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The Future of Allergen-Specific Immunotherapy

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Abstract

Allergen-specific immunotherapy (SIT) is the only known causal treatment of allergic diseases. The safety and efficacy of SIT have been demonstrated in humans in many clinical trials, which showed the essential role of SIT in preventing new allergies and asthma. However, SIT is not effective in all allergic individuals and is not equally effective in the treatment of various hypersensitivities to different allergens. For this reason, there is a strong need for research in the field of new SIT modalities to increase its effectiveness and safety. They include recombinant allergens or hypoallergenic variants that show the ability to activate T lymphocytes but decrease IgE binding, diminishing the anaphylaxis risk of the treatment. Growing evidence on different T cell subset functions provides new concepts on the safer and more effective vaccination strategies.

Keywords

allergy, allergen-specific immunotherapy, recombinant allergens

Introduction

Currently, only allergen-specific immunotherapy (SIT) has been demonstrated to be a disease-modifying or curative treatment of allergic diseases. Moreover, it has been shown that SIT can reduce sensitizations to other allergens¹ as well as prevent development of asthma,² which is a basic requirement for an allergen vaccine in achieving clinical efficacy without the risk of anaphylaxis. It has been extremely difficult to develop novel classes of therapy for allergies probably due to the complexity of underlying pathology.³ There are several essential requirements underlying novel strategies for the development of safe and more efficient SIT vaccines. However, a number of clinical trials in SIT have demonstrated that a shift in the nature of the immune response in the direction of allergen tolerance represents a key step in the development of a healthy immune response against allergens.⁴ Promising studies are being performed to improve the efficacy and safety of SIT, such as the use of recombinant proteins, peptides, allergen fragments or hybrid allergens, and novel adjuvants or novel routes of vaccination such as intralymphatic SIT. Except for recombinant protein vaccines, they are only in an early stage of human clinical trials.

Recombinant Allergens for SIT

The allergen extracts are standardized in terms of total allergenic activity, or potency, and possibly the concentration

of one individual major allergen, while product consistency is assessed in terms of protein and allergen profiles determined by various techniques including electrophoresis and immunoblotting. An extract may contain numerous proteins, only some of which are allergens. The composition is determined to a large extent by the quality of the raw material and the method of extraction and purification. Raw materials are provided by certified suppliers and produced under controlled conditions; nevertheless, there are differences. The use of recombinant DNA technology appears to provide a realistic means of achieving improvements aimed at obtaining more precisely defined preparations. Recombinant DNA technology has delivered the prospect of a new generation of preparations for SIT. The first clinical studies with recombinant allergens have yielded very encouraging results,⁵ which suggest that there is

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a very good chance that such preparations will become available for use in the routine management of allergic disease. This technology also provides the possibility to create allergen derivatives with reduced IgE reactivity, that is to say, hypoallergenic molecules that have a reduced risk for inducing undesirable allergic reactions during the course of immunotherapy but that retain their therapeutic activity. Numerous allergens have now been cloned for research purposes, but as yet, only a few have been developed to the stage at which they can be used in clinical studies.

Clinical studies with the recombinant hypoallergens showed that these molecules had reduced IgE-mediated side effects or even lacked these effects. However, late-phase side effects, most likely caused by the activation of allergen-specific T cells, were observed.^{6,7}

Composition of Vaccines

The availability of recombinant allergens makes it possible to perform component-resolved diagnosis and to produce vaccines tailored to individual IgE reactivity profiles. However, the more immediate prospect is for the application of standard cocktails of allergens from one source or, in some cases, single allergens. One allergen or allergen derivative will suffice for an effective vaccine in cat (*Felis domesticus* 1 [*Fel d* 1])–sensitized and birch (*Betula verrucosa* 1 [*Bet v* 1])–sensitized patients, the rationale being that one major allergen dominates and accounts for most or all of the specific IgE directed against the one sensitizing agent. However, in pollen or mite allergy, the sensitization patterns are more complex. Grass pollen has 11 different allergens that have been identified and characterized in detail, and some of these are known to occur as several different isoforms. Only some of these allergens have major general importance, being associated with a high prevalence of sensitization in the grass pollen–allergic population and together accounting for a large part of the specific IgE directed against the whole pollen extract.

The grass *Phleum pratense* is a member of the subfamily *Pooideae*, which in turn belongs to the family *Poaceae*. It shows very substantial cross-reactivity with other members of the subfamily⁸ and can therefore be considered as representative of grasses found in temperate regions. The group 1 and 5 allergens *Phleum pratense* (*Phl p*) are strong candidates for inclusion in a therapeutic vaccine. More than 90% of grass pollen–allergic patients react to group 1 and up to 85% to group 5.^{8,9} There are 2 isoallergens of the timothy grass pollen allergen *Phl p* 5, the principal difference between them being that two 14/15-amino acid sequences are missing from the N-terminal half of *Phl p* 5b as compared with *Phl p* 5a. The molecules show extensive homology, and although there is a very high degree of IgE antibody cross-reactivity, there are

nevertheless some immunological differences in terms of T cell reactivity that may justify the inclusion of both isoallergens in a vaccine. The allergens *Phl p* 2 and 6 show a prevalence of sensitization in the ranges 40% to 60% and 60% to 70%, respectively, and are thus classified as major allergens. Although as many as 80% of grass pollen–sensitized patients may have IgE antibodies directed to the group 4 allergen, the concentrations are relatively low compared with those specific for *Phl p* 1 and 5, as too is specific skin test reactivity. Further, allergens including *Phl p* 7, 10, 11, and 12 are classified as minor allergens and are therefore not strong contenders for inclusion in a vaccine. Prevalence of sensitization to the calcium binding protein designated as *Phl p* 7 is only about 10%,¹⁰ and patients reacting to *Phl p* 10 (cytochrome c) are seldom found.⁸ Both *Phl p* 11 (profilin) and 13 are glycosylated, and a substantial part of the IgE reactivity appears to involve cross-reactive carbohydrate determinants. It is not realistic to represent all allergens from a particular source in the vaccine. It is reasonable to include the group 1 and 5 allergens, and these may be supplemented by other relatively important allergens such as groups 2 and 6 and possibly 4. A study conducted using 2 purified natural allergens of *P. pratense*, which were subsequently identified as *Phl p* 5 and 6, proved to be significantly less clinically effective than a partially purified whole allergen extract, and one can now speculate that this might have been attributable to the lack of *Phl p* 1.^{11,12}

Clinical Studies

There have been a number of clinical studies performed using the recombinant wild-type allergens and hypoallergenic derivatives (Table 1).^{6,13} A double-blind placebo-controlled clinical trial was undertaken with 62 grass pollen–allergic patients suffering from rhinoconjunctivitis with or without asthma.¹⁴ The recombinant allergen adsorbate was administered in subcutaneous injections of increasing concentrations at 7-day intervals prior to the pollen season in 2002, starting with 0.02 mg total protein, followed by 0.16 mg and then doubling to 40 mg total protein (0.8 mL). The maximum dose contained 10 mg *Phl p* 1, 5 mg *Phl p* 2, 10 mg *Phl p* 5a, 10 mg *Phl p* 5b, and 5 mg *Phl p* 6. Maintenance injections were continued until after the subsequent pollen season. A combined symptom-medication score adopted as the primary endpoint showed a 39% improvement in the active treatment group relative to placebo ($P < .041$). Thus, the primary endpoint was met for the first time in the recombinant vaccine study. Symptoms alone improved by 37% ($P < .015$), and the use of symptomatic medication decreased by 36.5% relative to placebo. A validated rhinitis quality of life questionnaire showed significant differences between active and placebo treatment with an overall significant benefit ($P < .024$), providing further evidence of clinical

Table 1. Immunotherapy trials with recombinant allergens/allergen derivatives.

Vaccine	Allergen Source/Active Components	Study Designs	ClinicalTrials.gov Identification
Recombinant wild-type allergens	Birch pollen/ <i>Bet v 1</i>	SCIT, DBPC, phase II, safety and efficacy	NCT00410930
		SLIT, DBPC, phase I, safety, tolerability and pharmacodynamic effects	NCT00396149
		SLIT, phase I, safety, tolerability and pharmacodynamic effects	NCT00889460
	Grass pollen/ <i>Phl p 1</i> , <i>Phl p 2</i> , <i>Phl p 5a</i> , <i>Phl p 5b</i> , <i>Phl p 6</i>	SLIT, DBPC, phase IIb/III, safety and efficacy	NCT00901914
		SCIT, DBPC, phase III, safety and efficacy	NCT00309036
		SCIT, DBPC, phase III, safety and efficacy	NCT00671268
Hypoallergens	Peanut/ <i>Ara h 1</i> , <i>Ara h 2</i> , <i>Ara h 3</i>	SCIT, DBPC, phase II, safety and efficacy, dose response	NCT00666341
		SCIT, phase III	NCT01353755
	Birch pollen/ <i>Bet v 1</i> folding variant	Rectal	NCT00850668
		SCIT, OC, phase II, safety and efficacy	NCT00266526
		SCIT, DBPC, phase III, safety and efficacy	NCT00309062
	Birch pollen/ <i>Bet v 1</i> fragments/trimer	SCIT, DBPC, phase III, safety and efficacy	NCT00554983
		SCIT, DBPC, phase II, immunological and histological evaluation	NCT00841516
		SCIT, DBPC, phase IIb	Purohit et al, ⁷ Niederberger et al ¹⁵

Based on the National Institutes of Health clinical trial database (<http://clinicaltrials.gov>); also see Valenta et al.^{6,13} DBPC, double blind placebo controlled; OC, open controlled; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

efficacy. Active treatment induced highly significant increases in both IgG1 and IgG4 grass pollen-specific antibody concentrations together with a significant decrease in IgE. Specific IgE levels were not significantly different between groups at the beginning of the study, but thereafter, the active treatment group showed a downward trend with values significantly less than baseline. Four patients in each group had no *Phl p 5a/b*-specific IgE prior to the study but reacted to *Phl p 1* and other grass pollen allergens. None of these patients developed *Phl p 5a/b* IgE antibodies during the study, although the 4 patients receiving active treatment developed strong IgG4 and IgG1 *Phl p 5a/b* responses consistent with the induction of a protective immune response. Treatment-related adverse events were seen in association with 78 injections (10.7%) in the active treatment group and 44 injections (5.9%) in the placebo group. Local reactions involving erythema and swelling in the vicinity of the injection site, with or without pruritus, accounted for nearly all these reactions. Single systemic reactions were seen in 7 active treatment and 2 placebo patients, the former including general urticaria (2 cases), local urticaria (2 cases), dyspnea (1 case), rhinoconjunctivitis (1 case), and asthma (1 case) 2 days following the injection. All these patients continued treatment without further problems, and it was concluded that the preparation showed favorable safety when compared with findings from other immunotherapy studies.

Immunotherapy with wild-type recombinant *Bet v 1*, *rBet v 1*, has also been examined. In the first clinical immunotherapy study with recombinant allergen preparations, 2 different

hypoallergenic derivatives of the major birch pollen allergen *Bet v 1* and placebo were compared.¹⁵ Linhart et al¹⁶ presented results of vaccinations with hybrid molecules engineered by polymerase chain reaction-based cloning and expression of cDNA coding for the 4 major grass pollen allergens. The hybrid contained most of the B cell epitopes of grass pollen and could be used to diagnose allergy in 98% (n = 652) of patients allergic to grass pollen. Immunization of mice and rabbits with the hybrid induced stronger and earlier IgG antibody responses than equimolar mixtures of the components. IgG antibodies induced by vaccinations with the hybrid blocked immediate allergic reactions, as demonstrated by rat basophile degranulation assays in a murine model of grass pollen allergy.¹⁶ Natural allergen extracts can thus be substituted by pure recombinant wild-type allergens or single recombinant fusion proteins consisting of several wild-type allergens.⁶ Significant induction of IgG1, IgG2, and IgG4 against *Bet v 1* was measured both in the peripheral blood and in nasal secretions. Furthermore, a proof-of-principle phase II, multicenter, double-blind, placebo-controlled injection immunotherapy trial comparing *rBet v 1*, natural *Bet v 1*, birch pollen extract, and aluminum hydroxide was performed in 134 patients. A significant reduction in symptoms, medication consumption, and skin sensitivity in the *rBet v 1*-treated group was demonstrated. However, new sensitizations were reported in the SIT-undergoing patients.¹⁷

Clinical studies with *rBet v 1* tablets for sublingual SIT have also been initiated.¹⁸ Further studies examined hypoallergenic

vaccines for birch pollen allergy based on a folding variant obtained by means of denaturation of rBet v 1. The vaccine was reported to have a good safety profile and induced strong increases in Bet v 1-specific IgG1 and IgG4 antibody levels. A large phase III study is on the way that can lead to the first registered vaccine on the European market. Hypoallergenic products of other allergens are under investigation.¹⁹

Food allergy-specific immunotherapy is also under investigation. A phase I clinical study of recombinant modified peanut allergens (*Arachis hypogaea* [*Ara h 1*, *Ara h 2*, and *Ara h 3* encapsulated in heat/phenol-killed *Escherichia coli*]) for rectal immunotherapy is reported by the National Institutes of Health's clinical trial database.⁶

Other attempts have been undertaken to modify recombinant allergens in order to improve the therapeutic efficacy in SIT while reducing allergic side effects using modular antigen translocation (MAT) technology or vaccines consisting of nonallergenic peptides fused to carriers.²⁰ Martinez-Gomez et al²¹ applied the major cat allergen *Fel d 1* fused to a Tat-derived protein translocation domain and to a truncated invariant chain for targeting the major histocompatibility complex class II pathway (MAT-*Fel d 1*). The immunogenicity of such molecules was evaluated in mice, while potential safety issues were assessed by a cellular antigen stimulation test using basophiles from cat dander-allergic patients. As concluded, the MAT-*Fel d 1* allergen enhanced protective antibodies and Th1 responses in mice while reducing human basophile degranulation. Immunotherapy using the MAT-*Fel d 1* allergen therefore has the potential to enhance SIT efficacy and safety, thus shortening SIT.²¹ Focke and colleagues²² reported an approach for the rational design of B cell epitope-derived peptide allergy vaccines. Lack of a secondary structure in the peptide epitopes results in a lack of allergenicity of these molecules. It has been also shown that nonallergenic peptides are able to induce IgG-mediated immune responses due to chemical coupling to other proteins, like highly repetitive antigens in bacteria and viruses, thus enhancing the SIT efficiency,²³ but, on the other hand, may be responsible for new immune-related side effects of SIT. The peptide vaccines have been applied in cat allergy (*Fel d 1* peptides), ragweed allergy (published in an abstract only), and bee venom allergy (*Apis mellifera* [*Api m 1*] peptides) in clinical studies.^{24,25} Nie-spodziana et al²⁶ report results of a preclinical study of cat allergy-specific immunotherapy with fused proteins of the hepatitis B virus-derived PreS domain and 2 nonallergenic *Fel d 1*-derived peptides, expressed in *E. coli*. The recombinant fusion proteins contained less than 40% of the *Fel d 1* sequence and exhibited not only strongly reduced IgE-mediated immune responses but also were lacking many of the specific T cell epitopes.²⁶ Other related studies are on the way.⁶

In some studies, direct administration of vaccines into lymph nodes with the aim to enhance immunotherapy²⁷ has

been used. The intralymphatic allergen administration strongly enhances SIT, with a final reduction of allergen injection number to 3 and a 10- to 100-fold reduction in allergen dose. Data from mouse models and in clinical trials showed that this treatment mode is easy, practically painless, and safe. All the features positively influence patient convenience and compliance.²⁸ Zaleska et al²⁹ show results of the MAT-*Fel d 1* vaccine applied intranodally. *Fel d 1*-specific T cell tolerance was maintained in the treated group compared to the placebo group after 1 year from finishing the treatment. Relative changes in the level of specific IgE in the serum of treated patients measured by enzyme-linked immunosorbent assay were contrary to the lack of drug-related side effects and to the improvement of allergen tolerance in a nasal provocation test.²⁹

Conclusion

The studies on the clinical efficacy of new allergen preparations including recombinant vaccines provide a new approach for improved treatment of allergies. In monosensitized patients, standard cocktails of relevant major allergens provide optimal cures. In addition, new vaccines based on MAT technology or new routes of vaccine application seem to be very promising. The major problem to overcome is the conductance of successful phase III studies before the treatment can be offered as a routine patient treatment.

Declaration of Conflicting Interests

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