amended Directive 2003/63/EC published important regulatory guidance, proposing central specifications for allergen-products in both diagnostics and AIT (42, 67). Under these regulations, allergen products are classified as medicinal products. Given that they have the capacity to modify the immune system and since they are produced with an industrial process, they require a marketing authorization similar to all medicinal drugs. The European Medicines Agency (EMA) and national health authorities of the individual member states serve as regulatory agencies. Attaining marketing authorization for allergen-products is feasible via national or centralized

procedures as well as through mutual recognition (42, 67-69). In a national authorization, the allergen product is only approved for marketing in the respective European country in which the application has been submitted. However, the approval may be expanded to other European member states in a 'mutual recognition' procedure if the identical dossiers are submitted to these countries (68). Another possibility for EU-wide registration of medicinal products is the centralized procedure, where the application dossier is initially submitted to the EMA as coordinating regulatory authority (42, 68). The EMA determines two representative European countries as rapporteur and co-rapporteur in reviewing and evaluating these dossiers. The central authorization allows marketing authorization in all EU member states. The central procedure must be followed for marketing authorization for recombinant allergen vaccines and other products based on biotechnological processes (68). Other countries, such as the USA, currently follow a different set of procedures (69).

The quality, safety, and clinical efficacy of allergen products under these authorization processes are required to be documented through a straightforward development plan as outlined in the EMA-guidance on the "Clinical Development of Products for Specific Immunotherapy for The Treatment of Allergic Diseases" (CHMP/EWP/18504/2006; 2008). Applicants receive scientific advice from EMA or from the national competent authorities on the pre-clinical and clinical phases of the development of the respective allergen products (42). In addition to the development plan, the applicant must submit a pediatric investigational plan (PIP) before an application for MA may be submitted to the EMA. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500015814.pdf 2009.

BARRIERS AND FACILITATORS FOR AIT

In spite of the facts that AIT represents a well-established, evidence-based therapy and there has been great progress in both vaccine development and means of application in recent years, a number of key barriers and facilitators should be noted (Table 2).

Table 2. Barriers and facilitators for better use of AIT

Barriers	
The application of AIT is limited in many areas due to low awareness of AIT potential	World-wide acceptance and increased awareness that AIT reduces long-term costs and burden of allergies and potentially changes the natural course of the disease.
Regulations on AIT	Regulations on AIT have profound effects on allergy practice, allergen manufacturers, and research programs. Especially in the EU allergy vaccines should undergo registration as all other drugs. There is a need for a standardized approach between regulatory agencies from different regions of the world.
Adherence to AIT	The demand of prolonged treatment over several years may impair patients' adherence
Facilitators	
Evidence-based documentation	Standardization, validation and consensus on the clinical outcome measures for clinical trials. Identification and validation of biomarkers for AIT monitoring. Environmental exposure chambers as suitable surrogates for natural allergen exposure(66,67). Validated tools for assessing effectiveness of AIT in real life – postmarketing studies.
Guidelines and recommendations	Standardization of guidelines and recommendations at the global and national society levels is necessary.
Better selection of patients	Diagnostic tools for better identification of clinically relevant patient's sensitization profile for a proper vaccine selection. Proper use of component-resolved diagnosis to identify potential responders and non-responders.
More convenient AIT regimens	Validation of different regimens (preseasonal, perennial), mode of updosing, duration of therapy, maximal dose, cumulative dose in terms of efficacy and safety.
Novel approaches	Existing evidence of efficacy and safety of novel approaches should be confirmed in independent phase 3 DBPC trials.
Pharmacoeconomics	More evidence on the overall cost-saving effects of AIT application. Limit the high costs of current treatment and clinical development.
Joint commitment	Coordinated actions among regulators, industry and the scientific environment to find solutions that properly answer the health expectations of the allergic patients

Box 2: Improving the efficacy and safety of vaccine-based AIT by targeting allergen specific T and B cells and by-passing IgE binding

- Hypoallergenic recombinant allergen derivatives and immunogenic peptides
- New adjuvants and stimulators of the innate immune response,
- Fusion of allergens with immune modifiers and peptide carrier proteins,
- New routes of vaccine administration
- Combination of AIT with immune response modifiers including anti-IgE (omalizumab)

FUTURE OF AIT

Recent advances in immunology and bioengineering enable ongoing modifications of AIT (2, 70). Still, the quality level of current evidence for these advances can be variable and includes conceptual studies in experimental models, proof-of-concept clinical studies with a limited number of subjects, and large-scale multicentre clinical studies.

The most promising approaches to improve efficacy and safety of vaccine-based AIT include bypassing IgE binding and targeting allergen-specific T and B cells using hypoallergenic recombinant allergen derivatives and immunogenic peptides, new adjuvants and stimulators of the innate immune response, the fusion of allergens with immune modifiers and peptide carrier proteins, and as new routes of vaccine administration (24, 71-73). Similar approaches are being undertaken in the AIT of food allergy, and some progress has been made through the development of AIT encompassing 3 major forms of treatment: oral, sublingual, and epicutaneous immunotherapy (74).

The cloning of allergen proteins and genetic engineering have enabled the production of vaccines that have well-defined molecular, immunologic, and biological characteristics, as well as modified molecular structure (allergen-fragments, fusions, hybrids and chimeras (71, 72). These approaches

open the possibility of enhancing the tolerogenic T cell dependent-signal with the administration of higher doses of preparation with a low risk of anaphylaxis. Clinical trials with recombinant allergen preparation primarily for grass pollen, birch pollen and house-dusts mites showed good clinical efficacy compared to placebo. Because they do not show significantly better effect than natural extracts, however, the pharmaceutical industry has stopped development due to the problematic justification of the high costs of vaccine development and licensing (75, 76). Large multicentre clinical studies with peptide-vaccines for cat- and birch allergy are currently underway.

The application of more powerful adjuvants might be easier and economically justified. Detoxified lipopolysaccharide (MPL-A), CpG oligonucleotides, imidazoquinolines and adenine derivatives, all of which activate innate immune response, are the most suitable candidates for allergy vaccination with more effective induction of specific Th1 differentiation (77). Studies are being performed with 1,25—dihydroxi-vitamin D3 as an additive to increase Treg responses by affecting DC for their tolerogenic properties (78). Novel research provides an enormous number of immune stimulators and methods for coupling with allergens; however, both proof of concept and controlled large clinical studies are yet to be performed (71, 72, 77, 78). Another approach includes allergen covalently coupled to carbohydrate-based particles for targeting DC with enhanced adjuvanticity or the use of a carrier protein, such as the Pre-S domain of hepatitis B virus fused to two non-allergenic peptides (79). A good safety profile, a significant decrease in the risk of anaphylaxis, and improved rescue medication scores was also reported for the combination of AIT with immune response modifiers including anti-IgE (omalizumab) (80, 81).

In the treatment of allergic rhinitis and asthma, both SCIT and SLIT show efficacy in reducing symptom scores and medication use, improving quality of life, and inducing sustained disease-modifying effects based on changes in specific immunologic markers (2). Work is ongoing for new routes of administration such as the intralymphatic and epicutaneous routes (82). In addition, extending SLIT to other allergens in randomized phase 3 trials to develop new products is being pursued, as are schedules and efforts to shorten the duration of AIT (83, 84). Direct head to head studies comparing novel routes with SCIT are strongly needed (82, 85).

Box 3: Consensus statement on AIT mechanisms and recommendations for standardization and pharmacoeconomics

1. AIT is an immune-mediated biological treatment, which acts through the complex interplay between T and B regulatory cells, blocking IgG4 antibodies and tissue effector-mediated mechanisms.
2. Providing reagents for AIT requires application of modern biotechnological approaches for allergen standardization (AS) and vaccine preparation.
3. The majority of pharmacoeconomics studies demonstrate cost-effectiveness of AIT within 6 years of treatment initiation.
4. Regulatory agencies classified AIT vaccines as medicinal products, which require a marketing authorization similar to medicinal products.
5. Better undertanding of barriers and facilitators for AIT is essential for further developments in the field.
6. Recent progress in biotechnology and in the understanding of the mechansism of AIT open the window of new opportunities for a safer and more effective AIT

CONCLUSIONS

This portion of the ICON document provides a comprehensive overview of AIT mechanisms, recommendations for standardization, and pharmacoeconomics. In addition, we have critically appraised barriers to and facilitators of further study and provided perspective on what waits on the AIT horizon (Box 3).

References

1. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. *J Allergy Clin Immunol* 2014;**133**:621-631.
2. 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;**131**:1288-96 e3.

3. Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. *J Allergy Clin Immunol* 2015;**135**: 626-635.
4. Agache I, Sugita K, Morita H, Akdis M, Akdis CA. The Complex Type 2 Endotype in Allergy and Asthma: From Laboratory to Bedside. *Curr Allergy Asthma Rep* 2015;**15**:29.
5. Uermosi C, Zabel F, Manolova V, Bauer M, Beerli RR, Senti G et al. IgG-mediated down-regulation of IgE bound to mast cells: a potential novel mechanism of allergen-specific desensitization. *Allergy* 2014;**69**:338-47.
6. Romano A, Torres MJ, Castells M, Sanz ML, Blanca M. Diagnosis and management of drug hypersensitivity reactions. *J Allergy Clin Immunol* 2011;**127**:S67-73.
7. Novak N, Mete N, Bussmann C, Maintz L, Bieber T, Akdis M et al. Early suppression of basophil activation during allergen-specific immunotherapy by histamine receptor 2. *J Allergy Clin Immunol* 2012;**130**:1153-1158.
8. Shamji MH, Layhadi JA, Scadding GW, Cheung DKM, Calderon MA, Turka LA et al. Basophil expression of diamine oxidase: A novel biomarker of allergen immunotherapy response. *J Allergy Clin Immunol* 2015;**135**:913-921.e9.
9. Santos AF, James LK, Bahnson HT, Shamji MH, Couto-Francisco NC, Islam S et al. IgG4 inhibits peanut-induced basophil and mast cell activation in peanut-tolerant children sensitized to peanut major allergens. *J Allergy Clin Immunol* 2015;**135**:1249-1256.
10. Ferstl R, Frei R, Schiavi E, Konieczna P, Barcik W, Ziegler M et al. Histamine receptor 2 is a key influence in immune responses to intestinal histamine-secreting microbes. *J Allergy Clin Immunol* 2014;**134**:744-746 e3.
11. Harvima IT, Levi-Schaffer F, Draber P, Friedman S, Polakovicova I, Gibbs BF et al. Molecular targets on mast cells and basophils for novel therapies. *J Allergy Clin Immunol* 2014;**134**:530-544.
12. 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;**135**:913-921.e9.
13. Jutel M, Akdis CA. Immunological mechanisms of allergen-specific immunotherapy. *Allergy* 2011;**66**:725-732.
14. Suarez-Fueyo A, Ramos T, Galan A, Jimeno L, Wurtzen PA, Marin A et al. Grass tablet sublingual immunotherapy downregulates the TH2 cytokine response followed by regulatory T-cell generation. *J Allergy Clin Immunol* 2014;**133**:130-138 e1-2.
15. Lou W, Wang C, Wang Y, Han D, Zhang L. Responses of CD4(+) CD25(+) Foxp3(+) and IL-10-secreting type I T regulatory cells to cluster-specific immunotherapy for allergic rhinitis in children. *Pediatr Allergy Immunol* 2012;**23**:140-149.
16. Sugita K, Hanakawa S, Honda T, Kondoh G, Miyachi Y, Kabashima K et al. Generation of Helios reporter mice and an evaluation of the suppressive capacity of Helios(+) regulatory T cells in vitro. *Exp Dermatol* 2015;**24**:554-556.
17. 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;**130**:1108-1116 e6.
18. 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;**121**:1467-1472, 72 e1.

19. Tsai YG, Lai JC, Yang KD, Hung CH, Yeh YJ, Lin CY. Enhanced CD46-induced regulatory T cells suppress allergic inflammation after Dermatophagoides pteronyssinus-specific immunotherapy. *J Allergy Clin Immunol* 2014;**134**:1206-1209 e1.
20. Palomares O, Martin-Fontecha M, Lauener R, Traidl-Hoffmann C, Cavkaytar O, Akdis M et al. Regulatory T cells and immune regulation of allergic diseases: roles of IL-10 and TGF-beta. *Genes Immun* 2014;**15**:511-520.
21. Palomares O, Rückert B, Jartti T, Kücüksezer 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;**129**:510-520.
22. Meiler F, Zumkehr J, Klunker S, Ruckert B, Akdis CA, Akdis M. In vivo switch to IL-10-secreting T regulatory cells in high dose allergen exposure. *J Exp Med* 2008;**205**:2887-2898.
23. Fox EM, Torrero MN, Evans H, Mitre E. Immunologic characterization of 3 murine regimens of allergen-specific immunotherapy. *J Allergy Clin Immunol* 2015; **135**:1341-51 e1-7.
24. 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;**131**:875-885 e9.
25. Mehta AK, Duan W, Doerner AM, Traves SL, Broide DH, Proud D et al. Rhinovirus infection interferes with induction of tolerance to aeroantigens through OX40 ligand, thymic stromal lymphopoietin, and IL-33. *J Allergy Clin Immunol* 2016;**137**:278-288.e6.
26. 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;**131**:1204-1212.
27. 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;**135**:771-780 e8.
28. Meiler F, Klunker S, Zimmermann M, Akdis CA, Akdis M. Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors. *Allergy* 2008; **63**:1455-1463.
29. de Wit J, Jorritsma T, Makuch M, Remmerswaal EB, Klaasse Bos H, Souwer Y et al. Human B cells promote T-cell plasticity to optimize antibody response by inducing coexpression of T(H)1/T(FH) signatures. *J Allergy Clin Immunol* 2015;**135**:1053-1060.
30. Wachholz PA, Durham SR. Mechanisms of immunotherapy: IgG revisited. *Curr Opin Allergy Clin Immunol* 2004;**4**:313-318.
31. van der Neut Kolfschoten M, Schuurman J, Losen M, Bleeker WK, Martinez-Martinez P, Vermeulen E et al. Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. *Science* 2007;**317**:1554-1557.
32. Aalberse RC, Schuurman J. IgG4 breaking the rules. *Immunology* 2002; **105**:9-19.
33. 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;**67**:217-226.

34. 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;**135**:1207-7.e1-11.
35. Gold MJ, Antignano F, Halim TY, Hirota JA, Blanchet MR, Zaph C et al. Group 2 innate lymphoid cells facilitate sensitization to local, but not systemic, TH2-inducing allergen exposures. *J Allergy Clin Immunol* 2014;**133**:1142-1148.
36. Nagakumar P, Denney L, Fleming L, Bush A, Lloyd CM, Saglani S. Type 2 innate lymphoid cells in induced sputum from children with severe asthma. *J Allergy Clin Immunol* 2016;**137**:624-626.e6.
37. 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;**134**:1193-1195 e4.
38. Bartemes KR, Kephart GM, Fox SJ, Kita H. Enhanced innate type 2 immune response in peripheral blood from patients with asthma. *J Allergy Clin Immunol* 2014;**134**:671-678 e4.
39. Chapman MD, Briza P. Molecular approaches to allergen standardization. *Curr Allergy Asthma Rep* 2012;**12**:478-484.
40. Larenas-Linnemann D, Cox LS, Immunotherapy, Allergy Diagnostics Committee of the American Academy of Allergy A, Immunology. European allergen extract units and potency: review of available information. *Ann Allergy Asthma Immunol* 2008;**100**:137-145.
41. Turkeltaub PC. Biological standardization based on quantitative skin testing--the ID50 EAL method (intradermal dilution for 50 mm sum of erythema diameters determines the allergy unit). *Arb Paul Ehrlich Inst Georg Speyer Haus Ferdinand Blum Inst Frankf A M* 1987:169-173.
42. Kaul S, May S, Luttkopf D, Vieths S. Regulatory environment for allergen-specific immunotherapy. *Allergy* 2011;**66**:753-764.
43. van Ree R, Chapman MD, Ferreira F, Vieths S, Bryan D, Cromwell O et al. The CREATE project: development of certified reference materials for allergenic products and validation of methods for their quantification. *Allergy* 2008;**63**:310-326.
44. Chapman MD, Ferreira F, Villalba M, Cromwell O, Bryan D, Becker WM et al. The European Union CREATE project: a model for international standardization of allergy diagnostics and vaccines. *J Allergy Clin Immunol* 2008;**122**:882-889 e2.
45. Kaul S, Dehus O, Zimmer J, Vieths S. Validation of major allergen references and ELISAs--current state of the BSP090 project. *Arb Paul Ehrlich Inst Bundesinstitut Impfstoffe Biomed Arzneim Langen Hess* 2013;**97**:45-53.
46. Vieths S, Barber D, Chapman M, Costanzo A, Daas A, Fiebig H et al. Establishment of recombinant major allergens Bet v 1 and Phl p 5a as Ph. Eur. reference standards and validation of ELISA methods for their measurement. Results from feasibility studies. *Pharmeur Bio Sci Notes* 2012; **2012**:118-134.
47. Neske F, Schorner C, Buchheit KH, Costanzo A, Hanschmann KM, Himly M et al. BSP090--the follow-up to CREATE. *Arb Paul Ehrlich Inst Bundesinstitut Impfstoffe Biomed Arzneim Langen Hess* 2009;**96**:12-19; discussion 9-20.
48. Hankin CS, Cox L, Lang D, Levin A, Gross G, Eavy G 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.

49. Hankin CS, Cox L, Lang D, Bronstone A, Fass P, Leatherman B 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.
50. 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.
51. Ariano R, Berto P, Tracci D, Incorvaia C, Frati F. Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma. *Allergy Asthma Proc* 2006;**27**:159-163.
52. Creticos PS, Reed CE, Norman PS, Khoury J, Adkinson NF, Jr., Buncher CR et al. Ragweed immunotherapy in adult asthma. *N Engl J Med* 1996;**334**:501-506.
53. Berto P, Frati F, Incorvaia C, Cadario G, Contiguglia R, Di Gioacchino M 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.
54. Ariano R, Berto P, Incorvaia C, Di Cara G, Boccardo R, La Grutta S et al. Economic evaluation of sublingual immunotherapy vs. symptomatic treatment in allergic asthma. *Ann Allergy Asthma Immunol* 2009;**103**:254-259.
55. Schadlich PK, Brecht JG. Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. *Pharmacoeconomics* 2000;**17**:37-52.
56. 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.
57. Berto P, Passalacqua G, Crimi N, Frati F, Ortolani C, Senna G 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.
58. Omnes LF, Bousquet J, Scheinmann P, Neukirch F, Jasso-Mosqueda G, Chicoye A et al. Pharmacoeconomic assessment of specific immunotherapy versus current symptomatic treatment for allergic rhinitis and asthma in France. *Eur Ann Allergy Clin Immunol* 2007;**39**:148-156.
59. 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.
60. Canonica GW, Poulsen PB, Vestenbaek U. Cost-effectiveness of GRAZAX for prevention of grass pollen induced rhinoconjunctivitis in Southern Europe. *Respir Med* 2007;**101**:1885-1894.
61. 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.
62. Ruggeri M, Oradei M, Frati F, Puccinelli P, Romao C, Dell'Albani I et al. Economic evaluation of 5-grass pollen tablets versus placebo in the treatment of allergic rhinitis in adults. *Clin Drug Investig* 2013;**33**:343-349.

63. 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.
64. Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C 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**:vi, xi-xiv, 1-322.
65. 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.
66. Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911; **i**:1572-3.
67. Bonini S. Regulatory aspects of allergen-specific immunotherapy: europe sets the scene for a global approach. *World Allergy Organ J* 2012;**5**:120-123.
68. Lorenz AR, Luttkopf D, Seitz R, Vieths S. The regulatory system in europe with special emphasis on allergen products. *Int Arch Allergy Immunol* 2008;**147**:263-275.
69. Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann Allergy Asthma Immunol* 2009;**103**:451-459; quiz 9-61, 95.
70. Casale TB, Stokes JR. Immunotherapy: what lies beyond. *J Allergy Clin Immunol* 2014;**133**:612-9: quiz 20.
71. Jutel M, Akdis CA. Novel immunotherapy vaccine development. *Curr Opin Allergy Clin Immunol* 2014;**14**:557-563.
72. Jutel M, Van de Veen W, Agache I, Azkur KA, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy and novel ways for vaccine development. *Allergol Int* 2013;**62**:425-433.
73. Sharma P, Gaur SN, Arora N. Immunotherapy with B cell epitopes ameliorates inflammatory responses in Balb/c mice. *Clin Exp Immunol* 2015;**179**:128-136.
74. Jones SM, Burks AW, Dupont C. State of the art on food allergen immunotherapy: oral, sublingual, and epicutaneous. *J Allergy Clin Immunol* 2014;**133**:318-323.
75. Jutel M, Solarewicz-Madejek K, Smolinska S. Recombinant allergens: the present and the future. *Hum Vaccin Immunother* 2012;**8**:1534-1543.
76. 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; **135**:1207-1207 e1-11.
77. Fili L, Cardilicchia E, Maggi E, Parronchi P. Perspectives in vaccine adjuvants for allergen-specific immunotherapy. *Immunol Lett* 2013;**161**:207-210.
78. Grundstrom J, Neimert-Andersson T, Kemi C, Nilsson OB, Saarne T, Andersson M et al. Covalent coupling of vitamin D3 to the major cat allergen Fel d 1 improves the effects of allergen-specific immunotherapy in a mouse model for cat allergy. *Int Arch Allergy Immunol* 2012;**157**:136-146.
79. Linhart B, Narayanan M, Focke-Tejkl M, Wrba F, Vrtala S, Valenta R. Prophylactic and therapeutic vaccination with carrier-bound Bet v 1 peptides lacking allergen-specific T cell epitopes reduces Bet v 1-specific T cell responses via blocking antibodies in a murine model for birch pollen allergy. *Clin Exp Allergy* 2014;**44**:278-287.
80. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic

patients. *J Allergy Clin Immunol* 2013;**132**:1368-1374.
81. Larenas-Linnemann D, Wahn U, Kopp M. Use of omalizumab to improve desensitization safety in allergen immunotherapy. *J Allergy Clin Immunol* 2014;**+133**:937-937 e2.
82. Kundig TM, Johansen P, Bachmann MF, Cardell LO, Senti G. Intralymphatic immunotherapy: time interval between injections is essential. *J Allergy Clin Immunol* 2014;**133**:930-931.
83. Creticos PS, Esch RE, Couroux P, Gentile D, D'Angelo P, Whitlow B et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2014;**133**:751-758.
84. Patel P, Holdich T, Fischer 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 e1-2.
85. von Moos S, Johansen P, Tay F, Graf N, Kundig TM, Senti G. Comparing safety of abrasion and tape-stripping as skin preparation in allergen-specific epicutaneous immunotherapy. *J Allergy Clin Immunol* 2014;**134**:965-967 e4.
86. Rosner-Friese K, Kaul S, Vieths S, Pfaar O. Environmental exposure chambers in allergen immunotherapy trials: Current status and clinical validation needs. *J Allergy Clin Immunol* 2015;**135**:636-643.
87. 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;**135**:1494-1501 e6.

Abbreviations

AAAAI = American Academy of Allergy, Asthma and Clinical Immunology
ACAAI = American College of Allergy, Asthma and Clinical Immunology
AD = Atopic dermatitis
AIT = allergen immunotherapy
AR = Allergic rhinitis
AS = allergen standardisation
Breg = B regulatory cells
BAU = bioequivalent allergen unit
BU = biologically standardized units
CBER = Center of Biologics Evaluation and Research
CEA = cost-effectiveness analysis
CREATE = Certified Reference Materials for Allergenic Products and Validation of Methods for their Quantification
CTLA-4 = cytotoxic T lymphocyte antigen-4
CUA = cost-utility analysis
D50 = dilution of extract that on average produces a 50 mm erythema (sum of lengths and width)
DC = dendritic cells
EAACI = European Academy of Allergy and Clinical Immunology
EDQM = European Directorate for the Quality of Medicines
EMA = European Medicines Agency
EPC = European Pharmacopoeia Commission
EU = European Union
FDA = Food and Drug Administration
FOXP3 = Forkhead box protein 3
FcεRI = high affinity IgE receptors
GMP = good manufacturer practice
HDM = House dust mite
iCAALL = International Collaboration in Asthma, Allergy and Immunology
ICER = incremental cost-effectiveness ratio
ICON = international consensus
Ig = immunoglobulin

Abbreviations

IHRP	=	In-house Reference Preparations
IL	=	interleukin
ILC	=	innate lymphoid cell
LR	=	Local reaction
MA	=	marketing authorization
NNP	=	named-patient products
OIT	=	Oral immunotherapy
PD-1	=	programmed death-1
PIP	=	pediatric investigational plan
QALY	=	quality-adjusted life years
RUNX	=	runt homology domain transcription factors
SCIT	=	subcutaneous immunotherapy
SLIT	=	sublingual immunotherapy
SR	=	Systemic reaction
ST	=	standard treatment
TGF	=	transforming growth factor
Th	=	T helper cells
TLR	=	toll-like receptors
Tr1	=	type 1 regulatory cells
Treg	=	T regulatory cells
USA	=	United States of America
VIT	=	venom immunotherapy
WAO	=	World Allergy Organisation
WHO	=	World Health Organisation