

New Directions in Immunotherapy

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Abstract Allergen immunotherapy (AIT) is effective in reducing the clinical symptoms associated with allergic rhinitis, asthma and venom-induced anaphylaxis. Subcutaneous (SCIT) and sublingual immunotherapy (SLIT) with unmodified allergen extracts are the most widely prescribed AIT regimens. The efficacy of these 2 routes appears comparable, but the safety profile with SLIT is more favorable allowing for home administration and requiring less patient time. However, both require that the treatment is taken regularly over several years, e.g., monthly in a supervised medical setting with SCIT and daily at home with SLIT. Despite the difference in treatment settings, poor adherence has been reported with both routes. Emerging evidence suggests that AIT may be effective in other allergic conditions such as atopic dermatitis, venom sting-induced large local reactions, and food allergy. Research with oral immunotherapy (OIT) for food allergies suggest that many patients can be desensitized during treatment, but questions remain about whether this can produce long term

tolerance. Further studies are needed to identify appropriate patients and treatment regimens with these conditions. Efforts to develop safer and more effective AIT for inhalant allergies have led to investigations with modified allergens and alternate routes. Intralymphatic (ILIT) has been shown to produce long-lasting clinical benefits after three injections comparable to a 3-year course of SCIT. Epicutaneous (EPIT) has demonstrated promising results for food and inhalant allergies. Vaccine modifications, such as T cell epitopes or the use of viral-like particles as an adjuvant, have been shown to provide sustained clinical benefits after a relatively short course of treatment compared to the currently available AIT treatments, SLIT and SCIT. These newer approaches may increase the utilization and adherence to AIT because the multi-year treatment requirement of currently available AIT is a likely deterrent for initiating and adhering to treatment.

Keywords Allergy immunotherapy · Immunological adjuvants · T cell peptide · Intralymphatic immunotherapy · Epicutaneous immunotherapy · Recombinant allergens · Sublingual immunotherapy · Oral immunotherapy · Asthma · Allergic rhinitis · Food allergy · Hymenoptera hypersensitivity

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List of Abbreviations

AD	Atopic dermatitis
AE	Adverse reaction
AIT	Allergy immunotherapy
DBPC	Double-blind, placebo-controlled
EPIT	Epicutaneous immunotherapy
ILIT	Intralymphatic immunotherapy
LLR	Large local reaction
LPSR	Late-phase skin response
OIT	Oral immunotherapy

SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
SPT	Skin prick test
SR	Systemic reaction
TRSS	Total Rhinoconjunctivitis Symptom Score
VIT	Venom immunotherapy
VLP	Virus-like particles

Introduction

The Impact of Allergic Disease and Allergy Immunotherapy

Allergic respiratory conditions represent some of the most common and costliest conditions in the world. It is estimated that one in five persons (~50 million) in the United States (US) has some form of allergic condition. In the past three decades, the prevalence of allergic respiratory conditions has been increasing. In the US, asthma prevalence was reported at its highest level in 2010 at 8.4 % (25.7 million persons) after increasing from 7.3 % in 2001 [1]. In a US study that examined the incremental direct medical costs and productivity losses due to asthma morbidity and mortality, the estimated total direct and indirect costs to society was \$56 billion in 2007 [2]. It has been estimated that up to 30 % of adults and 40 % of children have allergic rhinitis [3]. Direct medical expenses for allergic rhinitis were estimated at \$11.2 billion in 2005 [4]. Approximately one-third of direct costs are due to outpatient care and prescription medications account for nearly the entire remainder (59 %). Indirect costs, which include lost productivity and over-the-counter medications, have been estimated at a little over 50 % of the direct costs [5]. In the US, indirect costs will likely increase as more prescription medications become over-the-counter.

Allergy treatment includes avoidance measures, pharmacotherapy and allergy immunotherapy (AIT). Allergen avoidance is the most ideal approach but rarely achievable. Pharmacotherapy is the most widely prescribed allergy treatment, and it can be very effective in controlling symptoms during treatment. However, pharmacotherapy benefits are not sustained after treatment is discontinued. In contrast, AIT can induce symptomatic relief during treatment, as well as long-term clinical remission after discontinuation [6, 7]. At present, AIT is indicated for the treatment of allergic rhinitis, asthma and hymenoptera-induced anaphylaxis. The two most commonly prescribed routes for AIT are subcutaneous (SCIT) and sublingual (SLIT). The route selected depends on several factors, but extract availability

or approval, patient preference and costs are likely the primary reasons.

In studies that have compared the costs of pharmacotherapy with both forms of AIT, substantial healthcare cost savings have demonstrated with AIT during treatment [8, 9]. This effect is even greater when one considers the persistent clinical benefits of SIT after discontinuation of treatment, an effect not seen with pharmacotherapy [10].

As with improved symptomatology, the cost-savings benefits associated with AIT appear to be sustained, with one 6-year prospective study demonstrating 80 % lower healthcare costs in the patients who received SCIT, 3 years after discontinuation compared with pharmacotherapy alone [11].

In addition to the clinical and cost-benefits during and after treatment cessation, AIT has been shown to prevent the development of asthma and new allergen sensitivities [12, 13].

The mechanism(s) responsible for AIT's clinical efficacy are still being elucidated, but the immunological changes observed with effective AIT appear to persist along with the clinical improvement [14]. Although, AIT offers significant benefits over pharmacotherapy, in terms of persistent and preventive effects, only an estimated 5 % of the allergic population in the US and Europe subscribe to it [15]. Inconvenience due to the requirement that SCIT should be administered in a supervised medical facility, with appropriate personal and equipment to treat anaphylaxis, is thought to be the primary reason for its low utilization. SLIT's more favorable safety profiles allows for home administration, which reduces inconvenience. However, the SLIT effective dose may be considerably higher than SCIT, which may increase treatment costs—another treatment deterrent. SLIT and SCIT are similar in that both require adherence to a multi-year treatment course. Adherence with both routes has been documented to be very poor in 'real life' surveys; less than 20 % adherence in the third year of treatment [16, 17, 18, 19, 20]. Efforts to improve the efficacy, safety and convenience of AIT, which have included alternative routes such as intralymphatic and epicutaneous or vaccine modifications (e.g., peptides, recombinants and adjuvants), will be discussed in this paper. The paper will include an evaluation of the status of SLIT in the US, focusing on the clinical trials seeking to establish a Federal Drug Administration (FDA)-approved SLIT formulation. Emerging evidence for AIT in conditions other than respiratory allergy, e.g., atopic dermatitis and food allergy will also be presented.

Allergy Immunotherapy: Routes and Immunological Mechanisms

AIT induces important immune modulatory effects, including induction of Treg, Th1 and IgG. The desired effects are

initiated after allergen presentation primarily by dendritic cells (DCs). In contrast, the undesirable allergic side effects associated with AIT are caused either by local mast cells or by basophils after unintentional vascular distribution of the allergen. Therefore, the ideal route for administration of AIT should be characterized by a high density of DCs but a low density of mast cells and blood vessels. Classical vaccinations are typically administered by the following routes: a) intramuscularly, b) subcutaneously, c) orally, d) intradermally, or e) to the epidermis by scarification.

- a) **Intramuscular:** with regards to allergen administration, intramuscular injection has not been attempted. The high density of blood vessels would make systemic allergic side effects likely.
- b) **Subcutaneous:** subcutaneous tissue is characterized by a low density of blood vessels and mast cells. However, as the density of DCs is also low, SCIT is also characterized by low immunologic efficacy.
- c) **Oral/sublingual:** the oral or sublingual route is promising for allergen administration. Mucosal epithelium has no vasculature and yet contains DCs, so that the latter could be pulsed without risk for systemic allergic side effects. The problem of this route, however, is that the epithelial lining is poorly permeable for proteins. Therefore, SLIT requires numerous high-dose allergen administrations over years.
- d) **Intradermal:** the dermis contains a high density of DCs, but also mast cells and blood vessels. When using allergen peptides, which cannot be recognized by IgE, this route holds great promise. The high density of DCs may also allow lowering the allergen doses. A recent clinical trial observed induction of allergen tolerance, assessed as suppressed allergen-induced cutaneous late response, after low-dose intradermal allergen administrations [21].
- e) **Epicutaneous/transcutaneous:** the epidermis forms a barrier with an outer layer of cornified keratinocytes, the stratum corneum, excluding entry of large molecules [22–24]. It also contains antigen-presenting Langerhans cells (LCs). The keratinocytes play a role in adaptive immune responses [25, 26]. Slight stress to the epithelium, such as abrasion, triggers keratinocytes to secrete IL-7-like cytokine thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, instructing Treg- and Th2-type responses [27–31]. Stronger epithelial damage triggers additional expression of IL-1 α , IL-6, and TNF- α , promoting Th1-type responses [26].

At present, SLIT and SCIT are the only two routes for AIT with registered or approved products that are prescribed in routine clinical practice. However, clinical trials investigating all these above other routes, with the exception of intramuscular, are in progress in various locations. In

addition to reviewing these alternative routes, discussion will include intralymphatic immunotherapy which entails the direct injection of antigen into a lymph node, where antigen presentation to T and B cells takes place.

SLIT

Status of SLIT in the US

The efficacy of SCIT efficacy was established over a century ago in a *Lancet* article that described successful treatment of grass pollen-induced hay fever patients with grass pollen “inoculations” [32]. Investigations with alternative AIT routes and formulations began not long these initial reports, with the goal of improving AIT safety and convenience.

Although the first controlled clinical trials of SLIT were conducted nearly 75 years after this publication [33], SLIT is currently prescribed at least as frequently as SCIT and in some countries, it represents 80 % or more of new SIT prescriptions.

In the US, where SCIT is the only route with a Federal Drug Administration (FDA)-approved formulation, only a small percentage of allergists prescribe SLIT, although surveys of US practicing allergists indicate the percentage of SLIT prescribers has significantly increased from 5.9 % in 2007 to 11.3 % in 2011 ($p < 0.007$) [34, 35]. Lack of an FDA-approved SLIT formulation was cited as the most common reason for not prescribing SLIT in both surveys, followed by “effective dose not known”. The first US SLIT clinical trial was an open-label, dose-escalation study investigating the safety and tolerability of 4 US-licensed standardized glycinized allergenic extracts, containing dust mite, timothy grass pollen, cat hair, and short ragweed (Greer Laboratories, Lenoir, North Carolina) [36]. The study involved a single session with seven incremental dose escalations followed by 8 weeks of daily administration of the maximal tolerated dose (MTD), which ranged from 50 to 2,090 BAU for cat hair and dust mite extract, 31 to 91 Amb a 1 mcg for short ragweed pollen extract, and 50 to 21,090 BAU for timothy grass pollen extract. This study was followed by a DBPC study that compared the safety and efficacy of two doses of short ragweed pollen extract (4.8 and 48 mcg of Amb a 1) versus placebo using the same 1-day, 7-dose escalation protocol. Both active treatment groups achieved a 15 % reduction in total rhinoconjunctivitis symptom scores compared with placebo, but the difference was not statistically significant [37]. However, an analysis of covariance correcting for preseasonal symptoms, found a significant improvement in both symptom and medication scores in the higher dose group compared with placebo. A subsequent study, utilizing the same extract, protocol and a MTD up to 42 mcg Amb a 1, reported a

43 % reduction in combined symptom and medication scores in the SLIT group compared to placebo ($p=0.0032$) [38]. DBPC dose-response studies utilizing a short ragweed lyophilized tablet (Schering-Plough, a division of Merck, Kenilworth, NJ, USA) have shown significant reductions in combined symptom–medication scores with the 12 mcg Amb A 1 dose, demonstrating the most favorable efficacy–safety profile [39, 40].

Three double-blind, placebo-controlled (DBPC) multicenter trials conducted in the US have studied and demonstrated the efficacy of two different grass pollen tablet products (GRAZAX, ~15 mcg Phl p 5: Schering-Plough; and OROLAIR: ~25 mcg Phl p 5 Stallergenes, Anthony, France) in the pediatric [41] and adult [42, 43] population with reductions in combined symptom–medication scores of 20 [43] to 28 % [42] compared with placebo. The safety–efficacy found in these US studies was similar to the multiple European studies, where both products are currently registered: GRAZAX since 2006 and OROLAIR since 2008 (see Table 1 for summary of US clinical trials).

In addition to these pharmaceutical company-funded studies, there have been investigator-initiated studies that have explored several unmet needs. One DBPC single-site study compared the efficacy of timothy grass pollen glycerinated extract alone with the *same* dose of timothy extract mixed with 9 additional allergens [44]. A significant improvement in multiple relevant outcomes was found in the *timothy alone* group versus only one outcome in the multi-allergen group. This study suggested that the clinical efficacy of SLIT may be reduced by the addition of multiple allergens, a common practice of US SCIT prescribers. The authors speculated that limitations in the sublingual absorptive capacity may be the reason for the reduced efficacy of multiallergen SLIT, but concluded that further studies were needed to confirm their observations and to elucidate the mechanism(s) if confirmed.

More recently, a DBPC study comparing the efficacy of dual-allergen SLIT with dust mite and grass pollen glycerinated extract in 30 subjects found significant reductions in symptoms scores, medication use and several immunological markers in dual SLIT as compared when compared with placebo [45].

Other studies utilizing US licensed glycerinated extracts for SLIT have demonstrated the efficacy of 4,200 AU of *D. farinae* (~70 mcg of Der f 1) administered daily for 12–18 months in terms of bronchial allergen challenge and *D. farinae*-specific IgG4 [46], but another study found no consistent change in biomarkers with cockroach SLIT with a dose of 5.2 Bla g 2 administered daily [47].

Collectively, SLIT efficacy and safety have been well established in several US clinical trials utilizing single allergen tablets or glycerinated extracts. Some questions remain in terms of the efficacy of some allergens, such as

cockroach and the use of multiple allergen extract solutions, the practice commonly used for SCIT.

SLIT Novel Indications

Atopic Dermatitis

A number of observational studies have suggested that AIT may be a promising treatment for atopic dermatitis (AD) [48]. A possible link between some forms of AD and IgE-mediated allergy has been suggested from controlled-interventional and observational studies, primarily with dust mites and foods. A systematic review on the role of AIT in AD identified 23 studies that had examined the role of AIT in AD. The review found considerable heterogeneity in terms of allergen, treatment schedules, duration, outcomes assessed and avoidance strategies or standard medications [49]. In addition, most of the studies were under-powered and not placebo-controlled. However, despite these limitations, an overall beneficial effect of AIT in AD was reported. Severe disease relapses following the treatment were estimated in 15–20 % of the cases. Trials conducted since this review, also limited by methodological shortcomings and small patient populations, have only provided modest support for the role of AIT in AD [50••]. In one study of 55 adult patients with moderate to severe AD treated with 12 weeks of co-seasonal birch-pollen SCIT, there was a significant improvement in quality of life (49 %, $p<0.001$) and SCORAD scores (34 %, $p<0.001$) during the course of treatment [51]. Eight patients (14.5 %) developed systemic reactions, but there were no premature study withdrawals.

There is conflicting data in terms of AD disease severity and benefit from AIT. A randomized DBPC study, investigating the effects of 18 months of dust mite SCIT as add-on treatment in 168 adults with AD, found no statistical difference between the SCIT and placebo groups [52]. However, a post hoc subgroup analysis found a statistically significant reduction of the median total SCORAD in the subgroup of patients with severe AD (SCORAD>50) compared with placebo. In contrast to this study, a DBPC study of 65 AD children treated with dust mite SLIT found a significant improvement only in the children with mild-moderate disease and this was after 9 months of treatment [53].

There is evidence that AIT may prevent the progression of the allergic disease in individuals with established atopic disease, i.e. secondary prevention. It has been speculated that it may also play a role in primary prevention if initiated early in the allergic disease. A randomized multi-national trial conducted by the Immune Tolerance Network is investigating the potential role of SLIT in the primary prevention of aeroallergen sensitization and asthma in AD children at risk for developing asthma and atopy [54]. High-risk AD

Table 1 Summary of US industry and investigator-initiated placebo-controlled clinical trials conducted since 2006

Allergen	Industry or Investigator ^a	Patient population	Regimen	Dose/formulation	Primary outcome P ^b
Grass	Schering-Plough (ALK-Abello) [41, 43]	Adults (439) and pediatric (345) (2 trials) ARC ± asthma	4 months pre- and co-seasonal	15 mcg Phl p 5 tablet	Adults: 20 % CS Pediatrics: 25 % CS
	Stallergenes [42]	473 adults ARC ± asthma	4 months pre- and co-seasonal	25 mcg 5-grass pollen tablet	28 % CS
	Nelson [43]	54 Adults ARC ± asthma	10 months: Sept–July	Timothy alone at 19 mcg Phl p5 or same dose with 9 allergens glycerinated extract solution	Timothy alone: significant improvement in multiple outcome vs. one in multiallergen
Ragweed	Schering-Plough (ALK-Abello) [39]	565 adults: ARC	4 months before for total of 52 weeks,	6 and 12 mcg Amb a 1 tablet	CS 12 mcg: 26 % 6 mcg: 21 %
	Greer [37]	115 adults: ARC	8–10 weeks pre- and co-seasonal	4.8 and 48 mcg of Amb a 1 glycerinated extract solution	15 % symptoms in both groups ($p>0.10$)
	Greer [38]	429 adults	At least 8 pre- and co-seasonal	Maximum tolerated dose up to 42 mcg glycerinated extract solution	43 % CS
Dust mite	Bush [46]	31 adults ARC ± asthma	12–18 months, endpoints assessed Q 6 months	1 and 70 mcg Der f 1 glycerinated extract solution	No difference in symptom –medication scores, significant improvement in allergen-specific BHR and specific IgG
	Nadeau [45]	30 adults and pediatrics	4 months before grass season for 12 months	15 mcg Phl p 1 20 mcg Der p 1 and 2 glycerinated extract solution	Decreased symptom, medication, titrated SPT and nasal challenge and favorable immunologic parameters

ARC Allergic rhinoconjunctivitis, CS combined symptom–medication score, SR systemic reaction, BHR Bronchial hyper-reactivity, SPT skin prick test

^a Company listed for industry sponsored and investigator if investigator-initiated trial^b Percentage improvement over placebo

children, aged 18–30 months, with atopic dermatitis, food allergen sensitization, family history of AD, asthma or allergic rhinitis, and no aeroallergen sensitization, were randomized to receive a mixture of house dust mite, cat, and timothy grass allergen SLIT or placebo for 1 year. They were then assessed for the development of asthma or atopy in 6 visits over the following 3 years. The results of this preventive study are pending.

The conflicting findings in the studies evaluating the efficacy of AIT in AD are likely explained by the fact that atopic eczema is a multifactorial disease, which includes complex genetic modifications, responsible for skin barrier impairment, and combinations of environmental and endogenous factors that can direct its course. For these reasons, the value of AIT in AD still remains unclear and more controlled studies are needed. Future studies should focus on particular subgroups of patients in order to identify those who might best benefit from the treatment with regard to the disease severity and the sensitization profile. In addition, long-term studies are required to determine if AIT has a disease-modifying potential of SIT in the context of the ‘allergy march’ from AD to allergic respiratory conditions.

Food Allergy

At present, the only treatment for IgE-mediated food allergy is dietary avoidance, but there is emerging evidence suggesting that AIT may induce tolerance to the treated food. The most common food allergens are milk, egg, peanut, hazelnut, wheat, peach, soy, and fish. The frequency of specific food sensitivity will vary geographically, depending on several factors, such as dietary customs, climate, and food processing techniques. Some allergens are ‘outgrown’ in the majority of individuals (e.g., egg, milk), but some are likely to be lifelong, with a significant percentage experiencing accidental exposures which can lead to severe, and sometimes fatal, reactions.

More than 10 years ago, preliminary studies investigating AIT in peanut allergy showed uncertain results for benefits and unacceptable high risk for systemic reactions with SCIT, prompting research to explore the potential of different administration routes [55, 56]. Oral immunotherapy (OIT) seems to be the most promising approach based on results from small uncontrolled and controlled studies (Table 2). Clinical investigation in this field began in 1984 with case reports of successful desensitization with milk, egg and other food allergens, associated with the immunological changes seen with effective aeroallergen SCIT [57–59].

Early, small, open studies with varying designs showed egg OIT to be relatively well tolerated, but did not confirm sustained tolerance. In one study, 7 egg-allergic subjects with no history of anaphylaxis underwent a 24-month egg OIT protocol followed by an oral food challenge (OFC)

after treatment cessation [60]. At the 24-month OFC, all tolerated more egg protein than before treatment, but only 2 subjects passed the OFC on the 3-month post-treatment challenge. In another open trial, clinical tolerance and immunologic suppression were achieved with individualized dosing regimens based on the patient’s serum egg white-specific IgE levels [61]. A safe desensitization was obtained with rapid up-dosing protocols in patients with history of severe [62] and mild [63] reactions.

In 2012, three open randomized controlled studies were carried out in egg allergic subjects. In the first, 10 children with moderate to severe egg allergy were successfully desensitized in a protocol that involved gradual daily dose increases over a 6-month period [64]. Another study demonstrated egg OIT efficacy in 40 egg-allergic children who were treated for an average duration of 10 weeks [65]. However, adverse reactions were common, occurring in 52 % of patients, classified as mild in 8 patients (38 %), but more severe in the others. Three patients were withdrawn from treatment because of persistent gastrointestinal symptoms. In children with “severe egg allergy”, 6 months of regular intake of egg resulted in partial protection as assessed by an open OFC, compared with no change in tolerance in the randomized control group [66]. These studies suggest that short courses with relatively low-maintenance doses may only provide transient desensitization, whereas true tolerance, if it does occur with OIT, may require longer treatment with higher doses. The largest and most definitive trial of egg OIT to date included 55 children (40 in the OIT group), who received 22 months of egg OIT or placebo [67•]. Seventy-five percent of the OIT group passed the OFC at 22 months and were considered desensitized. Eleven patients passed the subsequent OFC conducted 4–6 weeks after OIT discontinuation and were considered to have sustained unresponsiveness. The authors concluded “... that oral immunotherapy can desensitize a high proportion of children with egg allergy and induce sustained unresponsiveness in a clinically significant subset.”

Most children usually outgrow cow’s milk allergy (CMA) by the age of 3–5 years, but some will have persistent symptoms beyond childhood. Successful desensitization with cow’s milk OIT has been described in several case reports and open and placebo-controlled clinical trials [57, 68, 69]. These studies/reports used various protocols and demonstrated efficacy in subjects with severe disease but, as with egg OIT, adverse reactions were common [70–76].

In the first double-blind placebo-controlled (DBPC) study of OIT in CMA, there was a significant increase in the reaction threshold in children receiving OIT compared with placebo [74]. The median cumulative dose in the OIT group was 5,140 mg, whereas all of the placebo group reacted at 40 mg, which was the threshold dose in the baseline challenge in both groups ($p=.0003$). However, side effects occurred in 45 % in the active group compared with

Table 2 Sublingual immunotherapy novel indications

Year	Author	Food	Type	Age range (years)	Design	Total pts.	Completed treatment	Clinical outcome	Immunological outcome
1984	Patriarca [57]	Milk, egg, others	OIT	3–14	Open controlled, non-randomized	19	15/19	14/15 completed food challenge	–
2003	Patriarca [58]	Milk, egg, others	OIT	3–55	Open controlled, non-randomized	59	38/59	83.3 % completed the treatment	↓IgE, ↑IgG4
2004	Meglio [68]	Milk	OIT	5–10	Prospective case series	21	15/21	15/21 full tolerance; 3/21 partial tolerance	Unchanged IgE
2005	Enrique [86]	Hazelnut	SLIT	19–53	DBPC RCT	23	12/12	↑threshold to DBPC OFC, 5/11 completed OFC	Unchanged IgE, ↑IgG4, ↑IL10
2006	De Boissieu [193]	Milk	SLIT	6–17	Prospective case series	8	7/8	↑threshold to OFC	Unchanged IgE
2007	Buchanan [60]	Egg	OIT	1–7	Prospective case series	7	7/7	4/7 completed food challenge	↑IgG
2007	Staden [69]	Milk, egg	OIT	1–13	Open RCT	25	16/25	48 % tolerant, 16 % partly tolerant	↓IgE
2007	Morrisett [75]	Milk, egg	OIT	1.5–6.5	Open RCT	150	141/150	58/76 full tolerance ↓skin reactivity	↓IgE
2008	Longo [71]	Milk	OIT	5–17	Open RCT	30	27/30	11/30 full tolerance; 16/30 partial tolerance	↓IgE
2008	Skripak [74]	Milk	OIT	6–17	DBPC RCT	13	12/13	4/12 completed food challenge; ↑threshold to OFC	Unchanged IgE, ↑IgG4
2008	Staden [70]	Milk	OIT	3–14	Prospective case series	9	6/9	6/9 full tolerance; 3/9 partial tolerance	–
2008	Zapatero [76]	Milk	OIT	4–8	Prospective case series	18	16/18	16/18 full tolerance; 1/18 partial tolerance	Unchanged IgE
2009	Clark [78]	Peanut	OIT	9–13	Prospective case series	4	4/4	4/4 completed food challenge, ↑threshold to OFC	–
2009	Jones [79]	Peanut	OIT	1–16	Prospective case series	39	29/39	27/29 completed food challenge	↓IgE, ↑IgG4 ↑IL-10, IL-5, IFN-γ, and TNF-α ↑IgE, ↑IgG4
2009	Fernández-Rivas [87]	Peach	SLIT	Adults	DBPC RCT	56	33/37	↑threshold to DBPC OFC, ↓skin reactivity	Unchanged IgE, ↑IgG4, ↓IL4-IL5-IL2
2010	Blumchen [80]	Peanut	OIT	3–14	Prospective case series	23	14/23	3/14 completed food challenge	↓IgE, ↑IgG4
2010	Itoh [62]	Egg	OIT	7–12	Prospective case series	6	6/6	3/6 completed food challenge	Unchanged IgE, ↑IgG4
2010	Pajno [73]	Milk	OIT	4–10	Single-blind RCT	15	13/15	10/13 full tolerance; 1/15 partial tolerance	Unchanged IgE, ↑IgG4
2010	Vickery [61]	Egg	OIT	3–13	Prospective case series	8	6/8	6/6 completed DBPC OFC, ↓skin reactivity	↓IgE, ↑IgG4, ↑IL10, TGF-β
2011	Anagnostou [81]	Peanut	OIT	Median 11	Prospective case series	22	19/22	14/22 completed OFC	–
2011	Varshney [82]	Peanut	OIT	1–16	DBPC RCT	28	16/19	16/16 completed DBPC OFC, ↓skin reactivity	Unchanged IgE, ↓IL5, IL13, ↑IgG4, Suppressed CD63 upregulation
2011	Martorell [72]	Milk	OIT	24–36 months	Open RCT	60	60/60	90 % full tolerance, ↓skin reactivity	↓IgE
2011	García Rodríguez [63]	Egg	OIT	5–17	Prospective case series	23	20/23	20/23 tolerance, ↓skin reactivity	↓IgE, ↑CD4+FoxP3+

Table 2 (continued)

Year	Author	Food	Type	Age range (years)	Design	Total pts.	Completed treatment	Clinical outcome	Immunological outcome
2011	Kim [88]	Peanut	SLIT	1–11	DBPC RCT	18	11/11	↑threshold to DBPC OFC, ↓skin reactivity	↓IgE, ↑IgG4 ↑Salivary specific IgA, ↓CD63, no change IL13, IL10, IFN-γ, T-reg cells
2012	Meglio [64]	Egg	OIT	4–14	Open RCT	20	8/10	2/20 completed DBPC OFC, no change skin reactivity	↓ IgE for ovomucoid, unchanged for ovalbumin ↑IgG4 for ovalbumin, unchanged for ovomucoid, ↑IL5
2012	Fuentes-Aparicio [65]	Egg	OIT	5–15	Open RCT	72	17/72	37/40 achieved tolerance, ↓skin reactivity	Unchanged IgE, ↑IgG4
2012	Dello Iacono [66]	Egg	OIT	5–11	Open RCT	20	10/10	9/10 partial tolerance	–
2012	Burks [67•]	Egg	OIT	5–11	DBPC RCT	55	–	75 % tolerance, 11/40 sustained effect, ↓skin reactivity	↑IgG4
2012	Keet [85•]	Milk	SLIT/OIT	6–17	Open RCT	30	30/30	1/10 SLIT vs. 14/20 OIT completed OFC, ↓skin reactivity in all	↓IgE in OIT but not in SLIT, ↑IgG4 in all, ↓spontaneous histamine release in OIT

11 % of the placebo group. A recent meta-analysis of randomized trials that included 218 patients with CMA concluded that, compared to elimination diet alone, the “...potentially large benefit of OIT may be counterbalanced by frequent and sometimes serious adverse effects.” [77••]. In general, the overall low quality of evidence and numerous unresolved questions (e.g., appropriate patients and protocol, predictors of response and adverse reactions, persistence of the tolerant state, etc.) leave important uncertainties about cow’s milk OIT, which would need to be addressed before clear recommendations can be made regarding this treatment.

Peanut allergy is relatively common and, in most cases, does not resolve spontaneously. It is frequently implicated in severe and fatal food allergic reactions. Three open prospective investigations of peanut OIT demonstrated an increased tolerance threshold accompanied by an increase in specific IgG4 and decrease in specific IgE levels and Th2 cytokine production [78–80]. Side effects were common, but mild. Another open study demonstrated that a gradual up-dosing schedule with a higher maintenance dose produced a better outcome compared with rush protocols [81]. The efficacy of peanut OIT was confirmed in a DBPC, multicenter study, in which 16 out of 19 children ingested the maximum cumulative dose of 5,000 mg (approximately 20 peanuts) [82]. The long-term immune tolerance, however, is still under investigation. A Cochrane’s systematic review concluded that “in view of the risk of adverse events and the lack of evidence of long-term benefits, allergen-specific peanut OIT cannot currently be recommended as a treatment for the management of patients with IgE-mediated peanut allergy. Larger RCTs are needed to investigate the acceptability, long-term effectiveness and cost-effectiveness of safer treatment regimens, particularly in relation to the induction of clinical and immunological tolerance.” [83••]. This recommendation is consistent with other investigators’ views [84].

Compared with OIT, SLIT may be less effective for CMA food allergy, but may also be accompanied by less systemic side effects [85•]. However, there have been three DBPC trials that suggest SLIT may be effective for other food allergen sensitivities. A significant increase in hazelnut tolerance was demonstrated in 12 adults who received hazelnut SLIT compared with the placebo group [86]. Treatment was associated with a SR rate comparable to the SCIT rate 0.2 % of administered doses. All SR occurred during the build-up phase, which was conducted in a hospital setting. Similar results were found in peach-allergic patients, treated with a Pru p 3 quantified peach extract [87]. After 6 months of treatment, the SLIT group tolerated significantly more peach during OFC (3- to 9-fold) along with a significant decrease in skin prick test (SPT) reactivity, whereas there were no significant changes in the placebo group. Treatment was associated with numerous adverse events, primarily mild and self-resolving reactions, but 16

were classified as systemic. In a DBPC study utilizing 6 months of a dose escalation peanut SLIT protocol followed by 6 months of maintenance dosing, the SLIT group was able to tolerate 20 times more peanut protein than the placebo group during the OFC [88]. In addition to clinical desensitization, peanut SLIT was associated immunologic changes suggesting a significant change in the allergic response [88, 89]. Dosing side effects were "...primarily oropharyngeal and uncommonly required treatment." The clinical outcomes in all three studies were accompanied by the increase of IgG4 levels, but inconsistent variations in IgE levels, IL10 and other markers of immune-regulation. Lastly, SLIT with inhalant allergens may be effective in reducing oral allergic symptoms induced by the cross-reactive foods [90–92].

In summary, OIT and SLIT are promising approaches to treat food allergies. OIT appears to be more effective, but is also associated with more side effects and potentially serious systemic reactions. Further studies with both routes are needed to establish their safety, duration of short- and long-term protection, as well the optimal dosing, schedule and duration before either can be recommended for routine treatment of the food allergic patient.

Hymenoptera Venom Allergy

Venom immunotherapy (VIT) is the standard treatment for hymenoptera-induced anaphylaxis, resulting in an almost complete protection against sting reactions in nearly all treated patients.

Although there have been no reported fatalities specifically attributed to VIT, it is associated with a risk of severe systemic severe reactions, particularly with honeybee venom. Alternative routes of administration, such as sublingual and intralymphatic, have also been proposed, but to date there are only proof-of-concept studies, which do not provide enough evidence to support use outside an investigational setting.

One open study of 21 wasp-allergic subjects, treated with a cumulative weekly sublingual maintenance dose of 100 mcg of venom extract (administered over 3 doses), found no significant immunological changes during the treatment, although 3 of the 4 patients tolerated a wasp field-sting without any adverse SR [93]. A DBPC study exploring the effect of honeybee venom SLIT on large local reactions (LLR) compared sting challenge-induced LLR before and after 6 months of treatment [94]. Thirty subjects with a history of LLR confirmed by sting challenge were randomized to receive honeybee venom (maintenance dose 525 mcg/ month) or placebo for 6 months. A significant reduction of the wheal size was observed in the active group only, and, in 57 % of patients, the reaction was more than halved. No significant treatment-related adverse events were

reported. These encouraging findings remain in the context of proof-of-concept studies, and considerably larger clinical trials, which include dose-ranging, are needed to determine if SLIT is a suitable treatment for hymenoptera venom allergy and if so, the appropriate patient and indications for sublingual VIT.

Novel Immunotherapy Routes: Epicutaneous and Lymphatic Epicutaneous

Topical application of an antigen does not typically induce an immune response, because permeability of vaccines through the stratum corneum is low. The stratum corneum can be disrupted by scratching, called scarification [95], tape stripping and other abrasive methods [96, 97]. APCs of the epidermis and dermis can be targeted by microneedle arrays [22, 98–104] and physically activating keratinocytes [26, 105]. Alternatively, penetration of antigens through the epidermis can be enhanced by skin hydration [106], typically by application of a patch leading to sweat accumulation [107, 108]. Despite the ancient success of epicutaneous smallpox vaccination [109], this route of administration did not attract much attention until the end of the twentieth century, when effective transcutaneous vaccination against infectious diseases and cancer was demonstrated [95, 96, 110–115].

However, first records of administration of allergens via the skin date back to 1926 [116], not long after the risk of SCIT-associated anaphylaxis was recognized [117]. In a study of 29 hay fever patients, intradermal pollen extract administrations was found to be safe and effective, with all patients reporting symptom amelioration after only three doses [116].

In another report dating back to 1921, an asthmatic patient experienced complete symptom relief after administration of horse dander on scarified skin, a method called *cutiréactions répétées* [118]. EPIT efficacy was confirmed in subsequent studies that administered the allergen extract onto a slightly rubbed epidermis [119], and applied allergen drops onto scarified skin: *méthode de quadrillage cutané* [120, 121]. The treatment was associated with high success rates of approximately 80 % [122–124].

The first randomized double-blind placebo-controlled study testing EPIT in grass pollen-allergic patients was conducted in 2009 [125]. Patches with allergen applied weekly to tape stripped skin produced a 70 % improvement of hay fever symptoms compared with 20 % in the placebo group. No severe systemic allergic reactions were observed, but local eczematous skin reactions were frequent. A dose-finding trial with 132 patients confirmed the results at the highest dose, and with only six patch applications [126•]. These results were confirmed in grass pollen-allergic children [127].

EPIT may be effective in the treatment of food allergies. A pilot trial using occlusive patches in children with cow milk allergy, demonstrated a greater tolerance to cow milk provocation after EPIT [107].

Intralymphatic

A great number of pre-clinical and clinical studies have demonstrated the potency of intralymphatic administration of peptides, proteins, DNA, RNA, bacteria, viruses or DCs, as comprehensively reviewed [128–132]. Studies in mice have demonstrated that ILIT with bee venom phospholipase-A2, ovalbumin, and allergen extracts from grass pollen, birch pollen and cat dander stimulate robust anti-allergic and protective B and T cell immune responses [133–137]. Compared with SCIT, ILIT dramatically enhanced efficiency of immunization, inducing allergen-specific IgG2a antibody responses 10 to 20 times higher with only 0.1 % of the allergen dose. Moreover, ILIT enhanced IL-2, IFN- γ , IL-4 and IL-10 secretion when compared to SCIT, suggesting that ILIT did not polarize the response but generated overall stronger responses. The reason appears to be simple: ILIT delivers approximately 100 times more allergen to lymph nodes than any other route, as demonstrated in biodistribution studies after ILIT, both in mice [135] and men [129, 131]. Since injection AIT adverse side effects are related to the allergen dose, ILIT would be expected to have a lower incidence of adverse effects.

In a Swiss trial, 165 patients with grass pollen-induced rhinoconjunctivitis were randomized to receive either 54 SCIT injections with pollen extract over 3 years (cumulative allergen dose 4,031,540 SQ-U) or three intralymphatic injections over 2 months (totally 3,000 SQ-U) [138]. Increased nasal tolerance was demonstrated in the ILIT group within 4 months of treatment. Tolerance was long lasting and comparable to SCIT, who received 3 years of treatment. ILIT ameliorated symptoms, enhanced compliance, reduced skin prick test reactivity, and decreased specific serum IgE, and was associated with fewer adverse events than SCIT. It was deemed less painful than a venous puncture.

In a Danish trial on ILIT in grass pollen-allergic patients, three and six low-dose intralymphatic injections were found to induce IgG4, but there was no reduction in hay fever symptoms [139]. In this trial, ILIT was performed weekly, not monthly as in the Swiss trial [138]. Experience from vaccine immunology recommends time intervals of at least 3 weeks to allow for development of successive waves of antigen-specific primary B cell responses and for affinity maturation of memory B cells [140]. The positive results of the Swiss trial, when injecting grass pollen extract every 4 weeks, have meanwhile been reproduced by a Swedish group in a double-blind, placebo-controlled fashion [141].

In a randomized, placebo-controlled and double-blinded trial, ILIT with MHC class II-targeting cat dander allergen (MAT-Fel d 1) 1 was compared with ILIT with placebo [142•]. Three monthly injections with MAT-Fel d 1 improved nasal allergen tolerance and stimulated significant regulatory T cell responses and IgG4 without any significant adverse events.

Modified Allergen Vaccine: Recombinants, Viral-Like Particles and B and T Cell Epitope Peptides

The advent of recombinant DNA technology has facilitated the molecular cloning and sequencing of most important allergens. Recombinant native allergens are being evaluated for use in both diagnosis and treatment of allergic disease. Reduced allergenicity has been achieved through modification of recombinant allergens, such as the insertion of point mutations to disrupt structure [143–152], multimerization [153], cleavage into large fragments [153, 154], and identification of T cell and B cell epitopes that may be used to modulate allergen-specific T and B cell responses [155, 156]. Many such approaches are being evaluated in clinical trials. This section will summarize recent clinical studies evaluating such approaches.

Immunotherapy with Recombinant Native Allergens

In a DBPC study evaluating the efficacy of a mixture of five recombinant timothy grass pollen allergens, there were significant improvements in combined symptom/medication scores and quality of life after 18 months in the AIT group as compared with placebo [157]. Allergen-specific IgG antibodies increased approximately 60-fold (IgG1) and 4,000-fold (IgG4), but no significant changes in allergen-specific IgE concentrations were observed. Hypoallergenic variants of grass pollen allergens are currently under development for future therapy.

A multicenter, randomized, DBPC trial compared the safety and efficacy of recombinant Bet v 1a, purified natural Bet v 1, and standard birch pollen extract in birch pollen-allergic individuals [158]. All regimens led to significant decreases in daily mean symptom/medication scores and the magnitude of skin prick tests. Bet v 1-specific IgG1, IgG2 and IgG4 increased in all groups. Comparable safety profiles were observed, although swelling at the site of injection was frequently recorded in patients treated with the recombinant allergen.

Immunotherapy with Modified Allergens

Genetically modified hypoallergens have been evaluated as potential candidates for AIT. A trimeric construct of Bet v 1 [159] and two recombinant fragments of the same molecule

[160] displayed reduced IgE reactivity. Furthermore, a nasal provocation study comparing recombinant Bet v 1 with the two Bet v 1 fragments demonstrated that, in contrast to the whole allergen, the fragments did not induce an increase in allergen-specific IgE or nasal symptom scores, and nor did they induce a decrease in nasal flow determined by anterior acoustic rhinometry [161]. Treatment was associated with the induction of IgG1, IgG2, IgG4 and IgA specific for Bet v 1, which were capable of blocking basophil activation in vitro. Serum from treated subjects inhibited CD23-dependent facilitated allergen binding (FAB), a readout of “blocking antibody” function [162]. In a related study, Bet v 1-specific IgG4 in nasal secretions was associated with reduced nasal sensitivity to allergen challenge [163]. Both allergen preparations reduced skin test reactivity [164–166] and nasal sensitivity during provocation challenge [165]. There was a trend for the trimer to be more effective than the fragments in both these parameters [165]. Increases in IgG antibodies specific for food allergens associated with birch oral allergy syndrome were also observed, likely due to cross-reactivity between allergens between the Bet v 1 and related plant food allergens [153, 167]. Treatment was associated with reductions in the frequency of IL-5- and IL-13-secreting cells (trend for reduced IL-4) and increased IL-12 [164]. Seasonal increases in specific IgE were significantly reduced [153]. No significant differences were observed in the primary outcome (symptom and medications scores) in any of the treated groups.

Allergen Immunotherapy with Virus-Like Particles (VLP)

CpG oligodeoxynucleotides (ODN) are unmethylated prokaryotic DNA sequences that stimulate the innate antimicrobial response through interaction with Toll-like receptor 9 (TLR9), an intracellular pattern recognition receptor (PRR). ODN have been employed as adjuvants in recent clinical trials of allergen immunotherapy. Virus-like particles (VLP) are self-assembling structures that do not contain viral nucleic acids and are non-infectious, but may be used as vehicles to deliver allergens and adjuvants to the immune system. CpG ODN-VLPs have been evaluated as an adjuvanted delivery system for house dust mite immunotherapy. In a phase 1 clinical trial of 24 healthy volunteers, using VLP from the bacteriophage Qbeta (QbG10) decorated with a Der p 1 peptide known to contain B cell epitopes, there was an increase in IgG and IgM antibodies directed at both the VLP and Der p 1 during the first month after the initial vaccination [168]. Antibody titers gradually decreased to baseline levels after 18 months. An open-label phase 1/2a trial, evaluating the safety and efficacy of 10-week course of QbG10 as an adjuvant for dust mite SCIT, reported reduced skin reactivity, conjunctival sensitivity and improved symptoms as assessed by a patient questionnaire

[169]. At the end of treatment, patients “...were nearly symptom-free and this amelioration lasted for at least 38 weeks post-treatment.” Clinical changes were associated with a progressive increase in specific IgG subclasses.

B Cell Epitope Immunotherapy

SCIT and SLIT are associated with the induction of allergen-specific IgG. Although there is no absolute correlation between the amount of allergen specific IgG induced and clinical efficacy [170], it is widely thought that these “blocking” antibodies contribute to efficacy. Vaccines based on non-allergenic B cell epitopes may induce protective IgG antibodies. One such approach has been to couple allergen peptides to “carrier” proteins in order to provide strong Th1-dependent T cell help for antibody production. A recombinant hybrid molecule consisting of a rhinovirus protein VP1 coupled to a Phl p 1-derived peptide and expressed in *E. coli* did not react with IgE from grass-allergic individuals and lacked allergenic activity when exposed to basophils from allergic patients [171]. Sera from mice and rabbits immunized with the recombinant hybrid induced protective IgG Abs that cross-reacted with group 1 allergens from different grass species and prevented Phl p1-induced basophil activation. Clinical studies with this novel class of vaccines are currently underway.

T Cell Epitope Immunotherapy

Targeting of allergen-specific T cells has been achieved through the use of synthetic peptides containing T cell epitopes. Murine models of transplantation, autoimmunity and allergy have previously demonstrated the ability to modulate antigen-specific T cell function by delivery of synthetic peptides through a variety of routes. Early attempts to translate T cell-directed peptide immunotherapy into clinical trials employed two 27 amino acid polypeptides (IPC-1/IPC-2 ; AllervaxCat[®]) from the major cat allergen Fel d 1 administered subcutaneously. Four clinical trials evaluating safety and efficacy generated mixed results, with three studies [172–174] identifying some modest clinical benefit and the fourth showing no benefit [175]. Treatment was associated with a high incidence of adverse events including some acute allergic reactions and more frequent delayed symptoms of rhinitis, asthma and pruritus. Delayed symptoms of asthma were later characterized as IgE-independent, late asthmatic reactions caused by activation of mucosal (airway) allergen-specific T cells in asthmatic subjects [176]. The magnitude of the reactions was reduced with successive doses of peptide suggesting the induction of immunological tolerance. As a result of poorer than expected efficacy and a high incidence of adverse events, clinical development of IPC-1/IPC-2 was halted.

Subsequently, unrelated T cell epitope mapping studies identified shorter peptide sequences from Fel d 1 [177]. Mixtures of 12 peptides formulated in saline without adjuvant were evaluated in a series of small clinical trials performed in cat-allergic asthmatic subjects [178–183]. A single intradermal injection of the peptide mixture (5 µg of each peptide) reduced late-phase skin reactions (LPSR) to challenge with whole allergen [180]. Subsequently, a DBPC, multi-dose (cumulative dose 90 µg of each peptide) trial of the same peptide mixture showed significant reductions in early- and late-phase skin response to intradermal challenge with allergen extract [181]. A small open-label study evaluating a lower cumulative dose of peptides (21.1 µg) showed a significant reduction in airway hyper-responsiveness (measured by PC₂₀) [179], but no change in PC₂₀ was observed in a placebo-controlled study [181]. Neither study was adequately powered to detect a significant change in this outcome. Mechanistic studies undertaken throughout these studies demonstrated reduced proliferative and pro-inflammatory Th1 and Th2 cytokine responses, together with increased IL-10 production, the induction of CD4⁺ T cells with regulatory functional activity, and evidence that tolerance induced to the treatment peptides could extend to other peptide sequences within the Fel d 1 molecule; a phenomenon referred to as intra-molecular tolerance or, linked epitope suppression [184].

More recently, a 7-peptide formulation (Cat-PAD; Toleromune Cat[®]), based on the 12-peptide mixture described above, was evaluated in a phase IIa safety and tolerability study [185]. A single injection (in 5 separate dose cohorts), administered either intradermally or subcutaneously to subjects with cat allergen-induced allergic rhinoconjunctivitis, was well tolerated. The adverse events profile was indistinguishable from placebo. Intradermal delivery resulted in approximately 40 % inhibition of the LPSR at a dose of 3 nmol, comparable to earlier findings with a mixture of 12 peptides [180]. The same peptide formulation was subsequently evaluated in a phase IIb study, in which subjects received 4 fixed-dose injections of 6 nmol or 8 injections of 3 nmol over a 3-month period. Total Rhinoconjunctivitis Symptom Score (TRSS) outcomes were recorded over 4 consecutive days of allergen exposure (3 h per day) in an Environmental Exposure Chamber at baseline, 18–22 weeks, and 50–54 weeks. In the high-dose cohort, the difference in TRSS between (baseline vs. 50–54 weeks) active and placebo treatment was highly significant ($p=0.01$) [186]. The treatment was safe and well tolerated with an adverse events profile similar to placebo. The magnitude of the clinical effect appeared to be at least as good, if not better, than all current pharmacological and immunotherapy approaches that have been evaluated under similar conditions, e.g., change of 3.9 TRSS units with peptide AIT compared with a change of approximately 2 units with SLIT

[187] and with 1.3 units with a single dose of fexofenadine [188].

Bee venom allergy has also been treated with experimental peptide formulations. Three immunodominant T cell epitopes of the bee venom allergen Api m 1 were administered to five bee venom-allergic subjects with documented systemic allergic reactions [189]. Subjects received incremental doses (cumulative dose 397.1 µg starting at 100 ng) at weekly intervals [190]. All subjects were able to tolerate challenge with 10 µg of Api m 1 after treatment injection, and a live bee sting was tolerated by three of five subjects.

In a second study, four immunodominant peptides (three of which were similar to the previous study) of Api m 1 were identified using peptide-MHC binding assays [191]. The peptide mixture (incremental doses starting at 0.1 µg; cumulative dose 431.1 µg) was evaluated in a controlled open-label, single-blind study of subjects with mild bee venom allergy [192]. Treatment was well tolerated with no treatment-related adverse events observed. Consistent with studies employing Fel d 1 peptides, LPSRs to allergen were significantly reduced, and proliferative and cytokine (Th1 and Th2) responses were reduced, whereas IL-10 secretion was significantly upregulated. The small numbers of subjects and the unpredictable natural history of bee venom reactions mean that these results must be interpreted with caution.

In a third study, bee venom-allergic subjects were treated with three long synthetic peptides encompassing the entire Api m 1 sequence in a rush desensitisation protocol to a maintenance dose of 100 mcg of each peptide repeated at days 4, 7, 14, 42, and 70 [154]. Increased T cell proliferation to the treatment peptides was observed, along with increases in IFN-gamma and IL-10 levels, but not Th2 cytokines. Allergen-specific IgG₄, but not IgE, levels increased during the study. No significant changes in skin reactions to intradermal allergen extract challenge were seen. No severe adverse events were reported, but two subjects experienced redness and hand palm pruritus.

Conclusions

Allergen immunotherapy is effective in reducing the clinical symptoms associated with allergic rhinitis, asthma and venom-induced anaphylaxis. The two most commonly prescribed routes are SCIT and SLIT. Which route is prescribed depends on a number of factors, but extract availability/approval (or lack of) is the primary reason SLIT is prescribed by a small percentage US health care professionals. However, several clinical trials recently conducted in the US have met their primary outcome, and an FDA-approved product may be available in the near future. The efficacy of these 2 routes appears comparable, but the safety profile

with SLIT is more favorable. Both require regular treatment over several years, and poor adherence has been reported with both routes. Future efforts should focus on strategies to improve adherence with both until shorter, less time-consuming regimens are available.

Emerging evidence suggests that AIT may be effective in other allergic conditions, such as atopic dermatitis, venom stinging large local reactions, and food allergy. The data are conflicting on the role of AIT in AD in terms of which patients will benefit. To date, there has only been a proof-of-concept study that demonstrated AIT can reduce venom stinging-induced LLR. Research with OIT to treat food allergies has produced promising results in terms of demonstrating that many patients can be desensitized during treatment, but questions remain about whether this can produce long-term tolerance. Further studies are needed to identify appropriate patients and treatment regimens with these conditions.

Efforts to develop safer and more effective AIT for inhalant allergies have led to investigations with modified allergens and alternate routes. ILIT has been shown to produce long-lasting clinical benefits after three injections comparable to a 3-year course of SCIT. EPIT has demonstrated promising results for food and inhalant allergies.

Other promising approaches include modified vaccines, such as T cell peptides, and VPL adjuvants that may provide sustained clinical benefits after relatively short courses of treatment compared to the currently available AIT treatments, SLIT and SCIT. Hypoallergenic recombinant vaccines may provide safer treatments, but clinical efficacy has not been clearly established.

In conclusion, although SCIT and SLIT are well-established effective treatments for allergic respiratory conditions, the requirement for adherence to a multi-year treatment is a likely deterrent for initiating and adhering to treatments. AIT treatment strategies at reducing the time requirement while improving safety and efficacy are in progress, and when approved should make this disease-modifying treatment available to a greater percentage of the allergic population.

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Dr. Larche is a founder, shareholder and Dr. Kundig is named as the inventor on a patent on intralymphatic immunotherapy and as one of the inventors on a patent on epicutaneous immunotherapy; the patents are owned by the University of Zurich. consultant of/to Circassia Ltd., a company developing peptide-based immunotherapy and is scientific founder of Adiga Life Sciences Inc., a joint venture between Circassia Ltd. and McMaster University.

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