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Reviews

New approaches to allergen immunotherapy

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Key Messages

- Subcutaneous immunotherapy is effective for allergic rhinoconjunctivitis but requires long-term treatment and is expensive, labor intensive, and can cause local and systemic allergic side effects.
- Sublingual immunotherapy has emerged as an effective and safe alternative to SCIT and is effective for seasonal and perennial allergies.
- Immunotherapy for food allergy is currently experimental and has high rates of allergic side effects and there is no evidence of long-term efficacy. It should be confined to specialist centers.
- Alum and MCT are effective depot adjuvants. The TLR-4 agonist MPL in combination with SCIT has enabled a shortened course of immunotherapy. Concurrent omalizumab with immunotherapy is highly effective in decreasing side effects.
- Hypoallergenic allergen derivatives including allergoids and recombinant allergen variants could enable shorter courses of immunotherapy but thus far have not been shown to be more effective or safer than whole allergen extracts.
- Adequate randomized controlled phase 3 trials of novel approaches and head-to-head studies comparing validated immunotherapy methods are currently lacking. Efficacy observed at phase 2 often does not translate into clinical benefit at phase 3.

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ABSTRACT

Objective: New insights into mechanisms should enable strategic improvement of allergen immunotherapy, aiming to make it safer, faster, more effective, and able to induce long-term tolerance. We review novel approaches with potential to translate into clinical use.
Data Sources: Database searches were conducted in PubMed, Scopus, and Google Scholar.
Study Selections: Search terms were based on current and novel approaches in immunotherapy. Literature was selected primarily from recent randomized double-blinded placebo-controlled trials and meta-analyses.
Results: Alum, microcrystalline tyrosine, and calcium phosphate are adjuvants in current use. Toll-like receptor-4 agonists combined with allergen have potential to shorten duration of treatment. Other novel adjuvants, nanoparticles, and virus-like particles in combination with allergen have shown early promise. Omalizumab lessens systemic side effects but does not improve efficacy. Intralymphatic immunotherapy for aeroallergens, epicutaneous immunotherapy for food allergens, and use of modified allergens (allergoids), recombinant allergens (and hypoallergenic variants), and T- and B-cell peptide approaches have shown evidence of efficacy and permitted shortened courses but have only rarely been compared with conventional extracts.
Conclusion: Novel routes of immunotherapy, use of modified allergens, and combination of allergens with immunostimulatory adjuvants or immune modifiers have been developed to augment downregulation of T-helper cell type 2 immunity and/or induce “protective” blocking antibodies. Although these strategies have permitted shortened courses, confirmatory phase 3 trials are required to confirm efficacy and safety and head-to-head trials are required for comparative efficacy. Currently, subcutaneous and sublingual

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immunotherapies using in-house standardized crude extracts remain the only approaches proved to induce long-term tolerance.
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Introduction

Allergen immunotherapy with standardized crude extracts is highly effective and can induce long-term remission of symptoms.[1] However, ongoing problems include the duration of treatment, the safety of immunotherapy, and its cost and accessibility.

Allergic rhinitis affects 20% to 30% of the population in Western Europe and the United States,[2] adversely affecting sleep, productivity, and quality of life. Unlike with food and drug allergy, complete allergen avoidance is seldom possible.[3] Most patients are effectively managed with oral or intranasal antihistamines and intranasal corticosteroids. A recent advance has been the combination of an antihistamine and a corticosteroid in the same nasal spray.[3] In a recent meta-analysis, intranasal corticosteroids decreased symptoms by 17% compared with placebo.[3] Poor responses to treatment are often due to poor adherence, especially for intranasal corticosteroids.[4]

Aeroallergen immunotherapy with subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) is currently recommended for patients with moderate to severe symptoms on exposure to allergen with demonstrable relevant immunoglobulin (Ig) E sensitization, who do not respond adequately to antiallergic drugs, or who experience unacceptable side effects of medical therapy.[3,5]

Food allergy is increasing in prevalence, affecting approximately 5% of the population in Western countries.[6] The current mainstay of treatment is allergen avoidance and availability of rescue treatment with antihistamines and epinephrine auto-injectors. However, accidental exposure to even small doses can cause severe systemic reactions and even death. Food allergen immunotherapy is currently an experimental treatment and is not recommended for routine use.[6] It carries an increased risk of severe allergic reactions compared with aeroallergen immunotherapy and currently there is no evidence that it induces long-term tolerance.[7]

Subcutaneous Immunotherapy

Subcutaneous immunotherapy traditionally involves administration of natural extracts derived from whole allergen. Treatments are initiated at low doses of allergen and gradually increased, usually with weekly dosing, until a high-dose concentration is reached over several weeks. This dose is given monthly for 3 to 5 years. Weekly allergen dosing was initially used in early immunotherapy protocols because of its known effectiveness and the practicalities of ensuring regular patient visits.[8] Although 3 years of treatment with grass pollen immunotherapy has been shown to induce long-term remission, a recent study showed that 2 years was insufficient to sustain tolerance 1 year later.[8] Up to 22% of people undergoing SCIT develop a systemic allergic reaction and very rarely anaphylaxis. Exceptionally, there have been reports of death after injections. SCIT is safe when patients are selected appropriately, facilities are adequate, staff members are well trained, and emergency treatment is available.[3] There is high variability in the type of immunotherapy vaccine used and efficacy is allergen and product specific.[5]

Subcutaneous immunotherapy is very effective for seasonal allergic rhinitis caused by pollens[9] and perennial allergic rhinitis caused by house dust mite (HDM).[10] In large randomized controlled trials, the efficacy is approximately 30% compared with placebo treatment, achieving the minimally clinically important difference as decided by the World Allergy Organization (largely on empirical grounds) of 20% compared with placebo treatment.[11] There are few direct comparisons between optimum pharmacotherapy and immunotherapy.[12] In extrapolated pooled analyses, it has been shown to be as effective as or more effective than pharmacotherapy.[13]

In a survey of practicing allergists from the United States in 2011, SCIT was by far the most used mode of immunotherapy.[14] In practice, compliance and persistence with current immunotherapy have been shown to be poor; in a recent Dutch study, only 18% of users achieved the recommended 3 years of treatment.[15]

Mechanisms of Allergy and Immunotherapy

The allergic response is characterized by the presence of allergen-specific IgE, mast cell degranulation on exposure to allergen, and eosinophilic infiltration. Once recognition of the allergen has taken place, pro-allergic type 2 inflammation, with increased associated cytokines interleukin (IL)-4, IL-5, and IL-13, maintain and reinforce allergic inflammatory pathways. Current knowledge of the mechanisms of aeroallergen and food allergy have been recently reviewed (Fig 1).[16,17]

On initial exposure to allergen, the respiratory epithelium recruits and activates antigen presenting cells (APCs) including dendritic cells (DCs) to a pro-allergic phenotype potentiated by epithelial-derived cytokines (thymic stromal lymphopoietin, IL-33, and IL-25) and IL-4 and IL-13 from type 2 innate lymphoid cells and basophils. Under the influence of IL-4, APCs present allergen to polarize naive T-helper (T_H) cells to differentiate to T_H2 cells. IL-4 and IL-13 produced from activated T_H2 cells cause B cells to class switch antibody production to make allergen specific IgE (sIgE). This binds to IgE receptors on mast cells, basophils, DCs, and B cells.

Subsequent exposure to allergen cross-links adjacent receptor-bound allergen sIgE on the surfaces of mast cells and basophils, leading to degranulation and the release of histamine, tryptase, leukotrienes, and prostaglandins. The sIgE also forms allergen-IgE complexes that more effectively bind to high- and low-affinity IgE receptors on the surfaces of DCs (FceR1) and B cells (FceR2), respectively, thereby facilitating allergen processing and presentation to T cells, resulting in increased T_H2 T-cell activation and secretion of T_H2 cytokines. Eosinophilic maturation occurs in the presence of IL-5 from T_H2 cells. IL-4 and IL-13 allow eosinophilic infiltration into tissues by actions on the vascular endothelium.

Mechanisms of food allergy have several similarities to allergic rhinitis. Initial sensitization can occur from the mouth, gastrointestinal tract, skin, and rarely the respiratory epithelium.[17] Proteins and peptides in the gut lumen are transported across epithelial cells or directly detected by DC projections into the lumen. The gut is naturally a site of immune tolerance and mechanisms of tolerance such as a high presence of T regulatory cells can be deficient in individuals with allergy.[18] Defects in barrier function and gut microbial composition also can be associated with the risk of developing allergy. The integrity of the skin barrier plays an important part in the development of sensitization to food allergens, especially in childhood.[19]

Mechanisms of immunotherapy have been predominantly studied for aeroallergens. On receiving high-dose allergen in immunotherapy, there is a shift from allergic T_H2 inflammation toward T_H1 inflammation and the generation of suppressive “regulatory” immune cells. There are decreases in levels of IL-4, IL-5, IL-9, and IL-13 and the eosinophil chemotactic protein, eotaxin. This leads to decreases in mast cells, basophils, and eosinophils in the mucosa. There are increases in allergen specific T regulatory cells, T follicular regulatory cells, and B regulatory cells.[16]

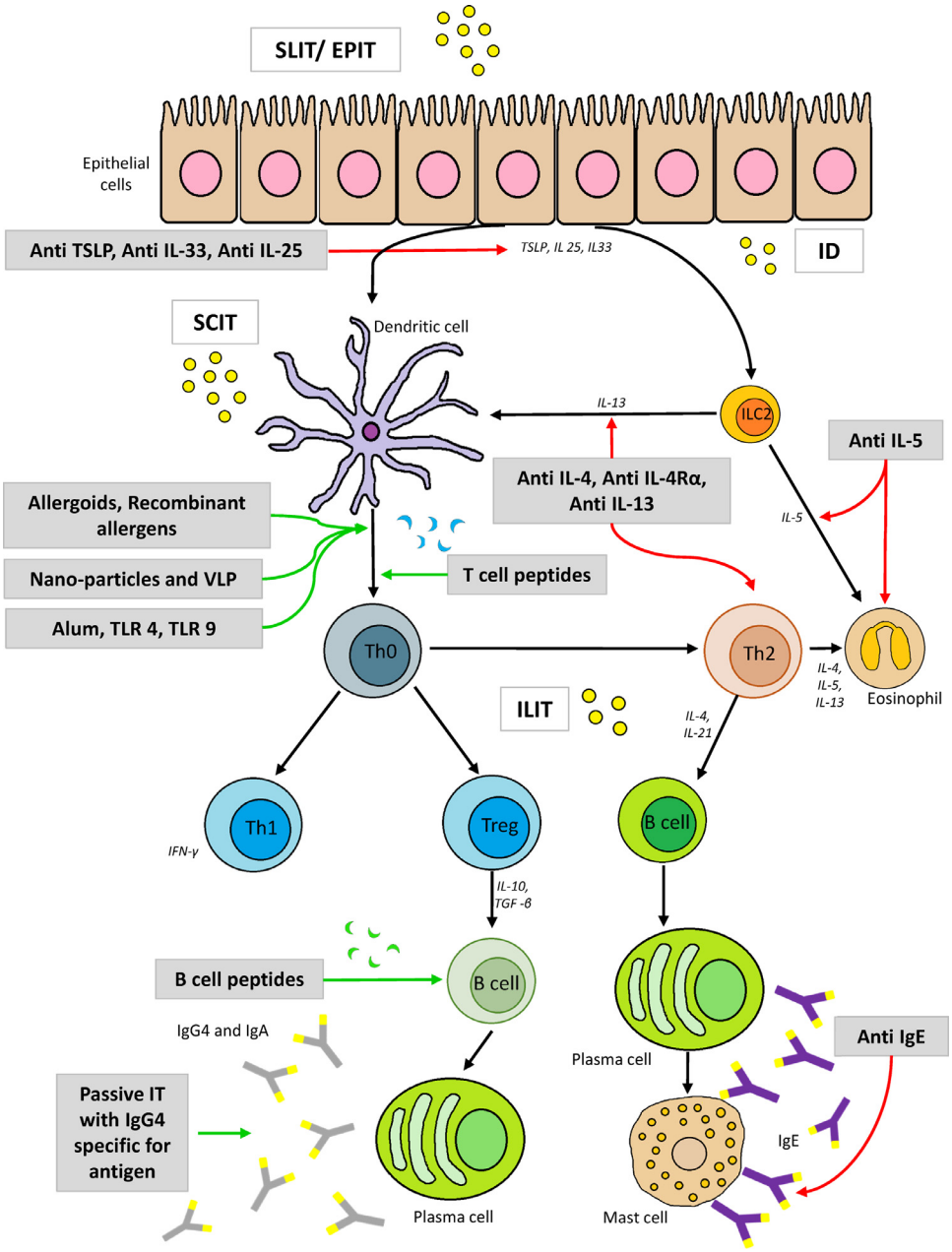

Figure 1. Mechanisms of immunotherapy and mechanistic effects of new approaches. Enhanced effects are illustrated by green arrows and inhibitory effects are illustrated by red arrows. EPIT, epicutaneous immunotherapy; ID, intradermal immunotherapy; Ig, immunoglobulin; IL, interleukin; ILIT, intralymphatic immunotherapy; IT, immunotherapy; MCT, microcrystalline tyrosine; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; Th, T-helper cell; TLR 4, Toll-like receptor 4; TLR 9, Toll-like receptor 9; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin; VLP, virus-like particles.

In terms of antibody production from B cells, after an initial increase on starting immunotherapy, there is a long-term maintained decrease in sIgE. SLIT and SCIT have been shown to increase IgG1, IgG4, and IgA antibodies under the influence of, respectively, interferon-γ, IL-10, and transforming growth factor-β. These antibodies have inhibitory effects on IgE binding and competitive inhibition of allergen binding and IgE complex formation. Blocking IgE receptors on mast cells, basophils, and B cells prevents further antigen presentation to T cells.

Adjuvants

Adjuvants have the potential to modify the pharmacologic and immunologic effects of allergen vaccines. They can modulate allergen delivery, act as a depot, stimulate immune responses, or limit antibody responses to lessen unwanted side effects.[20] Adjuvants can be used in combination with potentially cumulative effects.

Alum and Other Depots

Aluminium salts (alum) in combination with allergens are licensed for SCIT in Europe but not in the United States. Aluminium hydroxide adsorbs the allergen and, in addition to its actions as a depot, has been shown to trigger innate and adaptive immune responses, with inflammasome activation, T-cell activation, and enhanced antibody responses.[21] Although alum can increase T_H2 responses in mouse models with increased IL-4 and IL-5 production in the absence of IL-4 signaling, this is confined to sensitization protocols.[22] In humans, alum has been shown to inhibit established allergic secondary T_H2 responses[23] and enhance T_H1 responses both in vitro and in vivo in the target organ, the nasal mucosa, after challenge,[24]

and during natural allergen exposure.[25] Alum-based allergy extracts given over 3 to 5 years of immunotherapy have been used for more than 100 years and are well tolerated and safe. Although there is a theoretical risk of aluminium deposition leading to systemic side effects, this has not been observed in humans.[20]

Similar depots include calcium phosphate and microcrystalline tyrosine (MCT), which are found naturally and breakdown in the body. They have similar T_H1 stimulatory effects. MCT is currently licensed for use with allergoid treatment[26] (see below) and has been shown to be removed from tissues within 7 to 10 days in animal studies.

Toll-Like Receptor-4 Ligand: Monophosphoryl Lipid A

Toll-like receptors (TLRs) are a type of pattern-recognition receptor found predominantly on APCs that recognize specific highly conserved pathogen constituents to activate innate and adaptive immune pathways. Monophophoryl lipid A (MPL) is derived from bacterial lipopolysaccharide from the cell membrane of gram-negative bacteria and is a ligand of TLR-4. On activation, this generates a T_H1 response.[27]

Pollinex Quattro (Palladin Labs, Inc, St Laurent, Quebec, Canada) is glutaraldehyde-modified allergen (allergoid) immunotherapy combined with MPL and MCT that is available for treatment of grass, tree, and ragweed pollen allergy.[26] MPL and MCT have been shown to work synergistically.[20] It is effective compared with placebo for seasonal symptoms for grass pollen allergy after 4 pre-seasonal injections, which is considerably shorter than conventional immunotherapy.[28] In a double-blinded placebo-controlled randomized trial (n = 124) for grass pollen, there was a 24% decrease in seasonal combined symptom and medication scores compared with placebo.[28] Treatment with 3 consecutive years of pre-seasonal treatment decreased symptoms for up to 5 years after discontinuation. There were no reports of anaphylaxis and most side effects were local, with no increase in sIgE and induction of blocking IgG1 and IgG4 antibodies.[29] However, a phase 3 trial with the same extract involving 1,024 participants found a modest 13% improvement compared with placebo. In the absence of head-to-head studies, there might not be a benefit over current immunotherapy or conventional treatment. A phase 2 trial of MPL combined with grass pollen aqueous SLIT demonstrated a 20% higher rate of negative nasal challenge results compared with placebo or grass pollen SLIT alone.[30] The mechanism was considered likely due to the known high prevalence of TLR-4 receptors on oral DCs.

TLR-9 Ligand: Cytosine-Phosphodiester-Guanine Deoxynucleotide Motifs

Toll-like receptor-9 is predominantly expressed in B cells and plasmacytoid DCs. Cytosine-phosphodiester-guanine motifs are conserved pathogen-associated molecular patterns found in bacterial DNA that are recognized by TLR-9. On activation, this stimulates the innate immune response in T_H1-type fashion.[31] In a promising phase 2 trial, 6 injections given weekly combined with ragweed Amb a 1 (n = 25) suppressed seasonal symptoms scores, with effects lasting to the following season.[32] However, this was not replicated in a large phase 3 trial.[5]

Nanoparticles and Virus-Like Particles

Polymeric biodegradable nanoparticles such as polyesters (synthetic), polysaccharides and polyamides (natural), liposomes, and virus-like particles allow encapsulation of allergens or protein allowing uptake into APCs without IgE binding.[33] Most have not yet progressed to human clinical trials but have shown promising T_H1 immunostimulation in mice and in vitro studies without T_H2 activation.[33]

Lipophilic liposomes enhance lymph node allergen delivery. In a randomized controlled trial of 55 patients with asthma treated with liposome-encapsulated HDM SCIT or liposomes alone for 1 year, 45% had a decrease greater than 60% in medication and symptom scores, with 2 patients in the active group having systemic allergic reactions (1 with grade 3 with generalized urticaria, bronchospasm, and conjunctivitis).[34] Chitosan is a natural polysaccharide derived from crustacean shells that has been shown in murine studies to enhance delivery of allergen across the nasal mucosa.[20] Polylactide-co-glycolic acid is a polyester that also has been tested in murine models and shown to decrease T_H2 responses.

Virus-like particles are derived from viral capsids and can activate the immune system through innate mechanisms that might be independent of T-cell help.[20] They are rapidly taken up by APCs and activate cytotoxic T cells and the complement system. Allergen conjugation with these proteins results in enhanced uptake into the lymphatic system, thereby limiting allergen content in tissues, theoretically minimizing risk of mast cell degranulation. One phase 2 trial in participants with HDM allergy used SCIT with a cytosine-phosphodiester-guanine TLR-9 agonist and allergen encapsulated in virus-like particles.[35] There was an approximate 50% improvement in combined medication and symptoms scores compared with adjuvant alone. Paradoxically, there was a similar improvement in the group that received the virus-like particles and adjuvant alone, an effect that remains unexplained.[36]

Allergen Plus Monoclonal Antibody Strategies

Novel monoclonal antibodies have been developed that selectively target IgE and T_H2 immunity. Although they have been developed as single-agent therapies and shown to be effective in asthma, they have potential in combination with allergen to augment the effects of conventional allergen immunotherapy. The high cost of these antibodies, potential side effects, and requirement for parenteral administration have restricted their widespread use. Unlike allergen immunotherapy, the use of monoclonal antibodies, like conventional pharmacotherapy alone, has not been associated with persistent disease-modifying effects.

Omalizumab is a humanized murine monoclonal antibody that binds to the Fc region of the IgE molecule to form complexes, preventing free IgE binding to high- and low-affinity IgE receptors.[37] It is currently licensed for treatment of moderate to severe asthma and chronic spontaneous urticaria. Omalizumab decreases free IgE, downregulates IgE receptors on mast cells, basophils, DCs, and monocytes, and decreases cellular infiltration of eosinophils, T cells, and B cells.[38]

When given concurrently with immunotherapy, it lessens immunotherapy-associated side effects, increasing tolerability. This allows patients to receive higher doses faster,[39] immunotherapy to be given to higher-risk patients with asthma,[40] and rush protocols.[41] It has shown efficacy in birch,[42] grass,[42,43] ragweed,[41] and perennial allergen cat, dog, and HDM immunotherapy.[39] The combination of immunotherapy with omalizumab has been shown to decrease symptom scores up to 48% vs SCIT alone,[42] with a decrease in rescue medication use during seasonal exposure.[44] Whether the combination of anti-IgE with allergen induces more durable long-term tolerance than allergen alone has not been explored.

Patients undergoing food immunotherapy have high rates of significant side effects including anaphylaxis during treatment.[7] Omalizumab given in conjunction with food immunotherapy for milk[45] significantly decreased adverse events and allowed patients to reach higher doses, although it did not significantly improve response to immunotherapy or improve maintenance of tolerance. Given in conjunction with peanut immunotherapy,[46] patients could tolerate much higher doses of peanut with rapid desensitization.

A recent study looked at whether suboptimal doses of grass pollen immunotherapy alongside anti–IL-4 would be sufficient to decrease the grass pollen intradermal response as a surrogate marker for clinical response. Despite suppression of peripheral T_H2 cells as detected by FluoroSPOT assays, allergen immunotherapy was effective for the 2 groups, with no added advantage by the addition of anti–IL-4.[47] Anti–IL-4 and anti–IL-13 antibodies alone also have not shown significant benefit in asthma.[48] Anti–IL-4 receptor-α (dupilumab) has shown significant efficacy for the treatment of refractory atopic dermatitis[49] and recent studies have confirmed marked improvement in symptoms and decrease in exacerbations in moderate to severe asthma.[50,51] Currently, there are no published studies combining dupilumab and immunotherapy.

Anti–IL-5 mepolizumab and reslizumab and anti–IL-5 receptor-α benralizumab can deplete eosinophilic inflammation and have been shown to lower exacerbation rates in type 2 eosinophilic asthma.[52] Thymic stromal lymphopoietin, a major upstream inducer of T_H2 immunity, shows promise. Anti–thymic stromal lymphopoietin (tezepelumab) has been shown to inhibit bronchoconstriction during late asthmatic responses after allergen challenge in patients with allergic asthma[53] and more recently to lessen asthma exacerbations during 12 months of treatment.[54] Apart from anti–IL-4, no studies to date have compared the combination of these monoclonal antibody approaches with allergen immunotherapy.

Alternative Routes

Sublingual Immunotherapy

In recent years, SLIT has been established as a well-validated alternative to SCIT. Early studies focused on grass pollen-induced rhinoconjunctivitis, whereas recent randomized controlled trials have confirmed the efficacy of SLIT for HDM allergy, including in patients with moderately severe controlled asthma. The recent approval for SLIT tablet treatment for grass pollen, ragweed, and HDM by the US Food and Drug Administration and for Japanese cedar allergy by regulatory authorities in Japan is likely to increase the widespread use of SLIT even further.

Sublingual immunotherapy is taken as a tablet or drops under the tongue continuously for 3 years or starting 2 to 4 months before the season.[5] Several large randomized double-blinded placebo-controlled trials have shown repeated benefit of SLIT tablets over placebo and are presented in Table 1.[55–74] Doses are taken at home and compliance is improved if patients attend 3 monthly follow-up visits during treatment.[3] SLIT is associated with local side effects that include oropharyngeal itching and swelling of the mouth and tongue that is self-limiting. Local side effects generally resolve within 1 to 2 weeks, although it might be sufficiently bothersome to lead to discontinuation of treatment in approximately 5% to 8% of patients. There is a very low incidence of systemic side effects such that SLIT is recognized as an effective and safer alternative to SCIT that is suitable for self-administration after an initial supervision of the first dose followed by 30 minutes of observation by a clinician.

Sublingual immunotherapy is effective for seasonal[75] and perennial[5] allergies. A recent indirect meta-analysis compared SLIT with current pharmacologic treatment.[76] Although head-to-head controlled studies are required for confirmation, the results suggested that SLIT is at least as effective as currently available pharmacotherapy. Indirect comparative analyses also have suggested that SCIT might be slightly more effective than SLIT for grass pollen immunotherapy,[10] whereas there might be a slight advantage for SLIT over SCIT for HDM allergy. In a recent direct comparison that used nasal allergen challenge as a surrogate clinical end point, grass pollen SCIT was more effective than SLIT after 1 year, whereas the treatments were equally effective after the second year of treatment.[77] The considerable heterogeneity between studies is such that treatment decisions should be based on evidence for individual products that are available and accessible in different countries.[5]

Intralymphatic Immunotherapy

Injecting antigen directly into lymph nodes is likely to enhance antigen presentation and subsequent generation of local T- and B-cell responses. This process has been shown to be safe in animal studies and to generate tolerogenic immune responses while not increasing type 2 immunity.[78]

A randomized open-label trial of alum-absorbed whole grass pollen extract for SCIT over 3 years (n = 54) compared with just 3 doses of intralymphatic immunotherapy (ILIT) over 2 months (n = 58) showed a persistent effect of ILIT during the entire 3 years. There were fewer side effects with ILIT (6 grade 1–2 reactions vs 18 grade 1–2 reactions and 2 grade 3 reactions with SCIT) and significantly improved compliance (32 of 54 completed SCIT compared with 58 of 58 who completed ILIT). Results showed slightly less medication use in the ILIT group, with similar decreases in symptom score on nasal provocation and during the pollen season.[79] ILIT decreased the total allergen dosage by more than a 100-fold.[79] However, the low level of compliance in the SCIT group and the open-label nature of the study make these results difficult to interpret. Smaller placebo-controlled trials of ILIT have shown benefit for bee venom,[80] tree pollen,[81] and cat[82] allergy. Conversely, a randomized double-blinded placebo-controlled trial showed no significant effect of grass pollen ILIT compared with placebo[83] for combined symptom and medication scores during the season. Although ILIT has been shown to be relatively painless,[79] the technique requires specialist skills, experience, and ultrasound guidance of injections. Individual products and dose and timing of injections are yet to be determined.[83]

Epicutaneous Immunotherapy

The epidermis is avascular and has a large number of APCs. Epicutaneous immunotherapy aims to increase local antigen presentation while preventing systemic absorption of allergen. Allergen is applied through patches that are kept on the skin for several hours. The skin is prepared with adhesive tape to strip the epidermis, which also can activate keratinocytes, increase allergen exposure, and potentially increase DC responses.[84] The process involves no needles and aims to improve compliance, especially in children.

In a placebo-controlled randomized trial,[84] grass pollen extract in petroleum was applied to the skin stripped with adhesive tape (n = 48) weekly for 6 months pre-seasonally. There was a 48% improvement in seasonal symptom scores in the first year (placebo 10%) but no significant difference for combined treatment and medication scores. Two further randomized controlled trials achieved similar results, although at the effective higher doses there were high rates of local irritation and eczema and occasional systemic allergic side effects, such that there was no obvious advantage over currently available SCIT.

Peanut epicutaneous immunotherapy has been shown to be safe.[85] A phase 2b randomized placebo-controlled study[86] for 1 year continued as an open-label study for 2 years. Food challenge was used to assess tolerance (tolerance was defined as the ability to tolerate ≥1,000 mg of protein and/or 10 times the original eliciting dose). Two hundred twenty-one children and adults were randomized initially using a variable dose patch followed in the open-label period with 250-μg patches daily. The treatment effect was 25% over placebo for all age groups, with a significant difference seen in children that was not seen in the adolescent and adult groups. Adverse events were generally mild local reactions in half the participants, with 1 recorded case

Table 1
Sublingual Immunotherapy Tablets for Allergic Rhinitis

Allergen	Study	Extract	Length	Groups (n)	Design	Efficacy	Safety
Grass	Durham et al, 2006[55]	*P pratense*	18 wk	2,500 SQ (n = 136), 25,000 SQ (n = 139), 75,000 SQ (n = 294), placebo (n = 286)	RDBPCT 8 wk pre- and co-seasonal	16% decrease in SS and 28% decrease in MS with 75,000 SQ vs placebo	local reactions in 53%, local pruritus, edema, throat irritation; 1 serious TRAE (uvula edema)
	Dahl et al, 2006[56]; Durham et al, 2012[57]	*P pratense*	3 y, follow-up 2 y	Dahl et al, 2006[56]: 75,000 SQ (n = 316), placebo (n = 318); Durham et al, 2012[57]: 75,000 SQ (n = 189), placebo (n = 162)	RDBPCT 1 y initially, extended trial for 3 y and blinded follow-up off treatment for 2 y	30% decrease in SS, 38% decrease in MS vs placebo at 1 y; 27% decrease in weighted CSMS at 5-y follow-up; 33% average decrease in CSMS over 5-y study period	local reactions in up to 46%, oral pruritus (44%), mouth edema (19%), throat irritation (13%), ear pruritus (12%); no serious TRAE or serious allergic reactions
	Didier et al, 2007[58]	*A odoratum*, *D glomerata*, *L perenne*, *P pratense*, *P pratensis*	4 mo pre- and co-seasonal	100 IR (n = 157), 300 IR (n = 155), 500 IR (n = 160), placebo (n = 156)	RDBPCT	3.9% decrease in SS for 100 IR; 37.0% decrease in SS for 300 IR; 35.1% decrease in SS for 500 IR	TEAEs in up to 68.8% (placebo 48.7%); mainly mild to moderate local reactions, oral pruritus; 3 patients with SAE, none drug related; 8 systemic allergic reactions (rhinitis 8, urticaria 2)
	Didier et al, 2011[59]; Didier et al, 2015[60]	*A odoratum*, *D glomerata*, *L perenne*, *P pratense*, *P pratensis*	3 y, follow-up 2 y	300 IR 4 mo (n = 207), 300 IR 2 mo (n = 207), placebo (n = 219)	RDBPCT 2 or 4 mo pre- and co-season and follow-up after treatment	34.8−37.7% decrease in adjusted CSMS; 28% decrease with 4-mo group at follow-up	local reactions in 57% in year 1, decreased to 36% in year 3; mainly oral pruritus, throat irritation, mouth edema; 3 severe TRAEs
	Maloney et al, 2014[61]	*P pratense*	16-wk pre- and co-seasonal; 1 season	75,000 SQ (n = 749), placebo (n = 414)	RDBPCT in adults and children	23% decrease in CSMS in active vs placebo; 29% decrease in peak season	local reactions; throat irritation 23% and oral pruritus 19% in active group (3.5% and 2.7% in placebo group); 3 systemic reactions; 4 participants required epinephrine
	Mösges et al, 2017[62]	*P pratense*, *P pratensis*, *H lanatus* carbamylated allergoid	84 d pre-seasonal	300 UA (n = 36), 600 UA (n = 43), 1,000 UA (n = 39), 2,000 UA (n = 37)	RDBACT	maximum 59% of participants had negative response to CPT at 1,000 UA	mild to moderate TRAE in up to 31.6%; no serious TRAEs
Birch	Nony et al, 2015[63]	rBet v 1 purified recombinant allergen	4 mo pre- and co-seasonal	12.5 μg (n = 123), 25 μg (n = 120), 50 μg (n = 120), placebo (n = 120)	RDBPCT	17.1% decrease in CSMS for 12.5 μg vs placebo; 17.7% decrease in CSMS for 25 μg vs placebo; 17.0% decrease in CSMS for 50 μg vs placebo	TEAE in up to 87.5% (29.8% placebo); mainly local oral pruritus, mouth edema, throat pruritus, ear pruritus; 8 SAEs, none drug related
	Mäkelä et al, 2018[64]	*B verrucosa*	6 mo (start 16 wk before season)	0.5 U (n = 93), 1 U (n = 90), 2 U (n = 89), 4 U (n = 92), 7 U (n = 88), 12 U (n = 97), placebo (n = 88)	RDBPCT	per-protocol analysis of 7-U group showed 30% decrease vs placebo; no significance for symptom or medication scores in full analysis, all groups	local reactions in up to 81% (31% placebo); oral pruritus, throat irritation, ear pruritus, mouth edema; 1 participant in 1-U group required epinephrine
Ragweed	Creticos et al, 2013[65]	*A artemisiifolia*	1 y	1.5 U (n = 197), 6 U (n = 195), 12 U (n = 194), placebo (n = 198)	RDBPCT	27% decrease in CSMS for 12 U vs placebo	TEAEs in up to 54% (placebo 23%); 73% local reactions; severe TEAE in 12 treatment subjects (2 placebo)
	Nolte et al, 2013[66]	*A artemisiifolia*	1 y	6 U (n = 152), 12 U (n = 160), placebo (n = 166)	RDBPCT	26% decrease in CSMS for 12 U vs placebo	AE in up to 68.4% (placebo 28.2%); mainly local, throat irritation, swollen tongue, tongue pruritus, oral pruritus
HDM	Bergmann et al, 2013[67]	*D pteronyssinus*, *D farinae*	1 y, follow-up 1 y	300 IR (n = 170), 500 IR (n = 169), placebo (n = 170)	RDBPCT	17.9% decrease in CSMS for 300 IR vs placebo; 20.2% decrease in CSMS for 500 IR vs placebo; change maintained at 1 y off treatment	AEs in up to 88% (80% placebo); mild to moderate local reactions; oral pruritus, throat irritation, mouth edema; 9 SAEs, not treatment related

(*continued*)

Table 1 (*Continued*)

Allergen	Study	Extract	Length	Groups (n)	Design	Efficacy	Safety
	Mosbech et al, 2015[68]	*D pteronyssinus*, *D farinae*	1 y	1 SQ (n = 117), 3 SQ (n = 131), 6 SQ (n = 134), placebo (n = 107)	RDBPCT (AR symptoms in patients with AA)	17.4% decrease in CSMS for 1 SQ vs placebo; 26.0% decrease in CSMS for 3 SQ vs placebo; 28.8% decrease in CSMS for 6 SQ vs placebo	TEAEs up to 67% (57% placebo); oral pruritus, URTIs and asthma more frequent in treatment group; 4 severe TRAEs
	Demoly et al, 2016[69]	*D pteronyssinus*, *D farinae*	1 y	6 SQ (n = 336), 12 SQ (n = 318), placebo (n = 338)	RDBPCT	18% decrease in CSMS for 6 SQ vs placebo; 20% decrease in CSMS for 12 SQ vs placebo	oral pruritis 20%, throat irritation 14%, mouth oedema 8% in treatment groups; 1 subject received epinephrine for mild laryngeal edema
	Nolte et al, 2016[70]	*D pteronyssinus*, *D farinae*	1 y	12 SQ (n = 741), placebo (n = 741)	RDBPCT	17% decrease in CSMS vs placebo	local reactions in up to 67%; 1 non-serious systemic reaction; 3 subjects administered epinephrine
	Okamoto et al, 2017[71]	*D pteronyssinus*, *D farinae*	1 y	300 IR (n = 315), 500 IR (n = 296), placebo (n = 316)	RDBPCT	18.2% decrease in SS for 300 IR vs placebo; 13.1% decrease in SS for 500 IR vs placebo	local reactions in up to 73.1% (18.6% placebo); throat irritation, mouth edema, oral pruritus, and ear pruritus most common; 16 SAEs, none treatment related
	Hüser et al, 2017[72]	*D pteronyssinus*, *D farinae* allergoid tablet	84 d	3,000 UA (n = 26), 2,000 UA (n = 26), 1,000 UA (n = 27), 300 UA (n = 23), placebo (n = 29)	RDBPCT	88.5% of participants in 2,000-UA/d group had improved CPT tolerance vs 75% in placebo group	local reactions occurred in 3.4% in placebo group and 7.7% in 2,000-UA group; 20 TRAEs of mild severity were observed (local 9, systemic 6, unspecific 3, and unclassified 2)
Recent examples of sublingual immunotherapy tablets for allergic asthma							
Grass	Valovirta et al, 2018[73]	*P pratense*	3 y, follow-up 3 y	75,000 SQ (n = 398), placebo (n = 414)	RDBPCT in children 5–12 y, ARC to grass, no asthma; asthma development prevention study	no difference in time to asthma development; relative risk decrease 29.4% in asthma symptom and medication with 75,000 SQ vs placebo	TRAE in 15% treatment vs 4% placebo; no SAEs
HDM	Virchow et al, 2016[74]	*D pteronyssinus*, *D farinae*	1 y	6 SQ (n = 275), 12 SQ (n = 282), placebo (n = 277)	RDBPCT in allergic asthmatics with ICS decrease	9–10% decrease in asthma exacerbation risk at 6 mo, no dose differences	TRAE in up to 46% HDM group vs 17% placebo; no SAEs

Abbreviations: AE, adverse event; AR, allergic rhinitis; CPT, conjunctival provocation challenge; CSMS, combined symptom and medication score; HDM, house dust mite; ICS, inhaled corticosteroid; IR, index of reactivity; MS, medication score; RDBACT, randomized double-blinded active controlled trial; RDBPCT, randomized double-blinded placebo-controlled trial; SAE, serious adverse event; SS, symptom score; SQ, standardized quality; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; URTI, upper respiratory tract infection.

of anaphylaxis. Epicutaneous immunotherapy for milk has been trialed in a small pilot study, with no firm conclusions.[87]

Intradermal Immunotherapy

Intradermal allergen injections in doses known to illicit late skin responses, when given repeatedly at 2- to 4-week intervals, suppressed late cutaneous allergic responses and induced allergen-specific IgG antibodies.[88] However, a randomized controlled phase 2b trial of repeated pre-seasonal low-dose intradermal grass pollen allergen (containing 6 ng of major allergen Phl p 5) was ineffective in improving seasonal outcomes, with a worsening of nasal symptoms compared with placebo and an augmented T_H2 response at the site of the intradermal injection.[89] These data suggested that intradermal allergen has the potential to sensitize and tolerize against inhalant allergens and therefore is not recommended.

Hypoallergenic Variants

Changing or modifying allergens for immunotherapy by physical or chemical alteration of tertiary protein structure or by selection of non-IgE reactive epitopes aims to maintain or enhance immunogenicity to generate tolerogenic responses while preventing allergenicity.

Allergoids

Allergoids are allergens physically or chemically modified, for example, by treatment with glutaraldehyde. Modification of the tertiary structure of allergens aims to decrease the ability to cross-link IgE. Shorter linear T-cell epitopes are preserved, thereby retaining immunogenicity. Several allergoids have shown efficacy in placebo-controlled trials, including for ragweed,[90,91] grass,[92–94] tree pollen,[95,96] and mite[97–99] allergy.

A phase 3 trial[100] (n = 174) of a 6-grass pollen mix, formaldehyde-treated, alum-adsorbed allergoid showed a 26.6% decrease in combined seasonal symptom medication scores after 1 year compared with placebo. Five mild to moderate late systemic reactions were observed in the active group compared with 2 in the placebo group. There were no episodes of anaphylaxis or serious adverse events.

There are few direct comparative studies between allergens and allergoids.[92,101] Quantification of modified allergens is complex such that there might be batch-to-batch variation, making comparison of the relative hypoallergenic effects with whole allergen difficult, in vitro and in vivo.[102]

Recombinant Allergens

The manufacture of recombinant allergens directly from copy DNA sequences produced in bacterial strains has allowed differentiation of individual allergenic components from whole naturally occurring allergens. There are panels of major and minor allergen components for most inhalant and food allergens. This has enabled a dramatic improvement in precision for allergy diagnosis[103] and treatment and opened up the potential for individualized “tailor-made” allergen immunotherapy in the future. The process also has allowed the identification of precise T-cell and B-cell specific peptides.[104]

A phase 2 trial of a mixture of 6 grass pollen recombinant allergens was effective in seasonal allergic rhinitis and accompanied by increases in allergen-specific IgG and, in contrast to whole allergen extract immunotherapy, no increases in specific IgE.[105] A phase 3 randomized controlled trial[106] of recombinant birch allergen Bet v 1 was shown to be effective in seasonal allergic rhinitis, with an improvement in medication and symptom scores of approximately 50%. However, the efficacy and incidence of side effects were no different from those of parallel groups treated with the synthetic natural protein or the whole Bet v 1 extract.[106]

There are several small trials using recombinant cat,[107,108] peanut,[109] and fish[110,111] allergens. The current state of development is that several have had high rates of allergic side effects or minimal clinical effects. No recombinant allergens are currently licensed and further trials for individual recombinant allergens are necessary.[103]

T-Cell Peptide Immunotherapy

T-cell epitopes are HLA-restricted, discreet, linear peptides of shortened length (generally 10–20 amino acids) that are recognized by the T-cell receptor. They have no conformational structure and do not cross-link cell-bound IgE.[112] When presented in the absence of costimulation, peptides can induce T-cell unresponsiveness (anergy) to the whole allergen.[113,114] Alternative mechanisms of tolerance induced by peptides include T-cell clonal deletion of pathogenic allergen-specific T cells[115,116] and alteration of the dominant T-cell phenotype in favor of regulatory T cells. The absence of B-cell epitopes in such vaccines could explain their lack of impact seen on humoral antibody responses compared with whole allergen immunotherapy.[117]

Several phase 2 studies have measured responses in an environmental exposure chamber. In a phase 2b trial,[118] 282 subjects were randomized to 3 different dosing schedules of grass pollen peptides or placebo with measurements before and at 25 weeks by environmental exposure chamber. Eight injections every 2 weeks led to a 42% decrease in elicited symptom scores. There were no increases in side effects compared with placebo. Similar results have been achieved with studies involving cat[119] and HDM[120] peptides at phase 2, but with marked variability in the doses and schedules used. However, 2 large phase 3 field studies involving T-cell peptide immunotherapy for cat and HDM allergy[121,122] have been reported as not showing efficacy over placebo and further development of these peptides has been halted. T-cell peptide immunotherapy for peanut allergy is at the stage of epitope and peptide discovery.[123]

Contiguous overlapping peptides are longer sequences of amino acids that encode potentially all T-cell epitopes but have disrupted IgE epitopes to prevent allergen binding.[103] One study of birch pollen contiguous overlapping peptide immunotherapy showed positive results at phase 2.[124] A recent phase 2b dose-finding study of birch pollen peptides involving 421 subjects and short-course pre-seasonal injections showed a statistically significant but modest treatment effect (7%) over placebo at the highest dose of immunotherapy.[125]

An alternative approach has been the use of protein hydrolysis of whole allergens to produce medium-chain length peptides with decreased allergenicity that induce T- and B-cell responses, potentially providing more epitopes than synthetic allergen sources. Hydrolyzed rye grass allergen peptides were shown to be effective with shortened courses.[126] A recent large dose-finding phase 2b trial[127] (n = 554) demonstrated that 8 pre-seasonal subcutaneous injections given during 4 visits over 3 weeks resulted in an 18% decrease in combined medication and symptom scores during the entire season compared with placebo. Rates of local and mild systemic side effects were similar to those observed with conventional SCIT and so the major advantage appears to be a shortened course compared with usual SCIT.

B-Cell Peptide Immunotherapy

B-cell peptide immunotherapy aims to generate protective humoral antibody responses independent of IgE generation. In one approach, non-IgE reactive peptides were developed and bound to a carrier protein unrelated to the allergen. These conjugates harness alternative T-helper responses because of the carrier protein, thereby generating protective allergen-specific IgG responses without IgE stimulation.[128] BM-32 is a promising recombinant fusion protein in

Table 2
Summary of New Approaches to Immunotherapy

		Mechanistic Concept	Current stage of development	Efficacy (example studies)	Safety
Alternative delivery methods	epicutaneous	increased APCs in epidermis aims to increase allergen presentation	phase 3 for peanut, phase 2 for grass, phase 1 for milk	Senti et al, 2015[84]: grass (n = 48), RPCT, 6 mo pre-seasonal (5 grass, 6 grass extract in petroleum); Tx 38% improvement over placebo	Senti et al, 2015[84]: grass: localized skin reactions in >60%; 6 systemic reactions after skin abrasion (23%), 1 systemic reaction after tape stripping (0.4%)
				Sampson et al, 2017[86]: peanut (n = 221), RDBPCT; 25% improvement on DBPCFC after 250-μg patch daily for 12 mo	Sampson et al, 2017[86]: peanut: up to 96.4% TRAEs (48.2% placebo); local skin reactions most common; 20 SAEs, none related to study drug
				Dupont et al, 2010[87]: milk (n = 19), RDBPCT, no significance in tolerated dose on OFC	Dupont et al, 2010[87]; local AEs in 4/10 treatment vs 2/8 placebo. Local eczema higher in treatment group
	intralymphatic	direct delivery of lower doses allergen to lymph node	phase 2 for grass pollen, bee, tree pollen, and cat allergy	Senti et al, 2008[79]: grass (n = 165), RCT, 3 injections (1,000 SQ alum absorbed grass pollen extract) vs SCIT (alum absorbed grass pollen extract); similar decrease in symptoms	Senti et al, 2008[79]: no increase in AEs vs placebo or SCIT
				Senti et al, 2012[82]: cat (n = 20), RDBPCT, 3 injections, MAT-Fel d 1 (recombinant fusion protein); nasal tolerance on NPT increased by factor of 74	Senti et al, 2012[82]: cat: mild to moderate lymph nodal swelling in 3 placebo vs 4 treatment subjects (nonsignificant)
Hypoallergenic allergens	allergoids	physically or chemically modified whole allergen to decrease IgE binding while preserving immunogenicity	in clinical use for grass pollen and tree pollen; HDM under development	Corrigan et al, 2005[100]: grass (n = 174), RDBPCT, 6 grass pollen-mix formaldehyde treated alum adsorbed allergoid SCIT, 26.6% improvement in CSMS vs placebo	Corrigan et al, 2005[100]: local reactions in 19.5% treated patients, 6.4% systemic late in treated group (2.6% placebo); no serious TRAEs
				Mösges et al, 2017[62]: grass (n = 158), RDBT, *P pratense*, *P pratensis*, *H lanatus* carbamylated allergoid SLIT, maximum 59.0% negative response to CPT at 1,000 UA/d	Mösges et al, 2017[62]: TRAE in up to 31.6%; no serious TRAEs
				Hüser et al, 2017[72]: HDM (n = 131), RDBPCT, carbamylated monomeric *D pteronyssinus* and *D farinae* allergoid SLIT, 88.5% in 2,000-UA/d group had improved allergic severity (75% in placebo group)	Hüser et al, 2017[72]: local reactions in 7.7% in 2,000-UA group (3.4% in placebo group); 20 TRAEs of mild severity
	recombinant allergens	manufactured directly from cDNA, allows identification of relevant hypoallergenic allergens in immunotherapy	phase 2 for grass, birch pollen (rBet v 1) and Mal d 1	Jutel et al, 2005[105]: grass (n = 62), RDBPCT, SCIT 5 grass pollen allergens (Phl p 1, Phl p 2, Phl p 5a, Phl p 5b, Phl p 6) SCIT, nonsignificant difference in CSMS of 38.9% vs placebo	Jutel et al, 2005[105]: 10.7% injections TRAE (5.9% placebo), 91% local; 7 systemic reactions (0.96% injections), no anaphylaxis
				Pauli et al, 2008[106]: birch (n = 134), RDBPCT, 4 groups on SCIT; recombinant Bet v 1, natural Bet v 1 (purified from *B verrucosa*), *B verrucosa* extract, placebo; 48–58.3% improvement vs placebo, no difference between rBet v 1 and nBet v 1 or whole extract	Pauli et al, 2008[106]: 79 TEAEs in rBet v 1 group (46 in placebo); no serious TEAE, mainly local reactions; no significant difference between groups
				Kinaciyan et al, 2018[135]: apple (n = 60), RDBPCT, SLIT rMal d 1, rBet v 1 or placebo; rMal d 1 allowed 70% of participants to tolerate higher rMal d 1 sublingual challenge, 25% tolerated highest dose (rBet v 1 44%, placebo 42%)	Kinaciyan et al, 2018[135]: oral and ear pruritus in 95% of treatment groups (55% placebo) improved over time; no severe or systemic AEs
	T-cell peptides	non-IgE reactive amino acid sequences recognized by T cells	phase 3 for HDM and cat immunotherapy	Circassia[121]: HDM no change in CSMS vs placebo (unpublished)	
				Couroux et al, 2015[119]: cat (n = 86), RDBPCT; ID 7 synthetic T-cell epitopes from Fel d 1; significant decrease in nasal SS at EEC challenge	Couroux et al, 2015[119]: cat; no SAEs, more AEs in placebo group; no AEs related to treatment
				Circassia[122]: Fel d 1; no change in CSMS vs placebo (unpublished)	
	contiguous overlapping peptides	all possible T-cell epitopes with disrupted IgE epitopes	phase 2 for birch pollen	Spertini et al, 2016[124]: birch (n = 239), RDBPCT; SC Bet v 1 COPs at 2 doses; 50-μg dose 26% decrease CSMS vs placebo	Spertini et al, 2016[124]: late pulmonary symptoms 55% at higher 100-μg dose, 2 serious TRAEs, WAO grade 3 reactions
	B-cell peptides	non-IgE reactive peptides bound to carrier protein	phase 2 for grass	Niederberger et al, 2018[130]: grass (n = 181), RDBPCT; 4 recombinant fusion protein peptides from Phl p 1, Phl p 2, Phl p 5, Phl p 6 with hepatitis B–derived preS; 22% had decreased CSMS vs placebo but not statistically significant	Niederberger et al, 2018[130]: 55.8% local reaction treatment groups (52.8% placebo); 7.1% EAACI grade 2 reactions in treatment groups (1.9% placebo)

(*continued*)

Table 2 (*Continued*)

		Mechanistic Concept	Current stage of development	Efficacy (example studies)	Safety
	hydrolyzed peptides	hydrolysis whole allergen, epitopes for T and B cells, decreased IgE binding	phase 2 for grass	Mösges et al, 2018[127]: grass (n = 554), RDBPCT; 8-wk pre-seasonal SC peptide hydrolysates of *L perenne*; 17.9% improvement in CSMS vs placebo	Mösges et al, 2018[127]: 10.5% grade 1 reactions, 4 (1.1%) grade 2 reactions
	passive immunotherapy	anti-allergen IgG antibodies	phase 1 for cat	Orengo et al, 2018[133]: cat (n = 73), RDBPCT; single SC injection; 23% improvement over placebo at day 85 on NAC	Orengo et al, 2018[133]: no increased AEs vs placebo
Adjuvants	depots	adsorbs allergen, triggers innate and T_H1 responses	alum, MCT, and other depots are in clinical use	Leynadier et al, 2018[136]: n = 29, calcium phosphate + 5-grass pollen extract effective vs placebo for CSMS; Pollinex combined with l-tyrosine (see below)	Leynadier et al, 2018[136]: local injection site reactions in 37.5% of treatment group, none in placebo; alum: very rare local nodules, potentially granulomata
	TLR agonists	TLR-4 and TLR-9 agonists increase T_H1 immune responses and/or induce Treg responses	MPL (TLR-4 agonist) for grass and tree, HDM under development; phase 3 for CpG (TLR-9 agonist) for ragweed	Drachenberg et al, 2001[28]: n = 141, grass + MPL + l-tyrosine SCIT, RDBPCT; 45% improvement in CSMS vs placebo	Rosewich et al, 2010[137]: postmarketing surveillance studies; no anaphylaxis, mainly localized effects or mild systemic effect
				Creticos et al, 2006[32]: n = 25, RDBPCT, standard extract of *A artemisiifolia* and CpG motif; 2/3 decrease in SS in season vs placebo; same drug failed phase 3 (unpublished)	Creticos et al, 2006[32]: 63% local injection site reactions, no autoimmunity, 54% AEs in treatment, 46% in placebo
				DuBuske et al, 2011[138]: grass (n = 1,028), RDBPCT, modified allergens from 13 grasses, tyrosine adsorbed with adjuvant MPL SCIT, 13.6% improvement in CSMS vs placebo	DuBuske et al, 2011[138]: 70.2% AEs in treatment group (47.0% placebo); 1 severe TRAE
	nanoparticles	particles that encapsulate allergen, enhance delivery, prevent IgE binding	phase 1 for liposomes with HDM	Basomba et al, 2002[34]: liposomes + HDM SC (n = 55), RDBPCT; 45.8% achieved decrease in CSMS by ≥60% (12% placebo achieved similar decrease in CSMS)	Basomba et al, 2002[34]: 1 WAO grade 2 and 1 WAO grade 3 reaction in treatment group
	VLPs	derived from viral capsids, stimulate innate mechanisms	phase 1 for trial with HDM, phase 1 without allergen	Senti et al, 2009[36]: open study, no placebo (n = 21); HDM combined with QbG10 VLP given SC; increased tolerance of CPT and decreased CSMS	Senti et al, 2009[36]: 57.1% had AEs, mild in 59%; no severe AEs; 6 of 21 patients had asthmatic symptoms
				Klimek et al, 2011[35]: n = 299, RDBPCT; TLR-9 CpG inside VLP, no allergen, given SC; CSMS decrease of 48% in high-dose treatment group	Klimek et al, 2011[35]: mild to moderate local injection site reactions in 18% of treatment group; erythema, lymphadenopathy, influenza higher in treatment group
Monoclonal antibodies	allergen + anti-IgE (omalizumab)	binds free IgE, decreases allergic side effects and increases tolerability	phase 2 for in grass, ragweed, birch, HDM, cat, dog, milk, and peanut	Kuehr et al, 2002[42]: n = 221, RDBPCT; birch and grass pollen SCIT + anti-IgE: 48% decrease in CSMS over SCIT alone	Kuehr et al, 2002[42]: no SAEs, no difference in localized AEs; TRAEs 25% in SCIT + anti-IgE (16% in SCIT + placebo)
				Kopp et al, 2009[43]: n = 140, RDBPCT; depigmented glutaraldehyde polymerized grass pollen allergoid + anti-IgE SCIT, 39% decrease in CSMS over SCIT alone	Kopp et al, 2009[43]: fewer local reactions in anti-IgE group vs placebo
				Wood et al, 2016[45]: n = 57, RDBPCT, milk oral immunotherapy + anti-IgE; increased tolerance of milk on OFC and sustained unresponsiveness but did not reach statistical significance	Wood et al, 2016[45]: 91.5% anti-IgE treated had symptom-free doses (73.9% placebo), improvement across mild and moderate severity reactions
	allergen + anti−IL-4		phase 2 for grass pollen immunotherapy + anti−IL-4	Chaker et al, 2016[47]: n = 37, suboptimal grass pollen SCIT + anti−IL-4, RDBPCT; no difference in late-phase skin response	Chaker et al, 2016[47]: no difference in incidence of AEs; no serious AEs
	allergen + anti−IL-13, anti−IL-4Ra, anti-TSLP	block other key cytokines in generation of T_H2 response	no trials with other monoclonals	N/A	N/A

Abbreviations: AE, adverse events; APCs, antigen presenting cells; COPs, contiguous overlapping peptides; CpG, cytosine-phosphodiester guanine; CPT, conjunctival provocation testing; CSMS, combined symptom and medication scores; DBPCFC, double-blinded placebo-controlled food challenge; EAACI, European Academy of Allergy and Clinical Immunology; EEC, environmental exposure chamber; HDM, house dust mite; ID, intradermal; IgE, immunoglobulin E; IL, interleukin; MCT, microcrystalline tyrosine; MPL, monophophoryl lipid A; N/A, not applicable; NPT, nasal provocation test; OFC, oral food challenge; preS, surface protein derived from surface antigen of hepatitis B; RCT, randomized controlled trial; RDBT, randomized double-blinded trial; RDBPCT, randomized double-blinded placebo-controlled trial; RPCT, randomized placebo-controlled trial; SAE, serious adverse event; SC, subcutaneous; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SQ, standardized quality; SS, symptom score; T_H1, T-helper cell type 1; T_H2, T-helper cell type 2; TLR, toll-like receptor; TRAE, treatment related adverse events; Treg, regulatory T cell; Tx, treatment; VLP, virus-like protein; WAO, World Allergy Organization.

which grass pollen B-cell epitopes have been fused with hepatitis pre-S protein. A recent environmental chamber study reported modest benefit compared with placebo, although this did not reach statistical significance.[129] There was a pronounced protective humoral IgG response without generation of allergen specific IgE. A recent double-blinded placebo-controlled study of 181 patients with variable doses of 3 pre-seasonal injections over 2 seasons did not reach statistical significance compared with placebo for combined medication and symptom scores for any of the doses, although there was benefit for quality of life and asthma scores.[130]

Passive Immunotherapy

In 1935, Cooke et al[131] originally showed that intradermal injection of serum from patients having undergone ragweed immunotherapy afforded localized protection against ragweed skin prick test reactions in passively sensitized individuals. Transfer of blocking antibodies was considered responsible for this passive transfer of immunity. Although levels of allergen specific IgG generated after immunotherapy do not correlate to clinical response, the blocking capabilities of these antibodies and their ability to compete with IgE binding correlates significantly better than overall specific IgG responses that are detected by ImmunoCAP (Phadia AB, Uppsala, Sweden).[132] A recent phase 2 study involved administration of a single dose of a combination of 2 fully human anti–Fel d 1 IgG4 in patients with cat allergy. Responses in the 73 randomized participants were monitored by repeated nasal allergen challenges over 3 months. There was a consistent greater than 30% change compared with placebo in the total nasal symptom score at 0 to 1 hour after nasal challenge that was accompanied by IgE-blocking activity detectable in serum and nasal fluid that persisted for at least 85 days after the single injection.[133,134] This approach caused minimal side effects that were no different from placebo treatment. It is likely that this passive immunotherapy might be applicable to other allergens in which there is a dominant major allergen, for example, in ragweed, birch, or Japanese cedar allergy.

Conclusions

Subcutaneous immunotherapy is effective and safe in safe hands. New approaches have been promising in development, although a demonstrable improvement has yet to be shown in the induction and duration of tolerance over that obtainable by conventional SCIT. SLIT is a well-proved and safer alternative that is in widespread clinical use. Intralymphatic and epicutaneous immunotherapies need further optimization of products and dosage schedules for maximal efficacy while avoiding side effects. Novel approaches are presented in Table 2.[135–138]

MPL is an adjuvant that has been shown to significantly shorten the duration of immunotherapy for grass and tree pollen and is in current use, but not currently registered. Other “allergen plus” strategies such as the combination with virus particles, nanoparticles, and immune modifiers, including monoclonal antibodies, remain in development. Hypoallergenic T-cell peptide vaccines have shown promise in phase 2 trials, although thus far this promise has not translated into clinical benefit in phase 3 trials. The combination of omalizumab with allergen lessens allergic side effects but does not improve efficacy.

No hypoallergenic allergen variant has currently been developed that has been shown to be more effective and safer than whole allergen extracts. Recombinant gene technology has allowed better characterization of allergen structure and knowledge of the precise epitopes involved in allergic responses. In birch allergy, in which a large number of people are sensitized to a single dominant allergen, the recombinant allergen Bet v 1 represents a pure and standardized product that has similar efficacy as the crude extract, although without other clear advantages over and above the use of the crude extract. Passive immunotherapy has recently been highlighted as a viable option for cat allergy, in which a single injection of a combination of 2 recombinant high-affinity antibodies against Fel d 1 afforded protection for at least 3 months. This approach could be viable for other inhalant allergens in which there is a dominant major allergen such as birch, ragweed, or alder pollen. Greater understanding of the underlying mechanisms of immunotherapy will enable development of more effective approaches and biomarkers to monitor the clinical response to treatment.

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