



Allergen immunotherapy: an update on protocols of administration

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Purpose of review

Allergen immunotherapy (AIT) is still the only causal treatment for allergic rhinitis and asthma. However, conventional subcutaneous AIT administration schedules are time-consuming and safety issues still play a role; for sublingual AIT, the best efficacy is still investigated and for food allergy the best efficacy–safety balance is not yet completely discovered. Investigators have made progress in these fields lately.

Recent findings

Since January 2014, several (ultra) rush or cluster build-up phases with hypoallergic variants of extracts have been explored with success. Also, the efficacy of only preseasonal subcutaneous AIT was demonstrated for tree and grass pollen. Sublingual AIT was shown to be effective and well tolerated in allergic rhinitis and asthma with tablets and with highly concentrated liquid formulations (ragweed, house dust mite), but not cockroach. For food allergy, oral immunotherapy is promising, but close attention should be paid to the exact administration schedule, maintenance dose, and the definition of efficacy (desensitization or real tolerance, as defined by a negative challenge test at least 4 months off treatment).

Summary

The practicing physician should be watchful for advances in the field of aeroallergen AIT and food oral immunotherapy, analyzing the presented information in detail and interpreting conclusions product specifically, without generalizing.

Keywords

allergen immunotherapy, allergic asthma, allergic rhinitis, peptide immunotherapy, polymerized allergens, subcutaneous immunotherapy, sublingual immunotherapy

INTRODUCTION

As the pathophysiological background of allergic diseases, such as allergic rhinitis, allergic conjunctivitis, atopic dermatitis, allergic asthma, and food allergy, is based on an altered immune response, the only causal therapy is the one that restores the immune response to a healthy balance. This principle was applied with success for the first time over a century ago by Noon [1], and since, investigators in the field of allergy have been searching for ways to improve allergen immunotherapy (AIT). As the review presented here shall show us, this quest is still ongoing.

Historically encountered inconveniences of subcutaneous immunotherapy (SCIT) have been its efficacy, which is good, but still not optimal, the long duration of the build-up phase with one or two clinic visits a week for months, the 3 to 5-year maintenance phase, the fact some patients do not want injections, and last, the serious adverse events reported with SCIT. The latter has improved much

with guidelines' and practice parameters' recommendations on safe administration in high-risk patients, on the conduction of a preinjection health screening questionnaire and suggestions on how to handle administration gaps, adjustments during the allergen season, etc. [2,3]. However, in the last surveillance study [4[¶]], there was still one fatality reported.

Table 1 synthesizes some of these inconveniences of classical AIT and how investigators have been trying for decades to overcome them by adjusting the traditional administration protocol of injections of a natural allergen administered in incremental

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Curr Opin Allergy Clin Immunol 2015, 15:556–567

DOI:10.1097/ACI.0000000000000220

KEY POINTS

- With hypoallergenic formulations – alum adsorbed, polymerized, allergoids – (ultra) rush and cluster build-up schedules seem to have acceptable safety when carried out under strict medical supervision.
- For high-dose SLIT liquid or tablet formulations of pollen extracts, a precoseasonal schedule can eventually lead to long-term effects, but for median-strength SLIT, this effect starts seemingly somewhat slower than with continuous administration.
- Precoseasonal schedules with high-dose pollen SLIT might be more cost-effective.
- OIT schedules vary from less to more aggressive ones; the latter have a higher rate of adverse events but also a better final outcome.
- For OIT, the aim is tolerance with ad-libitum posttreatment consumption, and not only desensitization while the OIT is taken.

doses during a build-up phase, followed by stable doses during the course of the maintenance phase lasting for years. Adjustments of the administration protocol have been in the field of what is injected (e.g. instead of a natural allergen in an aqueous solution, polymerized allergoids or hypoallergenic recombinants combined with adjuvants), how it is injected (e.g. instead of slow build-up, a one-day ultrarush schedule), and overcoming the need for

injections in general (e.g. instead of injections sublingual, oral, epicutaneous routes of administration). Within the same table, we show in bold some very recent advances published over the past 18 months, exploring how to overcome the shortcomings of classical SCIT, altering this conventional administration protocol. The review presented here shall be based on these publications.

METHODS

Search strategy

Literature searches were conducted in PubMed and Embase to identify original articles on clinical trials with AIT in any age group, published between 1 January 2014 and 1 July 2015, and written in English or Spanish. Search terms and limits were all combinations of desensitization OR allergen immunotherapy (medical subject heading terms) AND clinical trial (medical subject heading terms) AND 2014/01/01–2015/07/01 AND (Clinical Trial) AND (English OR Spanish). We identified additional articles by manually searching references from the obtained articles, review articles, and the authors' own literature database. Study design was not a restriction; preferably full-text articles were included.

Study selection

In the first phase of screening, the titles and abstracts of the search results were examined, and

Table 1. Protocols of AIT administration under investigation to overcome inconveniences of conventional allergen immunotherapy

Inconvenience of conventional schedule	Conventional	Alternate forms under investigation
Efficacy not 100%	Reduction of 30% over placebo of patients already on pharmacotherapy	Enhanced efficacy on adding vitamin D, adjuvants, using stronger T-cell stimulators (T-cell epitope peptides), B-cell stimulators (B-cell epitope peptides), peptides as part of fusion molecules
Too long duration of build-up	SCIT: administration 1–2/week per 3–4 months	Rush, cluster, ultrarush
Too long duration of maintenance	SCIT: office administration every 4–6 weeks, continuous for at least 3–5 years	SCIT: preseasonal, precoseasonal SLIT: better safety → at home. First data on SLIT HDM tablet Intralymphatic and peptide immunotherapy: 2–3 months of injections with effect for years
	SLIT: daily for at least 3–4 years	Preseasonal, precoseasonal
Safety issues	SCIT: severe AE not uncommon (office administration warranted), extremely rare fatal reactions	Polymerization of allergens: adsorbed to AIOH Hypoallergenic formulations: allergoids, hypoallergenic recombinants Other administration routes: SLIT, epicutaneous, intralymphatic
SCIT for food allergy	Not safe	Hypoallergenic peptides of food, epicutaneous administration

AE, adverse event; HDM, house dust mite; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

clinical trials reporting on the conventional administration of AIT, without any novelty, were excluded. The second phase of screening was based on these full-text articles, which were obtained and assessed for inclusion with the predetermined selection criteria: first, AIT administered according to a pattern, different from the conventional one: a different extract, a different administration schedule, a different route, etc., in individuals of any age with confirmed allergic disease, and second, language of publication as defined. Only those trials were incorporated that reported clinical data and/or safety data and/or immunologic findings as outcome measures. When of interest to this review, preclinical studies – conducted in nonhumans – shall briefly be commented on, but they are not included in the summary table.

Data collection and analysis

Data of the articles of interest are collected in a summary table (see Table 2) [5[•],6,7[•],8,9,10^{••},11^{••},12[•],13,14^{••}–16^{••},17[•],18–22,23[•],24,25[•],26,27^{••},28–33] and shall be discussed in the text. All changes commented on in this review reached statistical significance, unless otherwise commented on.

SUBCUTANEOUS IMMUNOTHERAPY

Enhancing efficacy of subcutaneous immunotherapy: vitamin D

As was previously shown by a Polish study [34], investigators from Turkey confirmed that adding vitamin D as an immunoregulator might enhance the immunologic efficacy of immunotherapy. Children with asthma because of house dust mite (HDM) allergy were randomized to one of the following three 1-year treatment arms: SCIT along with vitamin D (650 U/day), SCIT, or pharmacotherapy alone. At the end of the year, asthma symptom scores and medication score were improved in both the SCIT groups, but the SCIT along with vitamin D group children had a higher rate of inhaled corticosteroid discontinuation (35 versus 20% and 0% in controls, $P=0.02$). Also, although the Der p 1-induced IL10 and TGF β production was similar, the vitamin D group showed higher fluorescence intensity of Foxp3 [13].

Shorting the build-up phase

Investigators have tried to shorten the build-up phase of SCIT by applying rush or even ultrarush schedules. Four of these trials were published in the

time span of this review. Tabar *et al.* [5[•]] demonstrated that a rush build-up with an extract of an alum-adsorbed *Dermatophagoides* mix in weekly incremental injections over 5 weeks was safe. Administrations started with 300, followed by 600, 3000, 6000, and finally, 15 000 SQ-U (ALK-Abelló, Hørsholm, Denmark). Although half of the patients experience local reactions, only 7% of the 102 patients had a systemic grade 1 reaction.

Bozek *et al.* [6] and Cardona *et al.* [7[•]] went even further in applying ultrarush build-up protocols reaching the full dose within 1 day. The former used an alum-adsorbed tree pollen extract in an ultrarush preseasonal schedule of seven injections, 15 min apart on a winter day, outside of the pollen season.

The latter used only two injections, 0.2 and 0.3 ml, 30 min apart directly of the maintenance concentrate of a dipigmented, polymerized HDM extract, followed by normal maintenance doses of 0.5 ml every month. Systemic reactions were reported in eight of the 575 patients, receiving almost 8000 injections in total (1.3% of the patients, 0.1% of the doses). No World Allergy Organization grade 3 reactions were reported. Although this is just a retrospective review, the total number of patients treated and injections administered powers the results; even so they have to be interpreted with caution, taking into account the flaw of the design [7[•]]. The last rush build-up protocol of our review was carried out in China, reporting an adverse reaction rate similar to the conventional schedule, but no further details can be obtained, as the publication was in Chinese [8].

Turkish investigators also tried to shorten the course of immunotherapy. They were able to show the efficacy of preseasonal SCIT for pollinosis. In a double-blind placebo-controlled trial in patients with seasonal allergic rhinitis, they documented the clinical and immunological efficacy of a purely preseasonal SCIT schedule with a six-grass alum-adsorbed allergoid. In comparison with the placebo group, the actively treated patients showed a 52.9% reduction in the combined symptom-medication score, as well as a statistically significant rise in serum-specific IgE and IgG4 and a reduction at the end of the season in the allergen-induced CD203c basophil activation [9].

Finally, a shortened 1-week cluster up dosing schedule with a high polymerized mixed grass-rye pollen extract was shown to be well tolerated and effective by Klimek *et al.* [10^{••}] in a well designed double blind placebo controlled (DBPC) trial of 121 dual grass-rye allergic patients. The short up dosing phase was well tolerated and systemic adverse events, mild in intensity, were reported in only 0.8% of the injections.

Table 2. Allergen immunotherapy trials 2014–2015: focus on novel administration protocols

Ref/yr	Author	Route	Allergen	Form Natural/recombination	Build-up			Maintenance			Safety	Efficacy	Remarks
					Dose	Frequency	Duration	Dose	Frequency	Duration			
2015	Tabar <i>et al.</i> [5]	SC	Dermatophagoides mix	Allergen + AIOH in high dose	300 SQ + 600–3k–4k–15k	Weekly	5 weeks	15k SQ	Monthly	Only up-dosing trial	Acceptable	Mechanistic: good	Open, N = 102 ARC. New up-dosing phase in 5 weeks. Safety: Adverse drug reactions (ADRs): 101 local (48 patients), 7 systemic (all grade 1) in 5 patients. Efficacy: sign rise IgE blocking factor, IgG4, sign reduction SPT
2014	Bozek <i>et al.</i> [6]	SC	Tree pollen	Allergen AIOH	Conventional: 0.1, 0.2, 0.4 ml/week, then 4 × 0.5 ml every 2 weeks; Ultrarush: same doses, 15 min apart, all on 1 day (December–January)			No main	Maintenance	3 × pre-seasonal	Same in both groups	Seems good (under-powered)	DBPC: 22 SAR. Preseasonal ultrarush versus conventional build-up schedule over 3 years. Reduction in symptoms and medication scores and prepost; difference between groups NS. CAVE: Study heavily under-powered
2014	Cardona <i>et al.</i> [7]	SC	HDM	Depigmented polymerized	1 day, 30 min apart; 0.2 and 0.3 ml of maintenance concentrate			0.5 ml	Monthly	Not stated	Good	Safety trial	Retrospective, 575 patients, 1–83 years. Safety: 8/8000 injections resulted in a systemic AE in 8/575 patients (2 were during build-up). All were grade 1 or 2
2014	Giu <i>et al.</i> [8]	SC			Rush: not detailed in abstract; full text in Chinese			?	Monthly	12 months	Good	Safety trial	Open controlled rush versus conventional build-up. N = 87. Rush as safe as conventional IT
2014	Kepil Özdemir <i>et al.</i> [9]	SC	δ-grass	Allergoid-AIOH	0.1–ml 1000 TU/ml	Every 1–2 weeks	2–3 months	Only pre-seasonal	No data	No data	No data	Good	DBPC, 31 SAR. Average combined Sympt-Med score 52.9% better in SCIT versus placebo. Rise in specific IgG4 and IgE. Reduction basophil activation at end SCIT and at peak pollen season in IT group
2014	Klimek <i>et al.</i> [10]	SC	δ-grass + rye pollen	AIOH	0.1 and 0.2 ml day 1; 0.3 and 0.5 ml day 7 of maintenance concentrate 10000 TU/ml			0.5 ml	Monthly	12 months	Good	Good	DBPC, 121 SAR patients. Short 1-week cluster up-dosing. Total combined Sympt-Med score reduced versus placebo. Mild AE in 0.8% of the injections
2014	Sperdini <i>et al.</i> [11]	SC	Bet v 1 peptides (T-cell epitopes)	Contiguous overlapping peptides + AIOH	3.8, 1.5, 2, 38, 95 mcg	30 min intervals	1 day	51 mcg and then 97 mcg	Days 7, 14, 21, 51		Acceptable (dyspnea and fatigue)	Seems good but NS (pilot)	DBPC, 15 SCIT, 5 placebo. Safety: final planned dose reduced to 95 mcg, because of severe fatigue in 1 patient the day after up-dosing. No TRSAE. Efficacy: 30% reduction in RC score at peak season versus placebo (NS). IgG4 40x rise after 1st season, and still 5x rise after 3rd season

(Continued)

Table 2 (Continued)

Ref/yr	Author	Route	Allergen	Form Natural/recombination	Build-up			Maintenance			Safety	Remarks
					Dose	Frequency	Duration	Dose	Frequency	Duration		
2014	Wood <i>et al.</i> [12]	SL	Cockroach	Allergen *0.50 ml = Bla g 2/1: 5/100 mcg	5 or 8 doses	1 day		0.42 ml*	Daily	15 days, 3 months, 6 months	Good	4 pilot trials, SLIT: 54 adults, 99 children, SCIT: 10 adults. Some DBPC, some open. Immunological changes SCIT > SLIT, especially IgG4 and blocking antibodies. Safety: no major concerns
		SC			Incremental	2/week	11–18 weeks	0.6 m*	Weekly	6 months	Good	
2014	Boris <i>et al.</i> [13]	SC	HDM	+ Vit D3 (650 U/day)	Gradual dosing	1/week	16 weeks	Der p/f 1: 5.5/7.8 mcg	Monthly	12 months	Good	RCT, investigator blinded N=SCIT + Vit D3–17, SCIT- 15, Control-18. SCIT + VitD higher rate discontinuation ICS and higher Fox p 3 fluorescence. But both SCIT groups reduced asthma Sympt and Med scores versus controls. Both showed rise in Der p 1 induced IL10 and TGFβ
2015	Mosbech <i>et al.</i> [14]	SL, tablet	HDM (ALK-Abellø, Hørsholm, Denmark)	Allergen	No	Up	Dosing	1 or 3 or 6 SQ	Daily		Good	DBPC. N=604, allergic rhinitis (asthma). Efficacy: For 6 SQ: 28.8% reduction total combined rhinitis score. 1 and 3 SQ numerically less effective. No safety concerns
2014	Bergmann <i>et al.</i> [15]	SL, tablet	HDM (Dpt and Df)	Allergen	300 IR: 3 days = 100, 200, 300; 500 IR: 9 days = 100, 100, 200, 200, 300, 300, 400, 400, 500 IR	Up	Dosing	300 or 500IR (=Der p/f 1 28/120 mcg)	Daily	12 months	Accept- table	DBPC. N=509, 18–50 years with allergic rhinitis. Efficacy average adjusted symptom score sign better than placebo 500/300 IR: –20.2/–17.9%. Sustained effect after 1-year offRx. No anaphylaxis, dropout due to local AE 11.8 and 10% of the 500 and 300 IR
2014	Mosbech <i>et al.</i> [16]	SL, tablet	HDM (Dpt and Df)	Allergen	No	Up	Dosing	1, 3, and 6 SQ	Daily	12 months	Good	DBPC. N=604, 14+ years, mild-moderate persistent asthmatic patients. Efficacy: reduction in ICS use maintaining control of asthma. Safety: more AE with 3 and 6 SQ. Several systemic AE. No anaphylaxis or probably treatment-related life-threatening AE
2014	Nolte <i>et al.</i> [17]	SL, tablet	Ambrosia	Allergen	No	Up	Dosing	1.5, 6, and 12 mcg Amb a 1	Daily	2 of 4 weeks, 2 of 52 weeks	Accept- table	Grouped data of 4 DBPC trials, 3 (12 Amb a 1 group) and 1 placebo used epinephrine. One nonsevere anaphylaxis. No SAE, no asthma worsening
2015	Potter <i>et al.</i> [18]	SL	HDM	Allergen, Staloral	1 to 100 IR	Daily	4 weeks	1 ml with 300 IR	3/week	24 months	Good	N=71, Efficacy: stat. sign reduction of total 5 symptom score in both, SLIT (65%) and placebo (53%) groups. Good responders showed cytokine changes at 24 months. Safety: mild local AE, more in active

2015	Nakonechna <i>et al.</i> [19]	SL	Grass, tablet – Grazax	Allergen	No	No	No	75k SQ-T	Daily: Preco or continuous	36 months	Good (low) quality	No data	Observational. Preco (N=9) versus perennial (N=30) Grazax: year-by-year reduction in VAS and RQLQ practically the same in both. CAVE: flaws in design
2014	Huang and Zhou [20]	SL	HDM	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	24 months	Good	No data	[In Chinese] RA. Open, random. N=60–60. Stat.sign improvement in all nasal symptoms after 24-month SLIT versus placebo. Still improvement 1 year after discontinuation, except for obstruction. Rise in medication use in placebo group
2014	Di Rienzo <i>et al.</i> [21]	SL	HDM	Allergen	No	No	No	SLIT one	Daily	72 weeks	Good (bias?)	Mild	Open, random. N=82. AD. No investigator blinding. SCORAD more reduced in SLIT versus open controls at weeks 48 and 72
2014	Irani <i>et al.</i> [22]	SL	Several pollen mix (stloral)	Allergen	?	?	?	300 IR	Daily	36 months	No clear data	No data	N=118. Prospective, observational. Stat.sign improvement against baseline, but no intergroup differences reported
2014	Bozek <i>et al.</i> [23]	SL	5-grass, liquid	Allergen	30–60–120–240 IR	Daily	4 days	240 IR	5/week	4 months preseasonal x 3 years	Good	Good	DBPC. N=41–37; elderly SAR. Reduction total nasal symptom score 64 versus 7%. SLIT: reduction medication score 51%, sign. more than placebo. No SAE, only transient local AE in active group
2014	Li <i>et al.</i> [24]	SL	HDM	Allergen	?	?	?	?	?	52 weeks	Good	No SAE	N=41 monosensitized, 35 polysensitized children. Significant improvement in all groups. No intergroup differences. CAVE: underpowered and other flaws
2014	Wang <i>et al.</i> [25]	SL liquid	HDM	Allergen	No	Up	Dosing	300 IR, Der p/f 1: 28/50 mcg	Daily	12 months	Good	No SAE	N=484 adult asthmatics. DBPC. Efficacy for moderate asthma: well/total control more frequent in active versus placebo and greater reduction of ICS. For mild persistent asthma: no benefit
2014	Shao <i>et al.</i> [26]	SL	<i>Dermatophagoides farinace</i>	Allergen	0.05–50 mcg	Daily	3 weeks	0.15 ml of 333 mcg/ml	Daily	12 months	Good	No SAE	RCT, 264 children, 3–13 years (133: 3–5 years). Efficacy: more improvement in SLIT versus controls the second part of the 1st year and less asthma medication ($P<0.01$). Same for children 3–5 as for older children. Also IgG4 increased versus controls. Safety: no severe systemic AE
2014	Creticos <i>et al.</i> [27]	SL liquid	Short ragweed	Allergen	20 min intervals	1 day in office	Max. tolerated dose (top: 50 mcg Amb a 1)	Daily	Precoseasonal	Very good	Good	Good	DBPC 429 adults with ARC. Efficacy: A 43% reduction versus placebo in RW-SLIT during RW season. No anaphylaxis

(Continued)

Table 2 (Continued)

Ref/yr	Author	Route	Allergen	Form Natural/recombination	Build-up			Maintenance			Safety	Remarks
					Dose	Frequency	Duration	Dose	Frequency	Duration		
2014	Von Moos <i>et al.</i> [28]	Epi-cutaneous	5-grass pollen	Allergen	No	No	No	1.5 ml of 200 IR/ml	8 h once a week	Preterm stop	Tape safer	N = 98. Safety of EPT, preparing skin with abrasion with footfile versus 10x tape-straping: more local and systAE ($P=0.033$) with abrasion. Study was suspended
2014	Murakami <i>et al.</i> [29]	Oral	Cedar pollen	Cry ¹ -galactomannan conjugate	No	Build	Up			2 months (start 1 month preseasonal)		Open control (n 23 Cedar pollen allergic. Improved symptoms and symptom score during the pollen season. Specific IgG4 and IL-10 from PBMAN rise in active group. Safety: no severe AE
Food allergy												
2015	Zuidmeer-Jongejan <i>et al.</i> [30]	SC	Carp c 1 (major allergen fish allergy)	Mutant (hypoallergenic, recombination)	x	x	x	x	x	x	Preclinical: good	Preclinical studies show good immunogenicity, but strongly reduced allergenicity
2014	Anagnostou <i>et al.</i> [31]	Oral	Peanut	Peanut powder	Dose increments every 2 weeks in the clinic: 2.5, 12.5, 25, 50, 100, 200, and 400 mg	Daily	1st phase 6 months, 2nd 6 months	2-800 mg	Daily	3% AE drop out	Preclinical: good	RCT. Efficacy: after 1st phase: 39 OIT 84% tolerated 5 peanuts daily, 46 controls: no tolerance. 2nd phase: Controls got 6-month OIT: 91% tolerated. Safety: mostly local AE. Adrenaline used in 1 patient
2015	Tang <i>et al.</i> [32]	Oral	Peanut + probiotic	Allergen	1-day rush, 8 months build-up	Daily	8 months, updose every 2 weeks	2 g + LR	Daily	Regular	Good	DBPC. Possible sustained unresponsiveness 2-5 weeks after discontinuation of treatment: 82% of probiotic and peanut OIT versus 3.6% in placebo. Safety: more AE in active group. Safety: children with severe AE 45 versus 32% (but 1 child with 13 SAE)
2014	Vickery <i>et al.</i> [33]	Oral	Peanut	Peanut powder	1-day initial dose escalation, followed by dose increments every 2 weeks in the clinic	Daily	5 years	Max. 4000 mg	Daily	Acceptable	In 5 years: 6/39 abandoned because of AE	Of the 39 children - 1-16 years - 24 finished 5 years. DBPCFC with 5000 mg peanut powder: 12/24 passed. Several immunological markers at baseline and at the moment of challenge related to tolerance: lower IgE for peanut; Ara h 1, Ara h 2, spIgE/total IgE, smaller SPT wheel; no differences in spIgG4 or its functional activity at the end

AE, adverse event; DBPC, double blind placebo controlled; ICS, inhaled corticosteroids; Ig, immunoglobulin; IL, interleukin; IT, immunotherapy; IR, *Lactobacillus rhamnosus* CGMCC 1.3724 2×10^{10} CFU; OIT, oral immunotherapy; SC, subcutaneous; SCIT, subcutaneous immunotherapy; SPT, skin prick test. Data from [40,41].

Subcutaneous immunotherapy with allergens that lack clear dosing guidelines

After the team of the inner-city consortium found that cockroach seems to be of major importance in patients with inner-city asthma, the investigators decided to search for the ideal schedule of immunotherapy. As sublingual administration is safer and easier to take at home, it was decided to try and find the optimal sublingual immunotherapy (SLIT) administration protocol. The first two trials were conducted with a maintenance dose of 0.42 ml daily (approximately 3685 Bioequivalent allergy units, containing 4.2/50 mcg of Bla g 2/1), and in a third arm of the last trial, this intermediate dose was tested against placebo and a four-fold higher dose (0.84 ml b.i.d.). However, after these first three trials of high-dose cockroach SLIT in both adults and children did not yield convincing immunological results, the consortium conducted a 10-patient pilot, biomarker-driven, trial with cockroach SCIT. The results of these four pilot trials on cockroach SLIT ($N = 18, 99$) and SCIT ($N = 10$ adults) were taken together and published in one manuscript in 2014. The investigators conclude that the capacity to induce immune changes seems to be higher in SCIT than in SLIT [12[¶]]. The lack of SLIT to induce consistent immunological changes might make them decide to choose SCIT as the direction for future trials of cockroach immunotherapy.

Subcutaneous immunotherapy with altered molecules

The European regulatory authorities published new guidelines, compelling in nature some 7 years ago. In these guidelines, authorities insist on the better definition of the allergen extracts, the precise determination of its allergen content, the demonstration of its stability, and the complete pharmacologic and toxicological documentation. This is often difficult to obtain with an extract based on natural allergens. As such, novel preparations based on single pure allergen molecules or synthetic peptides could be a viable option. Two interesting studies were published in this area in the time span of our review.

Apart from group 1 and 2 allergens, the recently discovered Der p 23 also seems to be an important HDM allergen. A group of investigators from Vienna identified a nonallergenic peptide from the C-terminal IgE epitope-containing part of Der p 23. This peptide was then fused to the PreS domain from hepatitis B virus and expressed in *Escherichia coli*. Upon immunization of rabbits, this fusion protein, PreS-2XP4P5, was able to induce a strong anti-Der p 23 IgG4 production with blocking capacity, inhibiting the binding of patients' IgE to Der p 23, as well as

the production of Th1-type cytokines, but without allergenicity [35].

Epitope-binding peptides such as this might be promising for immunotherapy in the future, as – compared with natural allergens – they might be able to reduce adverse events related to IgE binding and reduce the number of immunotherapy shots, because of their strong immunogenicity.

Very recently, a group of investigators published on the safety and immunogenicity results of preseasonal SCIT with AllerT, consisting of contiguous overlapping peptides of Bet v 1, which were T-cell epitopes, with undetectable IgE binding. After a 1-day dose escalation of four applications, followed by three weekly injections and a final injection on day 51, a marked rise in serum-specific IgG4 could be obtained, which lasted even 3 years after the immunotherapy schedule. However, several patients reported fatigue and some dyspnea in the active group, which calls for some attention, even though no serious treatment-related events were reported [11^{¶¶}].

SUBLINGUAL IMMUNOTHERAPY

Classical SLIT treatment, as started since 1986, has been with daily administration of drops from a liquid formulation of a grass or HDM extract, generally in patients with seasonal allergic rhinitis. About a decade ago, SLIT grass tablets have been developed and after multiple large DBPC trials documented their efficacy and safety, these are now on the market, both in Europe and in the USA.

Over the past 18 months, novelties in this area have been the documentation of SLIT efficacy for SAR in a large group of very young children [26] and in elderly patients [36], the comparison of SLIT efficacy when given in a pre-seasonal schedule versus a continuous schedule, dose-finding studies for SLIT tablets of HDM [14^{¶¶}–16^{¶¶}] and short ragweed pollen [17[¶]], dose-finding studies for liquid SLIT of short ragweed pollen [27^{¶¶}], and SLIT for allergic asthma [16^{¶¶}, 25[¶]].

Sublingual immunotherapy in the very young or elderly patients

Although SLIT efficacy has been shown for children from 5 years onward, a discussion still remained concerning its efficacy in children below this age limit. Shao *et al.* [26] conducted a randomized controlled study of SLIT with *Dermatophagoides farinae* in 264 children (3–13 years) with allergic rhinitis with or without asthma. Among these individuals, 133 were between 3 and 5 years of age. SLIT showed a significant improvement in symptoms

and medication after a year of treatment, as well as a rise in specific IgG4. Moreover, the investigators comment that there was no significant difference between children less than or more than 5 years old in terms of clinical efficacy, onset of action, immunologic parameters, and safety.

At the other extreme of life, Bozek *et al.* [23] recorded positive outcomes of SLIT in a DBPC trials in elderly patients with seasonal allergic rhinitis, reporting a reduction in total nasal symptom score of 64% as opposed to 7% in the placebo group, accompanied by a 51% reduction in medication score. Moreover, there were no safety issues with the liquid formulation of SLIT used in this trial, dosing 240IR, 20% lower than the regular SLIT dose of 300IR.

Precoseasonal versus perennial sublingual immunotherapy

Four years ago, a precoseasonal schedule of SLIT attained the same efficacy as perennial SLIT, but only after the third year [37]. One year later in 2012, a 2-year precoseasonal schedule of high-dose grass pollen SLIT was as effective as perennial administration to bring about clinical and immunological changes [38]. The short ragweed trial stimulating patients to take the highest tolerated dose – top 50 mcg – showed marked clinical improvement with only one course.

The short ragweed pollen desensitization program of a liquid SLIT product (Greer Inc., Lenoir, North Carolina, USA) has several novel aspects. First of all, patient selection was not based on the wheal but on the flare diameter presented at skin prick test (SPT) with short ragweed pollen extract. Furthermore, patients were given the maximum tolerated dose; treatment was started 8–16 weeks preseasonally with an in-office updosing with 20-min intervals until 50 mcg Amb a 1 or the maximum tolerated dose and continued throughout the short ragweed season. Selecting and treating the patients in this way led to an improvement in the combined symptom-medication score of 43% over placebo [27], one of the highest percentages reported in a SLIT trial. Moreover, a rise in serum-specific IgG4 and IgE was detected in the active group.

As for the precoseasonal administration versus the continuous, perennial administration of 3 years SLIT, new data were published in a brief manuscript [19]. However, as the study had some very serious flaws (being a retrospective chart review, heavily underpowered with only nine patients in the precoseasonal group and without adequate medication scores nor pollen season data), the conclusions are probably not solid. It is, however, a good idea to

simply have all patients, coming in for SLIT, fill in some questions to obtain more real-life data on SLIT efficacy. If this is all undertaken in a well planned, anticipated manner, the results might be of acceptable quality to be considered as valuable evidence.

Sublingual immunotherapy with nongrass tablets: house dust mite and short ragweed

After the good results with the grass pollen SLIT tablets, both manufacturers have published dose-finding data on HDM SLIT tablets over the past 18 months, be it one in patients with allergic rhinitis, the other in asthmatic patients. The first dose-finding trial with HDM SLIT tablets recruited 18 to 50-year-old patients with perennial allergic rhinitis. Tablets with 300 and 500IR were tested against placebo (500IR = 28 mcg Der p 1 and 120 mcg Der f 1, as measured with the kit from Indoor Biotechnologies, Charlottesville, Virginia, USA). The administration protocol consisted of a short build-up phase of 3 and 9 days for the 300 and 500IR tablets, respectively. After 1 year of daily dosing, the placebo group reduced the mean symptom score from 7 to just below 5. Even so, a 17.9 and 20.2% reduction in symptoms over placebo was detected for the 300 and 500IR groups, respectively. Interestingly, after only 1 year of treatment, investigators were able to show a statistically significant, sustained effect of symptom reduction 12 months off treatment, more or less in the same range over placebo, even though the placebo group reduced its mean symptoms even further from below 5 to below 4 [15].

Simultaneously, a safety trial was conducted with a fast-dissolving HDM SLIT tablet: 28 days of daily dosing showed that doses up to 12 developmental units were well tolerated, whereas one 16 developmental unit patient discontinued because of an adverse event and 32 developmental unit caused a severe adverse event in another patient, leading to discontinuation of this dosing group [39].

A few months later, the HDM SLIT tablet data from a three-dose, placebo-controlled trial (1, 3, and 6 developmental units) were published. Here, no clear dose effect could be shown, as the 1 and 3 developmental units did not differ from placebo, but the only effective dose was the 6 developmental unit. The 6 developmental unit was able to reduce the inhaled corticosteroids (ICS) daily dose with 81 mcg/day and 34% of the patients got completely off ICS [16]. In a post-hoc analysis of the subgroup of patients with allergic rhinitis symptoms at start, the 6 developmental unit dose was also the only statistically significant effective one [14].

Immunological changes

Comparing the immunological changes induced by SCIT and tablet SLIT in grass pollen allergic patients, it was shown that both induced similar changes of a rise in specific IgG4 and competition assays (IgE-blocking factor, facilitated antigen binding, and basophil activation test) in comparison with a control group; however, these changes appear earlier in the SCIT-treated patients, and in contrast with SLIT, the initial IgE rise is more pronounced [40].

OTHER ROUTES FOR IMMUNOTHERAPY WITH INHALANTS: INTRALYMPHATIC, EPICUTANEOUS, ORAL

A group of Swiss investigators has been developing a modular allergen translocation vaccine, in which part of the allergen is coupled to a translocation segment that leads the allergenic protein to the Golgi apparatus. The product was tested in the form of three intralymphatic injections that were able to induce allergen-specific peripheral tolerance of T cell [41].

Some preliminary data on oral immunotherapy (OIT) with a cedar pollen Cry j 1 galactosamannan conjugate in 23 patients with allergic rhinitis were promising, but these are just pilot data that definitely need confirmation [29].

An epicutaneous five-grass pollen immunotherapy (IT) trial was put on preterm halt, because of unacceptable adverse reactions [28].

ORAL FOOD IMMUNOTHERAPY

The recently conducted trials with oral food immunotherapy generally follow this protocol: a short but intensive rush dose escalation, of 1–2 days, conducted in the hospital, followed by a build-up phase of 6–8 months, consisting of 2-week intervals of daily sustained dosing at home, each terminating with an in-hospital rise in dose to the next level (see Fig. 1) [42,43]. Both SLIT and OIT with food exert effects on innate and adaptive immune responses driven by dendritic cells, albeit in a different way [43].

Oral immunotherapy peanut

In patients who pass a double-blind placebo-controlled food challenge (DBPCFC) at the end of a food immunotherapy trial, the main question always is if this detected unresponsiveness (also called desensitization) is dependent on the daily ingestion of the food, and thus lost after discontinuation of daily ingestion, or if this is a sign of true sustained unresponsiveness (also called tolerance).

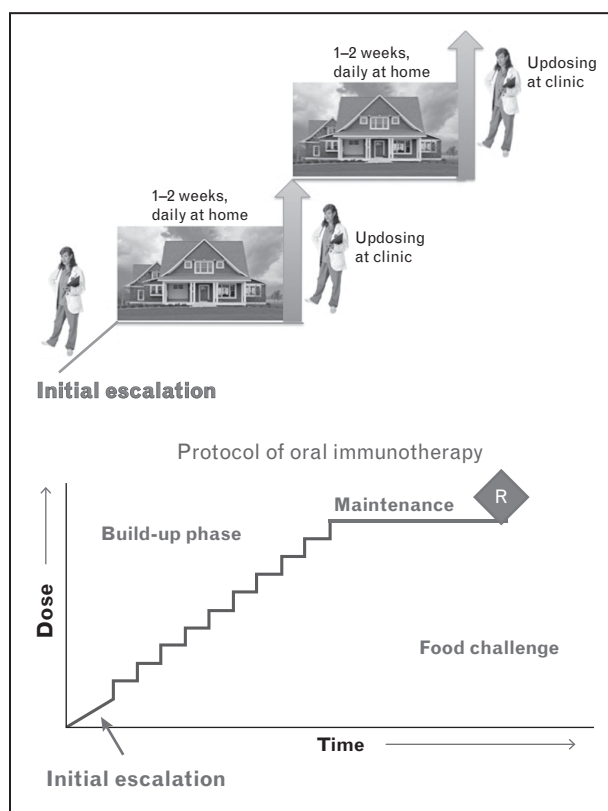


FIGURE 1. General administration schedule of food oral immunotherapy. The initial escalation phase is generally carried out during 1–2 days in-patient. Thereafter, the build-up phase consists of a dose augmentation every 1–2 weeks at the clinic, followed by home administration of the highest tolerated dose during this build-up. Adapted from [43].

Thus, in the most recent food immunotherapy trials, patients are called back for a last food challenge 1 month after discontinuing the food under investigation. Sustained unresponsiveness was first documented after egg OIT, but egg allergy is frequently outgrown. Vickery *et al.* [33] also showed for the first time sustained unresponsiveness after peanut OIT, with 4000 mg peanut powder daily. Twenty-four of the 39 patients, 1–16 years of age at study start, who completed a 5-year protocol of peanut OIT, underwent a DBPCFC to a total of 5000 mg peanut powder, 1 month after study end. Fifty percent (12/24) passed this challenge and in this reviewed manuscript, it was shown that passing this last challenge was related to a smaller SPT at baseline and after 5 years of treatment, as well as to lower serum levels of IgE directed to peanut, Ara h 1 and Ara h 2, and a lower specific IgE/total IgE ratio at baseline and the time of challenge. However, no differences in specific IgG4 or its functional activity could be found between those who passed and those who did not pass the challenge [33]. It is worthwhile commenting that even those who did not pass the

final DBPCFC tolerated a mean of 3750 mg of peanut powder, equivalent to 12 peanuts.

Investigators from Cambridge published the results of an up dosing protocol, slightly different from that used in the studies discussed earlier. Defatted peanut powder was mixed into food: gradual 2-week increments in peanut powder were administered in the clinic and then continued at home, without an initial escalation phase. Protein doses were 2, 5, 12.5, 25, 50, 100, 200, and 400 mg and the final target dose in this trial was 800 mg daily (approximately five peanuts), a fifth of the dose used in the protocol discussed earlier [31]. Half of the peanut allergic children, randomly selected, were given the desensitization protocol from the start of the study. The other half served as controls during the first 6 months. After a DBPCFC at this time point, the controls were also offered the desensitization protocol for the next 6 months, when another DBPCFC was conducted; 62% of the OIT group and 0% of the controls passed the first challenge and after the second phase of 6 months of peanut OIT of the controls, 54% of them also passed the challenge. Several differences with the protocol as discussed in the trials earlier should be noted: this latter OIT schedule does not use an initial dose-escalation day and the final OIT dose is only a fifth of the dosing by US investigators. Most importantly, the DBPCFC is conducted with only 1400 mg peanut powder, as opposed to 5000 mg in the US trials. Finally, the latter trial only documents desensitization at study end, but there is no challenge after a nondosing interval. Thus, it is not clear if this protocol also was able to achieve sustained hyporesponsiveness.

Immunologic changes with food immunotherapy

Several investigators reported the immunological changes brought about by SLIT and OIT with food, but a discussion of these goes beyond the scope of our review [43–45,46[■]].

CONCLUSION

Over the past 18 months, some new data on immunotherapy schedules have been published, both for respiratory and for food allergy (see Table 2). Administration protocols have been presented, differing from conventional IT in timing of dosing, dosing quantity, novel extracts being used, and novel routes being explored. In comparing data, it is mandatory to pay attention to the details of the administration protocols as commented on in this review, as well as the exact extracts used. These all probably

make the difference between success or failure and between acceptable or nonacceptable risks of certain treatment. Especially, we would like to draw the attention of the reader to the successful ultrarush protocols published, which were conducted with polymerized and/or hypoallergenic variants of the natural allergens.

This review leaves beyond doubt that this is still an ever-evolving field in which much has been learnt, but in which still much more is left to be learnt.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

D.L.L. has received honoraria in Mexico from Glaxo-SmithKlein, Boehringer Ingelheim, Mit-Pharma, Novartis, and MEDA. She is currently receiving a grant from Novartis, Sanofi, GlaxoSmithKlein, TEVA, MSD, Pfizer, Astrazeneca, MEDA, and Senosian. She is on the speaker's bureau for MSD, Pfizer, Astrazeneca, MEDA, Glenmark, and Mit-Pharma.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911; 1:1572–1573.
 2. Cox L, Nelson H, Lockey R, *et al.* Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011; 127 (1 Suppl):S1–S55.
 3. Larenas-Linnemann DE, Gupta P, Mithani S, Ponda P. Survey on immunotherapy practice patterns: dose, dose adjustments, and duration. *Ann Allergy Asthma Immunol* 2012; 108:373–378.
 4. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008–2012: an update on fatal and nonfatal systemic allergic reactions. *J Allergy Clin Immunol Pract* 2014; 2:161–167.
- US surveillance study on adverse events with AIT – still one fatal report in 2008–12.
5. Tabar AI, Gonzalez Delgado P, Sanchez Hernandez C, *et al.* Phase II/III clinical trial to assess the tolerability and immunological effect of a new up dosing phase of *Dermatophagoides* mix-based immunotherapy. *J Investig Allergol Clin Immunol* 2015; 25:40–46.
- A new, 5-weeks up dosing phase for SC-AIT with *Dermatophagoides* mix showing acceptable tolerability with 11% systemic grade 1 adverse events during up-dosing.
6. Bozek A, Kolodziejczyk K, Jarzab J. Safety and efficacy of tree pollen specific immunotherapy on the ultrarush administration schedule method using pure-thal trees. *Biomed Res Int* 2014; 2014:707634.
 7. Cardona R, Lopez E, Beltran J, Sanchez J. Safety of immunotherapy in patients with rhinitis, asthma or atopic dermatitis using an ultra-rush buildup. A retrospective study. *Allergol Immunopathol (Madr)* 2014; 42:90–95.
- Nicely designed retrospective, real-life trial in which safety data on 575 patients were obtained showing depigmented polymerized house dust mite extract has a good safety profile.
8. Qiu Q, Luc C, Chen J, *et al.* Safety of rush allergen-specific immunotherapy in allergic rhinitis patients. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2014; 28:776–779.

9. Kepil Özdemir S, Sin BA, Guloglu D, *et al.* Short-term preseasonal immunotherapy: is early clinical efficacy related to the basophil response? *Int Arch Allergy Immunol* 2014; 164:237–245.
 10. Klimek L, Uhlig J, Mosges R, *et al.* A high polymerized grass pollen extract is efficacious and safe in a randomized double-blind, placebo-controlled study using a novel up-dosing cluster-protocol. *Allergy* 2014; 69:1629–1638.
 11. Spertini F, Perrin Y, Audran R, *et al.* Safety and immunogenicity of immunotherapy with Bet v 1-derived contiguous overlapping peptides. *J Allergy Clin Immunol* 2014; 134:239–240.
 12. Wood RA, Togias A, Wildfire J, *et al.* Development of cockroach immunotherapy by the Inner-City Asthma Consortium. *J Allergy Clin Immunol* 2014; 133:846–852.
 13. Baris S, Kiykim A, Ozen A, *et al.* Vitamin D as an adjunct to subcutaneous allergen immunotherapy in asthmatic children sensitized to house dust mite. *Allergy* 2014; 69:246–253.
 14. Mosbech H, Canonica GW, Backer V, *et al.* SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms. *Ann Allergy Asthma Immunol* 2015; 114:134–140.
 15. Bergmann KC, Demoly P, Worm M, *et al.* Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol* 2014; 133:1608–1614.
 16. Mosbech H, Deckelmann R, de Blay F, *et al.* Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014; 134:568–575.e7.
 17. Nolte H, Amar N, Bernstein DI, *et al.* Safety and tolerability of a short ragweed sublingual immunotherapy tablet. *Ann Allergy Asthma Immunol* 2014; 113:93–100.
 18. Potter PC, Baker S, Fenimore B, Nurse B. Clinical and cytokine responses to house dust mite sublingual immunotherapy. *Ann Allergy Asthma Immunol* 2015; 114:327–334.
 19. Nakonechna A, Hills J, Moor J, *et al.* Grazax sublingual immunotherapy in pre-co-seasonal and continuous treatment regimens: is there a difference in clinical efficacy? *Ann Allergy Asthma Immunol* 2015; 114:73–74.
 20. Huang Z, Zhou A. Long-term clinical efficacy of sublingual immunotherapy in children with allergic rhinitis. *J Clin Otorhinolaryngol Head Neck Surg* 2014; 28:1011–1014.
 21. Di Rienzo V, Cadario G, Grieco T, *et al.* Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, open, parallel-group study. *Ann Allergy Asthma Immunol* 2014; 113:671–673.
 22. Irani C, Saleh RA, Jammal M, Haddad F. High-dose sublingual immunotherapy in patients with uncontrolled allergic rhinitis sensitized to pollen: a real-life clinical study. *Int Forum Allergy Rhinol* 2014; 4:802–807.
 23. Bozek A, Kolodziejczyk K, Warkocka-Szolysek B, Jarzab J. Grass pollen sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with seasonal allergic rhinitis. *Am J Rhinol Allergy* 2014; 28:423–427.
 24. Li P, Li Q, Huang Z, *et al.* Efficacy and safety of house dust mite sublingual immunotherapy in monosensitized and polysensitized children with respiratory allergic diseases. *Int Forum Allergy Rhinol* 2014; 4:796–801.
 25. Wang L, Yin J, Fadel R, *et al.* House dust mite sublingual immunotherapy is safe and appears to be effective in moderate, persistent asthma. *Allergy* 2014; 69:1181–1188.
 26. Shao J, Cui YX, Zheng YF, *et al.* Efficacy and safety of sublingual immunotherapy in children aged 3–13 years with allergic rhinitis. *Am J Rhinol Allergy* 2014; 28:131–139.
 27. Creticos PS, Esch RE, Couroux P, *et al.* Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2014; 133:751–758.
 28. Von Moos S, Johansen P, Tay F, *et al.* Comparing safety of abrasion and tape-stripping as skin preparation in allergen-specific epicutaneous immunotherapy. *J Allergy Clin Immunol* 2014; 134:965–967.
 29. Murakami D, Kubo K, Sawatsubashi M, *et al.* Phase I/II study of oral immunotherapy with Cry j1-galactomannan conjugate for Japanese cedar pollinosis. *Auris Nasus Larynx* 2014; 41:350–358.
 30. Zuidmeer-Jongejan L, Huber H, Swoboda I, *et al.* Development of a hypoallergenic recombinant parvalbumin for first-in-man subcutaneous immunotherapy of fish allergy. *Int Arch Allergy Immunol* 2015; 166:41–51.
 31. Anagnostou K, Islam S, King Y, *et al.* Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet* 2014; 383:1297–1304.
 32. Tang ML, Ponsonby AL, Orsini F, *et al.* Administration of a probiotic with peanut oral immunotherapy: a randomized trial. *J Allergy Clin Immunol* 2015; 135:737–744.
 33. Vickery BP, Scurlock AM, Kulis M, *et al.* Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol* 2014; 133:468–475.
 34. Majak P, Rychlik B, Stelmach I. The effect of oral steroids with and without vitamin D3 on early efficacy of immunotherapy in asthmatic children. *Clin Exp Allergy* 2009; 39:1830–1841.
 35. Banerjee S, Weber M, Blatt K, *et al.* Conversion of Der p 23, a new major house dust mite allergen, into a hypoallergenic vaccine. *J Immunol* 2014; 192:4867–4875.
 36. Bozek A, Ignasiak B, Kasperska-Zajac A, *et al.* Local allergic rhinitis in elderly patients. *Ann Allergy Asthma Immunol* 2015; 114:199–202.
 37. Pajno GB, Caminiti L, Crisafulli G, *et al.* Direct comparison between continuous and coseasonal regimen for sublingual immunotherapy in children with grass allergy: a randomized controlled study. *Pediatr Allergy Immunol* 2011; 22:803–807.
 38. Stelmach I, Kaluzinska-Parzyszek I, Jerzynska J, *et al.* Comparative effect of pre-seasonal and continuous grass sublingual immunotherapy in children. *Allergy* 2012; 67:312–320.
 39. Corzo JL, Carrillo T, Pedemonte C, *et al.* Tolerability during double-blind randomized phase I trials with the house dust mite allergy immunotherapy tablet in adults and children. *J Invest Allergol Clin Immunol* 2014; 24:154–161.
 40. Aasbjerg K, Backer V, Lund G, *et al.* Immunological comparison of allergen immunotherapy tablet treatment and subcutaneous immunotherapy against grass allergy. *Clin Exp Allergy* 2014; 44:417–428.
 41. Zaleska A, Eiwegger T, Soyer O, *et al.* Immune regulation by intralymphatic immunotherapy with modular allergen translocation MAT vaccine. *Allergy* 2014; 69:1162–1170.
 42. Kulis M, Wesley Burks A. Oral immunotherapy for food allergy: clinical and preclinical studies. *Adv Drug Deliv Rev* 2013; 65:774–781.
 43. Frischmeyer-Guerrero PA, Keet CA, Guerrero AL, *et al.* Modulation of dendritic cell innate and adaptive immune functions by oral and sublingual immunotherapy. *Clin Immunol* 2014; 155:47–59.
 44. Levy MB, Elizur A, Goldberg MR, *et al.* Clinical predictors for favorable outcomes in an oral immunotherapy program for IgE-mediated cow's milk allergy. *Ann Allergy Asthma Immunol* 2014; 112:58–63.
 45. Nozawa A, Okamoto Y, Moverare R, *et al.* Monitoring Ara h 1, 2 and 3-sIgE and sIgG4 antibodies in peanut allergic children receiving oral rush immunotherapy. *Pediatr Allergy Immunol* 2014; 25:323–328.
 46. Syed A, Garcia MA, Lyu SC, *et al.* Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). *J Allergy Clin Immunol* 2014; 133:500–510.
- Immunologic changes detected after oral peanut AIT.
- Report of several trials in the search of the ideal cockroach AIT, probably SC-AIT.
- Large dose-finding trial on HDM SLIT with the ALK tablet in AR: 6SQ-HDM best dose.
- Large dose-finding trial on HDM SLIT with the Stallergenes tablet: 6SQ-HDM best dose.
- Large dose-finding trial on HDM SLIT with the ALK tablet in asthma: 6SQ-HDM best dose.
- Grouped data of 4 DBPC Ragweed pollen SLIT tablet trials.
- One of the very few trials with SLIT in the elderly using a 5-grass liquid formulation.
- DBPC trials showing good efficacy of 300IR SLIT drops in 484 adult asthmatics.