

Immunotherapy: the next 100 years

Ira Finegold, MD,* and John Oppenheimer, MD†

INTRODUCTION

After contemplating the achievements of the past 100 years in the field of immunotherapy, it is exciting and challenging to consider the possibilities of the next 100 years of this therapy. In the next century through genetic and environmental manipulation many diseases, including allergy, may disappear and/or be substantially altered. However, barring these kinds of “star wars” genetic or molecular manipulations, it seems that allergen immunotherapy in several forms will remain a viable form of treatment. The goals of allergen immunotherapy should remain much the same as those for the first 100 years. The main goal is to provide an effective, preventive, safe, economical, and patient acceptable therapy. For the next century of immunotherapy, this goal is still in the process of being achieved.

This article reviews the general outlook for immunotherapy in the next century and to specifically look at some of the other current options for allergen immunotherapy that may emerge in the near future. We performed a literature review and selected studies related to the field of specific allergen immunotherapy for inclusion in this review. This was a review of the literature available in textbooks and journals.

In the past 2 decades many articles have dealt with the efficacy of immunotherapy for the treatment of allergic rhinitis, conjunctivitis, and asthma. The efficacy of treatment of insect sting hypersensitivity is well established. Immunotherapy for the treatment of atopic dermatitis is in its early stages. Advances in drug and food desensitization are also progressing. Although the mechanism may not be the same as allergen immunotherapy, the ultimate goal of tolerance is the same. The mechanisms involved in immunotherapy have also been elucidated and continue to be future fertile areas of investigation.

Safety is of prime concern for any therapy. A therapy that delivers to the patient the very substance his or her body is reacting to needs to be safe and if possible harmless. Over the years there has been a progression from administering immu-

notherapy empirically (to maximum tolerated dose) to dosing based on clinical studies. Allergens have become standardized in some cases and in others made under better standards of regulation. Educational programs and articles by groups from the major medical societies have addressed safety, and it would appear that these concerted efforts have been successful. A major factor has been the development of the Immunotherapy Practice Parameters,^{1,2} now undergoing a third revision, and the widespread dissemination of these parameters to practicing allergists.

The future of allergen immunotherapy safety resides in developing an allergen or antigen or suitable fragment that is immunogenic and will stimulate those factors that result in increased tolerance to allergen exposure tolerance and at the same time will be less allergenic without setting off those factors that result in allergic illness. In the past, efforts to do this were either unsuccessful or not widely used. Aluminum precipitated extracts offer some safety and efficacy. Most of the European studies of subcutaneous immunotherapy (SCIT) have used depot (alum-based) preparations. In the United States, although these agents have been on the market for a number of years, their use is relatively minor. There have been recent studies using allergoids for immunization. These are formaldehyde-treated extracts. Years ago Grammer and coworkers³ presented data on the use of these formaldehyde polymerized products, which were favorable but not sufficient to obtain Food and Drug Administration (FDA) approval for their use. In the future one can expect to see more of their use coupled with adjuvants that enhance the immune response. Such products are on the market in Europe and other countries but have not yet won FDA approval in the United States.

Recombinant allergens have been specifically designed to be immunogenic and not allergenic. Jutel et al⁴ have been able to demonstrate improvement in the symptom medication score in patients receiving recombinant allergens as opposed to placebo. Treated patients developed strong allergen specific IgG1 and IgG4 antibody responses.

After 100 years there remain issues to be resolved regarding SCIT, such as optimum dosage for all allergens, standardization for allergens, optimum schedules, and intervals of injections. Schedules of dosage increases (uploading), such as ultrarush, rush, and cluster, need to be standardized. How long should immunotherapy be administered? When should it be stopped? We also need better methods of evaluating efficacy of allergy treatments in general.

Affiliations: * St Luke's-Roosevelt Hospital Center, New York, NY, † New Jersey Medical School, Rutgers, NJ.

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THERAPEUTIC INTERVENTIONS

With improved understanding of the mechanisms of immunotherapy, opportunities for therapeutic interventions will occur at steps not yet defined to improve the process of inducing tolerance. In the past 100 years of immunotherapy, improved tolerance has been achieved but absolute desensitization has not (eg, the conversion of a skin test result to negative). This may occur in the next century.

Great strides in technology are not inexpensive. Yet society is intent on the reversal of the spiraling costs of medical care, and so any innovative therapy needs to be inexpensive. The outcome of this paradoxical situation is unclear. Immunotherapy needs to be accessible and available. The current decrease in the number of allergists will present problems for the provision of safe immunotherapy. Clearly, training programs and the number of trainees need to be increased.

Perhaps the most intriguing evolving situation is that regarding methods of providing allergens. The first 100 years used the subcutaneous route, but this was not exclusive. As early as 1928⁵ there were reports of oral desensitization to pollen. However, it was not until the 1980s that high-dose sublingual immunotherapy (SLIT) was able to lay claim to be comparable to SCIT.

When one examines the recent literature pertaining to allergen immunotherapy, most studies involve the use of SLIT. There appears to be a chasm between the United States and much of Europe, where SLIT is now used more frequently than SCIT.⁶ Specifically, in the United States the results of recent phase 3 regulatory study results are pending, regarding potential approval of this form of immunotherapy by the FDA. Three recent meta-analyses and a World Allergy Organization position paper speak to the strength of this form of immunotherapy.⁷⁻¹⁰ Certainly, from the perspective of the patient, the home dosing (beyond initial dose) protocol of SLIT is attractive; however, questions still remain with regard to SLIT. These questions include efficacy compared with SCIT, use of multiple allergens, and safety and dose schedules.

In the use of SLIT with multiple allergens, a recent study by Amar et al¹¹ questions the use of SLIT with a multiallergen mix. In this double-blind, placebo-controlled (DBPC), randomized study, the authors compared 10 months of therapy with timothy extract as monotherapy with the same timothy extract plus 9 additional pollens with placebo in 54 timothy extract allergic patients. Although active therapy demonstrated no significant reduction in symptom or mediation scores compared with placebo (presumed secondary to low grass pollen season during the year of study), the timothy extract monotherapy group demonstrated an improvement in the titrated nasal challenge ($P = .03$), an improvement in the skin prick test result ($P = .01$), a significant increase in serum specific IgG4 ($P = .005$), and a decrease in interferon γ levels ($P = .02$). In the case of the multiallergen group, however, there was no difference in any outcome compared with the placebo group except for a reduction in titrated prick

skin tests ($P = .04$). However, significant differences were seen between the active treatment groups.

When reviewing the SLIT data, it is evident that many of the studies vary in design, dose given (5-375 times the standard SCIT), and form of delivery (drops with or without swallow vs tablets). In a recent Cochrane analysis, 22 trials involving 979 patients were included (6 trials for house dust mite allergy, 5 for grass pollen, 5 for *Parietaria*, 2 for olive, and 1 each for ragweed, cat, tree, and *Cupressus*) of which 5 studies enrolled exclusively children.⁷ There was significant variability in the length of treatment, technique used, and scoring systems among studies; however, all of the studies analyzed were DBPC trials of parallel group design. Concealment of treatment allocation was considered adequate in all studies, and the use of identical placebo preparations was consistent. Overall, there was a significant reduction in both symptoms (standardized mean difference, -0.42 ; 95% confidence interval [CI], -0.69 to -0.15 ; $P = .002$) and medication requirements (standardized mean difference, -0.43 ; 95% CI, -0.63 to -0.23 ; $P = .00003$) with the use of SLIT. No significant reduction occurred in symptoms and medication scores in those studies involving only children; however, the total number of subjects was too small to form a reliable conclusion. Although the total dose of allergen administered may be important, there was insufficient data available to resolve this issue or to determine whether an optimal dose exists. Several studies have examined the efficacy of SLIT compared with SCIT; however, most were of open design. In the 2 trials that used a double-blind approach, a small number of patients was studied. The first study examined 20 grass allergic patients (SCIT vs SLIT with no placebo arm) and demonstrated similar reduction in symptoms and medication use, whereas the second examined 71 birch allergic patients and demonstrated that, although no statistical difference was seen between active groups, SLIT (14 patients completed) decreased the median disease severity to half and SCIT (19 patients completed) to one-third of placebo treatment.^{12,13} Thus, in light of these methodological issues, it is not surprising that the authors of the Cochrane meta-analysis concluded that the size of the benefit from SLIT should be further studied and compared with SCIT.

When assessing the data regarding adverse effects of SLIT, a recent prospective report by Rodriguez-Perez et al¹⁴ that prospectively studied 43 patients undergoing 26 weeks of SLIT found that 7 systemic reactions occurred in more than 23,000 doses of SLIT. All had grade 2 severity manifesting as bronchospasm or an increase in nasal symptoms, except for 1 patient, who had a grade 3 reaction with both bronchospasm and urticaria with angioedema. In the recent SLIT Joint Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology, the panel reviewed 72 studies and was able to analyze data regarding adverse events in 41 of the studies.¹⁸ They found an overall reaction rate of 2.7 per 1,000 doses of SLIT, and from the studies that described the type of reaction, it was found that systemic reactions were seen in

0.056% of doses administered. Further comfort regarding safety can be gleaned from no reports of fatalities with use of SLIT since its introduction in 1986. Despite this, there have been 4 case reports of severe reactions associated with the use of SLIT.^{15–18} Two of the cases involved use of multiple allergens simultaneously: one involved SLIT to latex and the other involved an overdose of SLIT to dust mite. The most recent case reports regarding the adverse effects of SLIT come from 2 episodes of anaphylaxis with use of SLIT tablets for grass. Both cases were associated with the first dose of therapy in patients who had previously had difficulty with SCIT to grass. Thus, one must question whether patients intolerant to SCIT are at added risk with SLIT.¹⁹ In another report, after large local reactions to grass SCIT suggested a change to SLIT, asthma became worse, and in another patient SLIT to dust mites after SCIT reactions led to a systemic reaction. The authors concluded that “SLIT does not represent a totally safe immunotherapy procedure.”²⁰ These last 2 studies suggest caution with the use of SLIT in patients who have had reactions to SCIT. There is little doubt that SLIT, although not 100% safe, is considerably safer than SCIT. However, at the time of this writing there have been no FDA-approved SLIT products.

As a consequence of our greater understanding of the potential immunotherapy mechanisms, there have been a plethora of studies exploring novel forms of immunotherapy. These include bioengineered recombinant allergens (hypoallergens), CD40-silenced dendritic cells, α -galactosylceramide-driven immunotherapy, T-cell peptide vaccines, and T_H1 immunostimulants, such as CpG and anti-IgE. The overall hope with these modalities is to maintain efficacy while improving safety and potentially reducing the inconvenience of prolonged time to maintenance dose of immunotherapy. In the case of T-cell peptide therapy, it is hoped that as short peptides derived from an allergen inhibit T-cell function but have restricted ability to cause anaphylaxis owing to loss of 3-dimensional B-cell epitopes, they could be used as effective forms of immunotherapy. A recent study by Oldfield and colleagues²¹ examined the use of this technology in cat allergic patients. Sixteen patients received active therapy with up dosing of Fel d 1 peptides during a 2-week period compared with 8 patients who received placebo therapy. Patients in the peptide group but not the placebo group demonstrated a significant reduction in the size of their late reaction to whole cat dander between baseline and follow-up evaluation, but the difference between groups was not significant (first follow-up [4–8 weeks and 3–9 months]: difference, -422.8 mm²; 95% CI, -1115.0 to 269.4 ; $P = .43$; second follow-up: difference, -1180.8 mm²; 95% CI, -2216.8 to -144.8 ; $P = .058$). The authors also found that the concentrations of interferon γ and interleukin (IL) 4 and 13 and the amount of proliferation significantly decreased between baseline and the second follow-up, and the concentration of IL-10 was significantly higher in patients receiving peptides therapy. The status of the peptide method was recently reviewed by Larche.²²

Another technology used to shorten the regimen to maintenance dose of immunotherapy is the conjugation of ragweed major antigen Amb a 1 to phosphorothioate oligodeoxyribonucleotide immunostimulatory sequence of DNA containing a CpG motif (AIC). This immunostimulatory sequence binds to tolllike receptor 9, which has been associated with the inhibition of immune responses mediated by T_H2 cells, including IL-4 and IL-5.²³ Using this technology, Creticos and colleagues²⁴ conducted a small, placebo-controlled clinical trial in which 25 patients who were allergic to ragweed were immunized with a 6-weekly injection regimen of the AIC vaccine before the first ragweed season and evaluated during the next 2 ragweed seasons. During the first ragweed season, the AIC group had better peak season rhinitis scores on the visual analog scale ($P = .006$), peak season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group. AIC induced a transient increase in Amb a 1 specific IgG antibody but suppressed the seasonal increase in Amb a 1 specific IgE antibody. A reduction in the number of IL-4-positive basophils in AIC-treated patients correlated with lower rhinitis visual analog scores ($r = 0.49$, $P = .03$). Clinical benefits of AIC were also seen in the subsequent ragweed season, with improvements over placebo in peak season rhinitis visual analog scores ($P = .02$) and peak season daily nasal symptom diary scores ($P = .02$). The seasonal specific IgE antibody response was again suppressed, with no significant change in IgE antibody titer during the ragweed season ($P = .19$). There was no pattern of vaccine-associated systemic reactions or clinically significant laboratory abnormalities. Interestingly, the primary end point, which was the vascular permeability after nasal challenge, was not significantly changed with therapy.

Another form of immunotherapy resulting in fewer injections and reduced allergenicity is being used in Europe. This method uses 3-acylated monophosphoryl-lipid A technology along with formaldehyde (allergoid)-treated allergens.²⁵ Clinical studies in the United States and Canada have been completed and are under review by the FDA.

A recent study examined whether the addition of omalizumab to immunotherapy in patients with symptomatic asthma not controlled with inhaled corticosteroids would improve the side effect profile of SCIT.²⁶ In this double-blind, parallel-group study 248 participants (126 omalizumab, 122 placebo) were randomized to treatment with omalizumab or placebo, after which they received specific immunotherapy to at least 1 perennial allergy (cat, dog, and house dust mite) via a 4-week, 18-injection cluster regimen, followed by 7 weeks of maintenance therapy. Individuals receiving omalizumab experienced significantly fewer systemic allergic reactions to immunotherapy than those receiving placebo (17/126 [13.5%] vs 32/122 [26.2%]; 95% CI, 2.91% to 22.56%; $P = .017$) and had fewer respiratory-related (grade 3) systemic allergic reactions (6 vs 24). Not surprisingly, more individuals in the omalizumab compared with the placebo group were

able to reach the maintenance immunotherapy dose (110 [87.3%] vs 88 [72.1%]; $P = .004$).

Another approach may be to combine other therapeutic agents with immunotherapy to enhance immunotherapy efficacy. Mueller et al²⁷ showed that adding fexofenadine enhanced immunotherapy to insect venom, but a recent study suggests that routine use of montelukast in asthmatic children undergoing SCIT is not justified.²⁸ On the other hand, adding vitamin D3 mitigated the negative effects on immunotherapy of corticosteroids given to asthmatic children.²⁹ More studies are needed to define the interaction of therapeutic agents with immunotherapy of all forms.

The next 100 years may see the effective extension of allergen immunotherapy for the treatment of food allergy. Currently, there are no curative procedures in the case of food allergy; however, there has been recent interest in the use of oral-induced tolerance in food allergic patients. Interestingly, this is not a new concept. As early as 1908, Schofield³⁰ reported the use of minute amounts of egg to treat egg allergy. By 1930 Freeman³¹ reported that with the use of SCIT a state of tolerance was induced in a fish allergic patient. More recent exploration of the use of SCIT to peanut, although effective, resulted in an unacceptable side effect profile.³² Recent reports have highlighted efficacy of oral immunotherapy and SLIT for various food allergies, including egg, milk, hazelnut, and peanut. Regimens have varied from rush protocols, generally being performed in a hospitalized setting, to slow up dosing, which in some cases is performed with dosing at home. A recent pilot study in egg allergic children instituted a more “practical and patient friendly” protocol by performing a weekly outpatient dose-increasing protocol, comprising 28 visits during approximately 4 months. Thirty children with confirmed cow’s milk allergy via DBPC food challenge were randomized to active therapy or sham protocol with the use of soy. However, unlike other protocols, there were no “home doses” between the clinic visits for “up dosing.” The primary outcome was the reduction in clinical sensitivity as demonstrated by the change in threshold dose via DBPC food challenge, with the secondary outcome of immunologic changes associated with the procedure. Oral immunotherapy was effective with the “full” DBPC food challenge milk dose (200 mL) tolerated in 10 of 13 patients and partial tolerance in 1 and 2 patients, who required discontinuation because of severe reactions associated with the oral immunotherapy protocol.³³ With regard to immunologic parameters, as seen in other studies, there is no change in specific IgE; however, in the actively treated group there is an increase in IgG4 to cow’s milk allergy.³⁴ Oral immunotherapy is by no means perfect because not all patients were able to achieve the desensitized state and there is potential for adverse events. This is reinforced in the cow’s milk oral immunotherapy study by Skripak et al,³⁴ who demonstrated reaction rates higher than would be expected for conventional SCIT for pollen and environmental allergy, with approximately 1 in 100 doses of active therapy resulting in multisystem reaction and 1 in 600 requiring use of epinephrine.^{25,35}

An important issue that has received recent attention is that such protocols must discriminate between the desensitized state, in which there are continued uninterrupted ingestions of the food allergen, and the tolerant state, in which cessation of ingestion is not followed by resensitization. The importance of distinguishing these 2 states is exemplified in a study by Staden and colleagues,³⁶ who performed a DBPC trial comparing oral immunotherapy to egg or milk vs placebo. Sixty-four percent of actively treated patients were found after a median of 21 months to demonstrate “good or at least partial response”; however, when they then underwent 2 months of elimination of the relevant food allergen and were rechallenged, they demonstrated a likelihood of protection that was similar to that seen in the control group. It is thus no surprise that a recent editorial from experts in the field cautions that oral immunotherapy is not yet ready for clinical use.^{28,37}

CONCLUSION

The first 100 years of immunotherapy was characterized by empirical success and then much later in the century by mechanistic explanations, which still are incomplete. The next 100 years of investigation builds on this superb foundation to explore new approaches to immunotherapy, which focuses on efficacy (both preventive and therapeutic), safety, and practicability to improve the lives of those with allergy. In this review some of the new methods are highlighted, especially the ones that seem close to becoming part of the allergy specialists’ armamentarium. An exciting path lies ahead for the next century of allergen immunotherapy with improvements for the health of patients with allergic disorders.

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