EXPERT REVIEWS

Current developments for improving efficacy of allergy vaccines

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Allergic diseases are prevalent worldwide. Allergen immunotherapy (AIT) is a current treatment for allergy, leading to modification of the natural course of disease. Mechanisms of efficacy include Treg through release of IL-10 and TGF-β and specific IgG_4 blocking antibodies. Subcutaneous and sublingual routes are popular, but uptake is limited by inconvenience and safety concerns. Inclusion criteria limit application to a small proportion of allergic patients. New forms of immunotherapy are being investigated for more efficacious, convenient and safer options with promising advances in recent years. The rationale of reducing vaccine allergenicity to increase safety while improving immunogenicity led to investigation of T-cell epitope-based peptides and recombinant allergen derivatives. Additionally, different routes of administration and adjuvants and adjunct therapies are being explored. This review discusses the current status of AIT and recent advances to improve clinical efficacy, safety and long-term immune tolerance.

KEYWORDS: adjuvant • allergen immunotherapy • allergic rhinitis • allergy vaccine • asthma • recombinant allergen • Treg • sublingual immunotherapy • T-cell anergy • T-cell epitope peptide

Allergic diseases are among the most prevalent conditions worldwide, with a major socio-economic burden. Allergen avoidance and pharmacotherapy to control symptoms and airway inflammation constitute the current best practice to treat allergic rhinitis (AR) and asthma [1–4]. Allergen avoidance underpins current management of food allergy [5,6], but inadvertent ingestion leading to anaphylaxis is frequent [7]. Similarly, the risk of *Hymenoptera* venom anaphylaxis is significant for a large proportion of individuals suffering from stinging insect allergy [7]. Allergen immunotherapy (AIT) is a disease-modifying therapy for AR, venom allergy and atopic asthma, leading to sustained clinical response after discontinuation of treatment [8–10]. Significant cost benefits compared with conventional pharmacotherapy are evident for the treatment of AR. Subcutaneous allergen immunotherapy (SCIT) is considered the most effective form of AIT but its widespread use is limited by the risks of systemic allergic reactions, including anaphylaxis (particularly relevant in asthma or food allergy), the inconvenience of repeated injections often over long periods and the need for supervised administration in a medical facility [9,11–14]. Sublingual immunotherapy (SLIT) is safer and more convenient than SCIT allowing home administration due to fewer serious adverse events when compared with SCIT [8]. Progress has occurred over the last decades in extract refinement and standardization with better preparations for SLIT, including dissolvable tablets as an alternative to drops, to overcome problems related to dose administration and inadequate absorption. Although SLIT is an established effective form of AIT, particularly popular in Europe, troublesome local side effects are frequent. Additionally, the long treatment regimens and need for daily use limits adherence [15]. Despite proven long-term clinical and cost benefits of AIT, it is estimated that only 5% of allergic individuals receive this treatment [16] and among the individuals who are treated, poor adherence is a significant issue. For example, some studies report adherence as <20% in the third year of treatment [17,18]. Other forms of immunotherapy are sought for more convenient and safer options to treat the large number of allergic individuals who could benefit greatly from

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AIT. The rationale of reducing the allergenicity of allergen extracts to increase safety while maintaining and improving immunogenicity has led to exploration of different routes for delivery and modification of allergens with promising advances over recent years [19,20]. Additionally, adjuvants, adjunct therapies and allergen-independent forms of 'immunotherapy', such as Toll-like receptor (TLR) agonists as monotherapy have been explored as potential new therapies. An exciting new era of AIT is fast approaching. This review provides an overview of the current status of AIT, including the underlying immune mechanisms and details the most recent advances to improve the efficacy and safety of allergen vaccines.

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Clinical efficacy of current AIT

The two currently approved routes for administration of allergen vaccines in clinical practice are the subcutaneous and the sublingual routes. SCIT involves repeated injections of allergen extracts to induce clinical and immunological tolerance and has been in use for many years in several countries, especially for the treatment of AR and venom allergy but also as an adjunct therapy in stable asthma [8,9]. SLIT involves administration of allergen extract drops or tablets under the tongue usually with a short updosing phase and a daily maintenance regimen [8]. Standardized SLIT drops have been in use for many years but to enhance reliability of dosing and adherence, tablet formulations were developed and licensed initially for pollen allergy. More recently, sublingual tablets for house dust mite (HDM) allergy also demonstrated clinical efficacy [21]. Randomized controlled trials (RCT) of SCIT and SLIT showed clinical efficacy, further confirmed by meta-analyses [13,22–25] and systematic reviews [26–29]. SCIT is effective in preventing systemic and large local allergic reactions to insect stings [27] with some data indicating similar success with the sublingual route [30,31]. Recent studies and subsequent meta-analysis have shown that AIT may be effective for atopic dermatitis (AD) [32] and food allergy [23]. Table 1 lists recent large studies evaluating SCIT and SLIT efficacy. Clinical efficacy varies with different allergens and allergic conditions, with considerable heterogeneity among the published studies. A recently published joint consensus endorsed by the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology considered the efficacy variations across the spectrum of allergic individuals in conjunction with safety concerns and unmet needs in AIT to date, providing some guidance on future clinical direction [9]. Overall, SCIT and SLIT are reported to have similar efficacy to standard pharmacotherapy for AR [22,33] but with long-lasting benefit of 7–12 years after discontinuation [34–36]. Additionally, both prevent progression of AR to asthma and decrease new allergen sensitizations in monosensitized individuals [9,37].

SCIT or SLIT: real-life & randomized trials

Allergic rhinitis

AR is the main indication for AIT via the subcutaneous and sublingual routes as demonstrated extensively in several large double-blind RCT and real-life studies [13,21,25,38–44]. There is a large body of evidence that both SCIT and SLIT significantly reduce AR symptoms, medication requirements and improve quality of life, especially for pollen allergy [25,45–47]. Similar findings have been reported for HDM allergy [48,49]. Comparable treatment effects are suggested in mono- and poly-sensitized subjects [50], although this is contentious.

Adequate head-to-head studies comparing efficacy of SLIT and SCIT for the treatment of AR are scarce [13,50]. SCIT is reported to be superior to SLIT in decreasing symptom and medication scores in seasonal AR based on a meta-analysis of the small number of head-to-head studies [43] and on indirect comparisons [11,28]. Notably, there is significant variability and inconsistency in symptom and medication scoring methods across trials of SLIT for seasonal AR, which is a limitation of indirect comparison studies of SLIT and SCIT [51]. In addition, scoring methods from clinical trials may not reliably capture the impact of AIT in real life. A recent real-life multicenter study evaluating prospectively 248 patients treated with SCIT for 1 year demonstrated a reduction of average annual days with symptoms from 189 to 145 days and the number of annual sick days was reduced from 3.7 to 1.2 days [41]. Improvement in quality of life and disease control was also demonstrated.

A recent large RCT trial involving 509 HDM-sensitized AR subjects indicated that HDM SLIT tablets are effective in reducing AR symptoms when compared with placebo with maintained efficacy in the following year [21]. SCIT is more effective than the antihistamine desloratadine to reduce ocular and nasal symptoms [33] and a recent meta-analysis of indirect comparison data demonstrated that grass pollen SLIT tablets had comparable clinical impact to nasal corticosteroids and greater clinical impact than antihistamines and the leukotriene receptor inhibitor, montelukast [22].

Asthma

The efficacy of AIT for the treatment of mild-to-moderate stable asthma has been demonstrated in several studies for both SLIT and SCIT [10]. SCIT significantly reduces asthma symptoms, medication requirements and decreases bronchial hyperreactivity [25,42]. Similarly, high level of evidence supports SLIT for improvement of asthma symptoms with 8 out of 13 studies demonstrating improvement greater than 40% versus the comparator and moderate grade of evidence was observed for decreased requirement for asthma medications (decrease of medication use for asthma >40% in 16 out of 41 studies evaluated) [38]. A comparative review of SCIT versus SLIT showed low-grade evidence that SCIT is superior to SLIT in reducing asthma symptoms [43]. However, the safer profile of SLIT makes this route more attractive, as asthma is a risk factor for serious adverse events in AIT. Unstable asthma is an absolute contraindication for AIT and, therefore, SLIT and SCIT options are limited to individuals with mild asthma or selected individuals with controlled moderate asthma and no additional risk factors for SCIT-related severe reactions.

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Table 1. Summary of recent large studies evaluating subcutaneous allergen immunotherapy and sublingual immunotherapy efficacy.

Study (Year)	Vaccine	Condition	Allergen	Formulation/ regimen	Duration	Study type	Subjects	Main end point	Magnitude of effect	Ref.
Abramson *et al.* (2010)	SCIT	Asthma	Various	Various	Various	Meta-analysis	1314 (adults/ child)	Symptoms	–0.49 (95% CI: –0.83 to –0.35)	[25]
Dretzke *et al.* (2013)	SCIT	Allergic rhinitis (± asthma)	Various	Various	Various	Systematic review	17 trials	Symptoms	–0. 65 (95% CI: –0.85 to –0.45)	[13]
	SLIT	Allergic rhinitis (± asthma)					42 trials		–0.33 (95% CI: –0.42 to –0.25)	
Erekosima *et al.* (2014)	SCIT	Allergic rhinitis (± asthma)	Various	Various	Various	Systematic review	3577 adults (66 trials)	Symptoms	Moderate to strong evidence	[42]
Lin *et al.* (2013)	SLIT	Allergic rhinitis	Perennial and seasonal allergens	Tablets, liquid	Variable	Meta-analysis	2985 (AR)	Symptom score	40% (↓)	[38]
		Asthma	HDM				625 (asthma) (adult/child)		40% (↓)	
Bergmann *et al.* (2014)	SLIT	Allergic rhinitis	House dust mite	Tablets	1 year	RCT	509 adults	Symptom score	–20.2% (p = 0.0066)	[21]
Creticos *et al.* (2014)	SLIT	Allergic rhinitis	Ragweed	Liquid extract	Pre/co-seasonal	RCT	429 adults	Total combined score (symptom/ medication)	(–0.83) 41% (↓) (95% CI: –1.30 to –0.37)	[39]
Mosbech *et al.* (2014)	SLIT	Asthma	House dust mite	Tablets	1 year	RCT	604 (>14 years)	Inhaled steroids use	50% (↓)	[40]
Cox *et al.* (2012)	SLIT	Allergic rhinitis	Pollen (grass mix)	Tablets pre/co-seasonal	6 months	RCT	473 adults	Daily combined score (symptom/ medication)	28% (↓) (95% CI: 13–43%)	[47]
Radulovic *et al.* (2011)	SLIT	Allergic rhinitis	Various	Tablets/drops	Various	Systematic review Cochrane	4589 adults/ children 3379 adults/ children	Symptoms (49 studies) Medications (38 studies)	–0.49 (95% CI: –0.64 to –0.34) –0.32 (95% CI: –0.32 to –0.21)	[46]

RCT: Randomized controlled trial; SCIT: Subcutaneous allergen immunotherapy; SLIT: Sublingual immunotherapy.

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Hymenoptera venom allergy

Stings from insects of the order *Hymenoptera* (bees, wasps and ants) are common and can result in systemic allergic reactions including anaphylaxis. Venom immunotherapy (VIT), delivered by the subcutaneous route, has been used successfully for many years and is the current recommended gold standard treatment for subjects with severe insect sting allergy associated with anaphylaxis [27,52]. Two small studies exploring the sublingual route [30,31] showed some benefit but larger trials are needed. The severity of previous reactions informs the choice of VIT as a correlation is established between the frequency of systemic reactions to subsequent stings and the severity of previous reactions, with 40–60% risk of further severe reactions in subjects who have experienced prior anaphylaxis [53]. The high efficacy of VIT has been demonstrated in randomized controlled studies and confirmed by a Cochrane systematic review of a total of 392 subjects [27]. VIT significantly reduced the occurrence of systemic reactions to a future sting to one-tenth (risk ratio: 0.10; 95% CI: 0.03–0.28). Only 2.7% (3 out of 113) of participants receiving VIT developed further systemic reactions on a subsequent sting as compared with 39.8% (37 out of 93) of individuals who did not receive VIT. The same meta-analysis concluded that VIT also significantly prevented the occurrence of large local reactions to a future sting and improved quality of life.

Atopic dermatitis

AD is a multifactorial condition where environmental, genetic and endogenous factors play a role. AD patients are frequently allergic to HDM and, for children, egg and milk. SLIT and SCIT for HDM allergy have shown efficacy in reducing topical corticosteroid use and improving the extent and intensity of AD [32,54]. A recent meta-analysis including a total of 385 subjects with AD treated with SCIT (6 studies) or SLIT (2 studies) demonstrated benefit of SCIT (>1 year) in patients with severe AD [32]. Only two trials evaluated SLIT and the subgroup analysis of these studies failed to show significant efficacy. A recent randomized study of HDM SLIT drops (*Dermatophagoides farinae*) as an adjunct to pharmacotherapy compared with pharmacotherapy alone in the control group showed significant reduction in daily medication scores and visual analogue scale scores compared with the control group at 12 months follow-up [55]. Larger controlled trials evaluating efficacy, potential disease-modifying benefit and utility in primary prevention are warranted.

Food allergy

Dietary avoidance is standard practice for individuals with food allergy. The most common food allergens are peanut, milk, egg, hazelnut, fish, wheat, soy [5,20] and peach [20]. Whole allergen food extracts for SCIT have been investigated. In the two peanut SCIT studies, the majority of subjects experienced systemic reactions and one study was terminated prematurely after a fatal dispensing error [56,57]. Epicutaneous delivery of peanut extract caused local reactions in ~85% subjects, and patches applied 24 h/day for 365 days only desensitized 50% children, with no significant improvement in adults or adolescents [58]. Peanut oral immunotherapy (OIT) and SLIT caused numerous adverse reactions in multiple subjects, some of which required epinephrine [59–64]. Even with exclusion of highly allergic subjects, three studies reported anaphylactic adverse events [60,62,65]. For both OIT and SLIT, following initial dosing, subjects typically were required to consume peanuts daily at home to sustain clinical desensitization. During this phase, further allergic reactions were common and could be triggered by concurrent illness, poor asthma control, ingestion on an empty stomach, exercise, a warm bath or menstruation [59,63,64]. Consequently, treatment of peanut allergy with whole extracts cannot be recommended for routine clinical practice [61,66–68].

Recent alternative specific strategies have been reported. A *preventive study* of regular peanut consumption in high-risk infants reported a significantly lower incidence of peanut allergy by 5 years of age, although sustainability is unknown [69]. The study excluded known peanut allergy or peanut skin prick test >4 mm suggesting likely peanut allergy, but still adverse events occurred during treatment and ~10% developed peanut allergy [70]. Another study co-administered probiotics with whole peanut OIT and showed evidence of desensitization after 18 months treatment [59]. However, sustained tolerance beyond 2–5 weeks was not studied and 45% of the active group had one or more unpredictable adverse events including anaphylaxis, as consistently reported in other peanut OIT trials. The relative contributions of probiotic and peanut OIT are not known and no biomarkers can predict patient susceptibility to adverse events with whole peanut extracts. In summary, these trials highlight the urgent need for a safe, disease-modifying therapeutic that can provide long-term clinical and immunological tolerance for peanut allergy sufferers.

Role of allergen immunotherapy in the elderly patient

The world aging population is steadily increasing and allergic diseases in the elderly are a growing problem with recent studies showing incidence of atopy and allergic diseases in the elderly varying from 15% [71] to 26% [72]. Often nasal symptoms in older patients are overlooked or underestimated due to other comorbidities and local nasal pathology and AR may be missed [72,73]. AIT is seldom offered to older patients due to safety concerns and the perception that the allergic disease is already 'too advanced' and unlikely to benefit from AIT. A recent study has demonstrated significant clinical efficacy of HDM SLIT in subjects of age >60 years who had a long history of perennial HDM AR [74]. Another recent double-blind placebo-controlled study from the same group evaluating the clinical efficacy of grass pollen SLIT (78 allergic subjects aged 60–70 years) reported 64% decrease in nasal symptoms versus 7% with placebo [75]. The revised Practice Parameter on Allergy Immunotherapy does not include a specific summary statement on immunotherapy in the elderly patient but has outlined that there is no upper age limit for initiation of immunotherapy.

A recent study assessing the impact of comorbidities and concomitant treatment on asthma control and severity in older adults identifies a higher incidence of chronic comorbidities

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and a higher number of prescribed medicines, but the severity of asthma and the intensity of anti-asthma treatment were similar to younger patients. There was no correlation between the presence of comorbid conditions and asthma control, severity or frequency of exacerbations in older patients [76]. To our knowledge, there are no studies demonstrating clear differences between efficacy of AIT between elderly and younger adults. Furthermore, a recent review demonstrated better adherence of 'veterans' to AIT, particularly in subjects older than 66 years (adherence 78.7 vs 58.4% for 36–65 years and 46.7% for 18–35 years) [77]. Clinical trials of AIT in this population specifically will be informative and modified allergens and peptide immunotherapy in particular may hold promise.

Contraindications for AIT

Practically, the main contraindications for AIT are severe or uncontrolled asthma (forced expiratory volume in 1 s < 70% predicted); serious immunopathologic diseases and immunodeficiencies, malignancies; significant cardiovascular diseases (except for VIT); severe psychological disorders; adherence doubts; severe AD; treatment with β-blockers (even topical); pregnancy (avoid initiation of AIT but maintenance AIT can be continued); chronic mouth disease (for SLIT) and previous anaphylaxis with AIT [78].

Immune mechanisms of current AIT

Investigations into the immune mechanisms underlying clinically effective AIT inform strategies for refining this treatment for improved efficacy and safety as well as potential biomarkers for monitoring efficacy. Studies show a similar successive series of immune events for SCIT and SLIT (see detailed reviews [79,80]). Basophil and mast cell susceptibility to degranulation is reduced within hours of commencing AIT, likely linked with the rapid upregulation of the histamine receptor 2 (HR2) on these cells [81]. These changes are followed by generation of Treg and Breg and suppression of allergen-specific effector T cells, ultimately resulting in a skewing of the immune response away from inflammation.

AIT effectively reverses the imbalance in T-cell subsets that underlies allergic diseases. In healthy individuals, high IL-10-producing Treg, known as Tr1 cells, are the dominant subset of T cells in response to allergens, whereas in allergic individuals allergen-specific IL-4-secreting T cells (Th2-like) predominate. The development and function of Treg requires the transcription factor forkhead box protein 3 (Foxp3), which converts non-regulatory $CD4^+CD25^-$ T cells into T cells with regulatory activity. AIT induces Tr1 cells that suppress both Th1 and Th2 cytokine responses to specific allergen stimulation and also results in immune deviation from a Th2 to a Th1 response with increased synthesis of IL-12 and IFN-γ and decreased synthesis of IL-4. It seems that the Treg response dominates early and immune deviation from Th2 to Th1 profile is more pronounced later in the course of immunotherapy as suggested by studies that detected an increased number of $CD4^+CD25^+$ T cells with increased Foxp3 and IL-10 within the first 4 weeks of treatment with increased IFN-γ, and reduced IL-4, IL-10 and Foxp3 mRNA expression being observed after 1 year of treatment [82]. Allergen-specific T cell deletion may also contribute to the observed progressive decrease in allergen-specific lymphocyte proliferation throughout the course of therapy. A recent study using peptide-MHC class II tetramers to identify specific T cells in timothy grass pollen allergic individuals showed that AIT was associated with preferential deletion of allergen-specific Th2 cells without a significant change in the frequency of Th1/Tr1 cells [83].

IL-10 is the main suppressor cytokine of Treg in AIT, with direct and indirect effects on effector cells involved in the allergic inflammatory process, including eosinophils, mast cells and basophils as well as T and B cells, with suppression of allergen-specific T-cell subsets and costimulatory pathways and skewing of B-cell production of specific IgE to IgG_4 [84]. Similarly to Tr1 cells, IL-10 secreting B cells (Br1 or Breg) contribute to immune tolerance via IL-10-mediated suppressor effects. For example, it was shown that B cells specific for the major bee venom allergen phospholipase A isolated from non-allergic beekeepers had increased expression of IL-10 and IgG_4, and the frequency of $IL\text{-}10^+$ phospholipase A-specific B cells increased in allergic patients receiving AIT [84].

Treg also use other suppressive factors and molecules to induce immune tolerance including TGF-β, cytotoxic T lymphocyte antigen 4 and programmed death 1 [79]. Natural killer cells, epithelial cells, macrophages and glial cells also express IL-10 and TGF-β, potentially contributing to suppression and regulation of the immune response [85]. Runt-related transcription factors are induced by TGF-β and further contribute to the generation and suppressive activity of Treg [86].

In parallel with the progressive changes in T-cell subsets during AIT, there is altered production of specific antibody isotypes [84,87–89]. There is an early and transitory increase in specific IgE levels and a steady increase in specific IgG_4 resulting in a reduced IgE/IgG_4 ratio after several months of treatment [79,90]. It is suggested that increased levels of IgG_4 lead to capture of the allergen before it reaches effector-cell bound IgE, therefore, preventing activation of mast cells and basophils. Specific IgG_4 can also inhibit IgE-facilitated allergen uptake by dendritic cells [91]. There is a decrease in the number of mast cells and eosinophils in tissues and a decrease in the release of their mediators accompanied by a reduction in type I skin reactivity to allergen usually after 6 months of treatment. Decreased skin late-phase responses occur in parallel to decreased lymphocyte and eosinophil infiltration [79].

Together, the above-described changes in the immune response to allergen during AIT lead to sustained immunological and clinical tolerance. By targeting critical events in this process, AIT can be refined to promote treatment efficacy, duration and compliance.

Summary of current status of AIT

Despite the large number of research studies, the role for SCIT and SLIT in the treatment of allergic diseases remains unclear.

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SCIT carries greater risk of systemic adverse events than SLIT and is less convenient due to requirements for medical supervision. SLIT has a much safer profile and is administered at home but oral itching and non-life-threatening lip and tongue edema frequently impact adherence. Inconsistency in reporting of SLIT-related adverse events in AR is common. There is wide discrepancy in the prevalence of side effects in clinical trials and real-life with greater frequency of local adverse events in real life [92]. SCIT-induced adverse reactions range from mild pruritus to life-threatening anaphylaxis and even death. Reported SCIT-related fatal reactions have declined over the last decade [12] and the current rate of systemic reactions to SCIT is 0.1% of injections [93]. Safety guidelines incorporated in clinical practice in association with identification of risk factors for severe events have improved safety of SCIT but vigilance and administration in a clinical setting equipped to treat anaphylaxis remains mandatory and does limit uptake. Other unmet needs include better extract standardization, standardizing clinical outcome measures across studies, strategies for improved patient adherence and strategies to measure efficacy of SCIT and SLIT in real-life [9,94].

Improving efficacy: current developments for allergy vaccines

Despite proven efficacy of AIT in meta-analyses, clinical improvement is not satisfactory for all treated patients and only a proportion of total allergic patients meet inclusion criteria for current AIT with whole allergen extracts. The duration of treatment is typically considerable and the risk of serious adverse events is concerning. There is a need for development of improved vaccines. Current advances and research focus on novel routes of administration, modification of allergens and utilization of new adjuvants and adjunct therapies to improve efficacy and safety, ensuring wider applicability of AIT.

Current research into novel routes of administration

Oral

Over recent years, there has been increasing research interest in the oral route as an efficacious form of AIT particularly in food allergy. OIT involves supervised progressive introduction of increasing amounts of the food with the goal of achieving sustained clinical and immunological tolerance. Early case reports and small trials suggested clinical desensitization, mainly for milk, egg and peanut allergy, with some immunological changes but without convincing evidence for sustained tolerance. A recent systematic review and meta-analysis of research studies in OIT for food allergies, with 18 RCT and 3 controlled clinical trials, demonstrated that OIT can achieve desensitization to a range of foods with some evidence for immunomodulatory changes, including a decrease in skin prick test response to the relevant food allergen and an increase in allergen-specific IgG_4 [95]. Experimental evidence has demonstrated that IgG antibodies suppress IgE-mediated food hypersensitivity via the inhibitory receptor FcγRIIb [96].

In contrast to cow's milk allergy, peanut allergy does not usually resolve spontaneously. Clinical efficacy of research OIT for peanut allergic subjects was accompanied by immunological changes including increased specific IgG_4, decreased IgE levels and Th2 cytokine production [60,97,98] and supported by the meta-analysis of three randomized trials assessing 86 subjects [23]. However, adverse events sometimes requiring epinephrine are frequent and unpredictable imposing a current barrier to use in clinical practice. A well-designed study [99], the only study included in a Cochrane review [66], evaluating 28 children with peanut allergy demonstrated that the children receiving peanut OIT tolerated the maximum 5 g peanut protein (equivalent to 20 peanuts) after 1 year of therapy. The group of children who received placebo tolerated a median cumulative dose of 280 mg and none tolerated the maximum dose. Children receiving OIT demonstrated increases in Treg and peanut-specific IgG_4 levels, transient increases in specific IgE and decreases in skin prick test responses, serum IL-5 and IL-13 [99]. A recent Phase I study with 23 patients receiving peanut OIT for 2 years compared with 20 non-allergic control subjects who abstained from peanut ingestion determined that antibody and basophil activation measurements failed to discriminate between subjects who achieved tolerance (n = 7) versus non-tolerant individuals (n = 17), but T-cell function and demethylation of Foxp3 CpG sites in antigen-induced Treg were significantly different between tolerant and non-tolerant patients 3 months after stopping OIT. Four of the seven tolerant participants regained peanut sensitivity along with increased methylation of Foxp3 CpG sites in antigen-induced Treg [100]. Another recent study with 24 peanut allergic individuals after 5 years of peanut OIT reported tolerance in half the subjects but sustained tolerance beyond 2–5 weeks was not studied and 45% of the active group had one or more unpredictable adverse events including anaphylaxis, as consistently reported in other peanut OIT trials [101]. OIT favorably modified the peanut-specific immune response in all subjects completing the protocol and smaller skin test results and lower allergen-specific IgE levels were predictive of successful outcome. There were no differences in peanut IgG_4 levels or functional activity at the end of the study [101]. Currently, peanut OIT cannot be recommended for clinical practice.

A Cochrane meta-analysis of five research trials assessing 196 children with cow's milk allergy determined clinical efficacy of OIT (62 and 27% children receiving OIT could ingest a full and a partial serving of milk, respectively) [102]. Only 8% tolerated a full serving with none tolerating a partial serving in the control group. Adverse events were frequent and mostly mild but overall for every 11 patients receiving OIT, one required intramuscular adrenaline. A second systematic review corroborated these findings and concluded that although OIT for cow's milk is beneficial this should be counterbalanced by the frequency of significant adverse events [103]. A recent study evaluating 40 children undergoing OIT for cow's milk allergy showed that adverse reactions were associated with low IgG and IgG_4, but high IgG_1 levels to ovalbumin. Specific IgA, IgG, IgG_1 and IgG_4 to cow's milk proteins significantly increased and specific IgE decreased during OIT in children who achieved clinical desensitization. Interestingly, high specific IgA, IgG classes and IgE prior to OIT

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failed to predict unsuccessful therapy [104]. Immune tolerance achieved with cow's milk OIT waned after treatment cessation. There is evidence that only one-third of patients can tolerate milk with no or minimal symptoms 3 to 4 years following cessation of therapy [105]. A study comparing SLIT and OIT in cow's milk allergic patients suggested stronger efficacy of OIT but greater adverse events. Symptoms recurred as early as 1 week off therapy in a few patients. Specific IgA and IgG class antibodies to cow's milk increased and IgE decreased during immunotherapy.

Egg allergy, another common food allergy, has attracted OIT research. A meta-analysis of 4 RCT assessing a total of 167 children (100 receiving OIT and 67 controls) [106] included one placebo study and three studies utilizing a control avoidance diet. Each study used a different OIT protocol. Thirty-nine percent of OIT participants tolerated a full serving of egg compared with 11.9% controls and 40% children receiving OIT could ingest a partial serving of egg (1–7.5 g). Adverse events were again very frequent, occurring in 69% children receiving OIT.

In summary, food allergen-specific OIT holds promise in research studies but evidence for sustained tolerance is not convincing and adverse event frequency is unacceptably high.

Epicutaneous

The epidermis is an attractive site for research into novel AIT as it contains antigen-presenting Langerhans cells and injury to the epidermis results in indirect modulation of Treg, and downregulation of effector cell responses via secretion of cytokines by keratinocytes. The most popular form of epicutaneous immunotherapy (EPIT) is the application of an allergen-containing patch which has been investigated in seasonal AR and milk allergy and in studies on EPIT for peanut allergy. A trial of grass pollen EPIT in 132 individuals with grass pollen allergic conjunctivitis involving the application of grass pollen allergen patches to tape-stripped skin on a weekly basis prior to and during the pollen season demonstrated clinical efficacy [107] corroborating previous studies. In this study, EPIT for pollen allergy resulted in 30% improvement of symptoms after six patches with no serious systemic adverse events. A study of EPIT in 18 children with milk allergy involving a 48-h skimmed milk powder patch application weekly for 3 months showed an increase in the cumulative dose of ingested milk after therapy with an acceptable safety profile as only local adverse events were observed [108]. There are no published peer-reviewed studies evaluating EPIT for peanut allergy to date but a Phase IIa study in France and a large multicenter dose-finding Phase IIb study in the USA and Europe suggest promise for desensitization with a good safety profile.

Intralymphatic

The direct administration of allergen into lymph nodes as a form of AIT is based on the concept that strong immune responses are initiated in secondary lymphoid organs and less allergen may elicit significant beneficial immune changes. Trials suggest clinical efficacy for bee venom, grass pollen and cat allergy after only three injections into inguinal lymph nodes [109–111] with a good safety profile. A RCT evaluating grass pollen intralymphatic immunotherapy (ILIT) failed to demonstrate improvement in combined symptom-medication scores despite changes in IgG_4 levels [112]. In this study, weekly injections were administered which could potentially explain the negative results as it has been suggested that a minimum interval of 4 weeks is required for optimal clinical efficacy [113]. ILIT injections were described as painless and comparable to SCIT, by 6 patients in a small pilot open study immediately followed by a double-blind randomized study of 15 subjects treated with grass or birch pollen ILIT. Patients reported mild to moderate discomfort with ILIT injections and ILIT resulted in improvement in seasonal AR symptoms and post-nasal challenge symptoms and inflammation, not observed in the placebo group [110]. Except for one patient who developed mild late nasal symptoms, only mild local reactions (pruritus, redness or swelling) were observed with ILIT. Additionally, patients receiving ILIT demonstrated an initial increase in allergen-specific IgE levels and peripheral T-cell activation. ILIT results in upregulation of specific IgG isotypes (including Th1-dependent IgG_{2a} that protects against anaphylaxis), and increases in T-cell IL-2, IL-4, IL-10 and IFN-γ secretion using 100-times lower doses of allergens compared with SCIT [114]. Investigation of ILIT with a novel vaccine of the major cat allergen Fel d 1 targeting the MHC using a modular allergen translocation (MAT) technique (MAT-Fel d 1 vaccine) indicated that three intra-lymph node injections of MAT-Fel d 1 vaccine-induced allergen tolerance mediated by increased cellular internalization of the allergen, modulation of inflammation and generation of allergen-specific peripheral T-cell tolerance [115]. The MAT-Fel d 1 vaccine was efficiently internalized by APC triggering secretion of IL-1β, induction of specific T-cell proliferation and an IL-10- and IFN-γ-dominated T-cell response with decreased Th2 cytokines at 100-times lower doses than Fel d 1. Early Fel d 1-specific T-cell activation was followed by full T-cell unresponsiveness to allergen after 1 year in the MAT-Fel d 1 group, characterized by increased allergen-specific Treg, decreased circulating Fel d 1 tetramer-positive cells, increased IL-10 and Foxp3 expression and change in the HR2/HR1 ratio toward HR2 [115]. ILIT holds potential as an effective form of AIT, but requires larger RCT to define optimal regimens.

Nasal

Local nasal immunotherapy has been explored in AR [19]. Clinical response was observed in HDM allergic subjects who received HDM allergen delivered intranasally via HDM-coated strips placed on the nasal septum for 10 min weekly for 10 months [116]. Although some clinical efficacy was observed, local side effects, including persistent nasal symptoms after strip application, occurred frequently and suggested major limitations.

Developments in modification of allergen preparations for AIT

As the route of administration of AIT influences efficacy, patient compliance and, to some extent, safety of AIT, as

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discussed above, major effort is being directed at modified allergens. The key allergenic components of allergens are well characterized in most cases and advances are being made in understanding the immune mechanisms that determine whether an adverse allergic reaction or tolerance ensues following allergen administration (as discussed above). This allows refinement of allergen preparations for AIT in order to retain immunomodulatory properties but lack the ability to induce IgE-mediated adverse events. Use of such refined preparations will allow wider application of AIT to those with food allergy and severe asthma as well as achieving higher dose administration and thus potentially greater efficacy. Additional benefits are greater ease of manufacture and standardization of well-defined, modified allergen preparations.

T-cell epitope peptides

The most exciting advance in modification of allergen form for treatment of allergic diseases has been with the use of sets of short allergen-derived peptides, carefully selected and designed to comprise the dominant T-cell-reactive sites of the major allergen sequences but lacking IgE binding and inflammatory cell-activating potential [117]. The concept of using T-cell epitope peptides to induce anergy in allergen-specific T cells was first introduced in the 1990s by O'Hehir and collaborators, when short-term incubation of clonal Der p 1-specific T cells with high concentration of a dominant T-cell epitope peptide of Der p 1 was found to induce a state of non-responsiveness in the T cells to subsequent challenge with immunogenic concentrations of that peptide, or indeed whole HDM [118]. Validation of the potential of this approach for clinical use was demonstrated using a murine model of HDM allergy, which confirmed the *in vivo* applicability of linked suppression [119]. Since these early studies, the pivotal role of T cells in orchestrating the immune response to allergen both following natural exposure as well as immunotherapy has been demonstrated in numerous *in vitro* and *in vivo* models of allergy and T-cell epitopes have been defined for a large number of clinically important allergens (see reviews [120,121] and the Immune Epitope Database [122]). Peptides can induce T-cell tolerance more efficiently than whole allergen by directly binding HLA molecules on APC without activating proinflammatory signals (as caused by whole allergen extracts). Providing clinical utility for an HLA-diverse population, T-cell epitope peptides show promiscuity of presentation by MHC class II molecules, with presentation by the less polymorphic HLA-DQ and HLA-DP of particular advantage. Importantly, T-cell epitope peptides are now undergoing clinical trial for several allergies with very promising results. Placebo-controlled large Phase II and III trials using T-cell epitope peptides for cat allergy and Phase II trials for grass and HDM allergy (Circassia Ltd, Oxford, UK) confirm that these peptides are just as effective at inducing clinical desensitization as whole allergens (by SCIT, SLIT or OIT), and can do so in a much shorter time frame without allergic side effects [123,124]. Each of these vaccines consists of a mixture of several peptides <20 residues in length which encompass dominant $CD4^+$ T-cell epitopes of clinically relevant major allergens. Pilot studies indicated that four intradermal injections of 3–12 nmol/peptide (optimal dose dependent on the allergen) given at 4-week intervals were most effective at reducing symptoms following subsequent allergen challenge. At least 2 years duration of efficacy of the Fel d 1 peptide treatment has been shown by sustained significant reduction in total rhinoconjunctivitis symptom score following cat allergen exposure in an environmental exposure chamber [125]. This form of treatment potentially heralds a new class of allergy therapy recently called synthetic peptide immuno-regulatory epitope (SPIRE) therapy, to differentiate this approach from conventional AIT, as underlying immunological principles seem more dependent on specific T-cell anergy induction and possibly specific Th2 cell deletion as discussed below [126].

In similar but smaller studies on bee venom allergy, dominant T-cell epitope peptide formulations have also been shown to induce clinical tolerance to bee sting allergen without severe adverse events [127]. However, these studies did not progress due to concerns with the unpredictable natural history of bee venom reactions. As evidence of clinical and immunological tolerance increases with the newer SPIRE therapy, it is likely that bee venom peptide research will progress.

The selection of suitable peptide panels for SPIRE therapy requires extensive screening and validation to ensure inclusion of dominant peptides recognized by a large cohort of allergic subjects, mapping of core epitope sequences, refinement of sequences for solubility and stability as well as careful screening for lack of IgE binding or basophil activation to ensure safety [128].

Mechanisms of action of SPIRE therapy for allergy appear to overlap with those for conventional AIT with evidence for immune deviation and Treg induction but roles for specific T-cell anergy and Th2 cell deletion also seem evident in SPIRE therapy [126]. Effects on antibody responses are less clear. Some studies with aeroallergens report a small increase in allergen-specific IgG, but this may be due to ongoing exposure to environmental allergen. Further studies are needed to fully delineate mechanisms of action.

Recently, a different approach for peptide immunotherapy was proposed based on long contiguous overlapping peptides (COPs). This strategy aims to encompass all possible T-cell epitopes of an allergen but with disrupted conformational IgE epitopes. Phase I/IIa clinical trial of COPs for bee venom and birch pollen allergy showed no immediate allergic reactions in allergic patients [129] with evidence for increased specific IgG_4 antibodies and in the case of the birch pollen allergy, improved nasal provocation test index following a short course of five injections over 2 months. In these studies, higher COP peptide concentrations were associated with late asthma responses as seen in the early cat peptide studies which were not observed with the lower peptide concentrations. These are consistent with the reported surge of Th2 cytokines, particularly IL-4 which is a known bronchoconstrictor, seen early in the induction phase of T-cell epitope peptide anergy [130,131]. Convincing proof of efficacy awaits further trials with larger patient numbers.

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Recombinant allergens

Recombinant technology is an alternative approach to generate hypoallergenic molecules with retained or potentially enhanced immunomodulatory activity. While the peptide approach described above requires use of a peptide panel to encompass the multiple T-cell-reactive sites recognized differentially by individuals, a recombinant molecule can be produced which retains the natural T-cell epitopes but has been modified to ablate IgE reactivity. Different strategies have been used taking into account the particular molecular properties of the allergens (see review [132]). Site-directed mutagenesis to disrupt IgE conformational epitopes is a common strategy, for example, substitution of cysteine residues to prevent disulfide bond formation. Other novel recombinant approaches include production of deletion mutants, oligomers, fragments and chimeras and constructs of peptides fused with virus-like particles or vitamin D3 (see reviews [133,134]). Recombinant allergen derivatives can be prepared in large quantities and at high purity using reproducible, standardized methods. Of importance is elimination of contaminating endotoxin from bacterial-derived preparations and very careful screening for lack of IgE-binding and cross-linking activity.

Recombinant constructs of trimers of Bet v 1, peptides fused to virus-like particles and fragments have all been trialed clinically up to Phase III with evidence of reduced symptom scores [135]. It is suggested that induction of blocking IgG antibodies is a major underlying immune mechanism [136]. A mutant form of the major fish parvalbumin Cyp c 1 allergen produced by ablation of the functional calcium binding sites required for native conformation is currently under Phase I/IIa trial [137].

Adjuvants

Different adjuvants have been proposed to enhance immunotherapy efficacy either by increasing the duration of antigen presentation or by direct effects on the immune response cascade [19]. The most frequently used adjuvant is aluminum hydroxide (alum), which is used in SCIT to increase the duration of antigen presentation. The use of alum-based extracts leads to clinical improvement. A fast updosed immunologically enhanced SCIT formulation, by optimizing the allergen/adjuvant ratio, has resulted in significant immunological changes underlying good clinical efficacy [138].

TLR engagement on APC plays an important role in regulating adaptive immunity and TLR ligands can be selected to promote Treg responses and immune deviation from Th2 to Th1 profile. The use of TLR agonists as immunotherapy adjuvants has been explored as enhancers of immune response triggered by immunotherapy and as vectors to re-direct allergic inflammation away from the airways [139]. Monophosphoryl lipid A (MPL), a TLR-4 agonist, is a detoxified derivate of *Salmonella minnesota* that is used in the novel Pollinex Quattro allergy vaccine (Allergy Therapeutics, Worthing, UK), which is a glutaraldehyde-modified L-tyrosine adsorbed pollen allergen that can be administered via subcutaneous or sublingual routes and is currently under investigation in a Phase IV clinical trial for asthma. When used subcutaneously, only four injections pre-seasonally are required. Clinical efficacy, sustained tolerance, prevention of new sensitizations and/or development of asthma have been demonstrated in several studies with MPL-adjuvant immunotherapy for AR [140–142]. Importantly, clinical improvement is associated with Treg induction, immune deviation to Th1 response and a shift from IgE to blocking IgG4 production and there is evidence of reduction of lung inflammation demonstrated by a decline in inflammatory markers in the exhaled breath condensate of asthmatics [141].

A new direction has emerged exploring TLR agonists as monotherapies for allergy with the advantage of not exposing allergic subjects to allergens thus avoiding side effects. It has been shown that a TLR-8 agonist administered weekly via a nasal spray can improve symptoms after four administrations [143]. More recently, a randomized controlled study in 63 subjects with asthma receiving bacteriophage Qbeta-derived virus-like particles with CpG-motif G10 inside (QbG10), a novel TLR-9 agonist packaged into virus-like particles, demonstrated improvements in asthma outcomes despite corticosteroid withdrawal as compared with deteriorations observed with placebo [144]. After 3 months, 60% QbG10-treated patients had their asthma 'well controlled'. Forced expiratory volume in 1 s decreased significantly in patients on placebo and remained stable in QbG10 patients. Adverse events were mostly injection site reactions occurring after QbG10 administration [144]. This is a promising therapy for allergic asthma and larger studies are currently being performed.

Adjunct therapy

Omalizumab

The anti-IgE drug omalizumab has been investigated as an adjunct therapy for allergy and has been shown to improve efficacy and safety of SCIT. A multicenter placebo-controlled randomized trial evaluating omalizumab or placebo in 140 subjects as an added therapy to SCIT over 2 years for the treatment of seasonal AR during the pollen season demonstrated that the concomitant use of omalizumab reduced symptom severity by 39% over SCIT alone and also improved asthma control and asthma and AR quality of life [145]. A subsequent study by the same group failed to demonstrate sustained effects of omalizumab throughout the remaining duration of SCIT for pollen allergy [146]. Preliminary data for the use of omalizumab as adjunct therapy to treat cow milk allergy and bee venom allergy have shown some encouraging results but larger well-designed studies have not been conducted to date.

Vitamin D

Vitamin D has immunomodulatory effects including priming dendritic cells to promote the development of Treg and inhibition of IgE production by activation of the vitamin D receptor. B cells can synthesize calcitriol from its inactive precursor 25-hydroxyvitamin D3 upon antigenic stimulation [147]. In a murine allergy model, coadministration of 25-hydroxyvitamin D3 with ovalbumin-specific immunotherapy has been shown to reduce allergic airway inflammation and responsiveness upon

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ovalbumin challenge and to reduce Th2 cytokine expression [147]. Serum levels of vitamin D have correlated with clinical response [148]. A recent study evaluating vitamin D as adjunct therapy in 50 children with asthma, in comparison with SCIT or pharmacotherapy alone, demonstrated that, while no statistical differences in changes from baseline in symptom and medication scores were observed for the two immunotherapy groups, symptom scores were lower in the SCIT + vitamin D group at 6 months. Whereas the levels of Der p 1-induced IL-10 and TGF-β were similar between both immunotherapy groups, the mean fluorescence intensity of Foxp3 was highest in the SCIT + vitamin D group at 12 months [149]. Further studies are required to clarify the potential efficacy of vitamin D as an adjunct to immunotherapy.

Expert commentary

Allergy vaccines have been studied for more than a century as immune-modulating therapy for AR, asthma and insect venom hypersensitivity. The subcutaneous route has been extensively investigated and proven effective in reducing symptoms with evidence for long-term immune tolerance. Due to the use of whole allergen extracts in routine clinical practice via SCIT or SLIT, current AIT is associated with a risk of systemic IgE-related adverse events including anaphylaxis. The sublingual route is safer but adherence to this therapy is poor and further optimization is needed to improve its clinical efficacy. Several research studies indicate that patients with food allergy can achieve clinical desensitization with OIT but sustained clinical and immunological tolerance after treatment discontinuation have not been consistently achieved, preventing current recommendations for clinical practice. Alternative routes of administration providing improved allergen exposure and triggering prompt immune changes have been explored with the intralymphatic route showing promising results to treat pollen, cat and bee venom allergy. Nevertheless, the few small studies to date suggest that larger RCT are indicated to define optimal regimens. The epicutaneous route using peanut and grass pollen patches has shown encouraging results in the treatment of food allergy and AR, respectively, but larger trials are ongoing. The use of omalizumab as an adjunct therapy may be advantageous but requires further evaluation. Investigation of modified allergen extracts such as T-cell epitope-based peptides and recombinant allergen derivatives suggests safer profiles and clinical efficacy. Adjuvants for immunotherapy may improve efficacy and enhance a beneficial immune response to allergen. Studies using the TLR-4 agonist MPL, in the Pollinex Quattro allergy vaccine demonstrate clinical efficacy, sustained tolerance and the prevention of new sensitizations and development of asthma. The exploration of TLR agonists also as monotherapy to induce immune tolerance without the risk of allergen-related adverse effects has achieved good clinical response and a safer profile. A TLR-8 agonist and the novel TLR-9 agonist packaged into virus-like particles are strong candidates for effective and safe immunotherapy with shorter courses of treatment. Modified allergens including T-cell epitope-based peptides and recombinant allergen derivatives are probably the most promising of the current developments in refined vaccines and the results of current Phase III studies are awaited.

Five-year view

New directions for allergy vaccines should progress with further development of T-cell epitope peptide vaccines, hypoallergenic recombinant vaccines and adjuvants leading to safer and more effective immunotherapy. With increased knowledge of the immune mechanisms underlying the newer immunotherapy approaches, stronger immune responses will be achieved with the focus on modulation of Treg and Breg through the immune effects of IL-10 and TGF-β. The importance of specific T-cell anergy induction and specific Th2 cell deletion should be clearer including whether enhancement of IgG_4 antibody response is playing a significant role in the newer classes of therapy, particularly SPIRE therapy.

Financial & competing interest's disclosure

R O'Hehir and J Rolland are inventors of peanut SPIRE therapy. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Key issues

- Allergic diseases are a major health and economic burden worldwide and current therapies are limited in application and efficacy.
- Current allergen immunotherapy (AIT) results in clinical improvement in patients meeting selection criteria and modifies the natural course of allergic diseases.
- AIT with whole extracts is associated with IgE-related side effects including large local reactions and systemic adverse events including anaphylaxis, limiting its application in clinical practice.
- Adherence to subcutaneous and sublingual immunotherapy is poor and better strategies to improve regimens, absorption, safety and efficacy are needed.
- Long-term tolerance is an important goal of allergy vaccines which is variably achieved with current regimens and extracts.
- Optimization of new allergy vaccines, in particular synthetic peptide immuno-regulatory epitopes, and delivery routes, in particular transdermal, should improve efficacy, safety and long-term immune tolerance.

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