# Editorial

# Status of immunotherapy: Current and future

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Allergen immunotherapy has been used for more than 90 years for the management of allergic disorders, including seasonal and perennial allergic rhinitis, allergic asthma, and hymenoptera sensitivity. In a 1998 article in the Journal, Norman[1] reviewed the past and present status of immunotherapy. In this issue of the Journal he provides an overview of recent progress in understanding the mechanisms of action of immunotherapy and potential future directions.[2] What is striking to me after reading these reviews and other related articles is that the actual practice of immunotherapy has not changed much. Recent safety and efficacy studies have not demonstrated a substantial change in the risk/benefit ratio of immunotherapy for the treatment of allergic disorders. Yet our understanding of how immunotherapy works on an immunologic basis has dramatically increased. Why is there such a disparity in the translation of our basic science knowledge of this treatment modality to the nuts and bolts of giving immunotherapy to patients?

One potential reason for this disparity is that the practice guidelines for immunotherapy are not universally followed. Aaronson and Gandhi,[3] in this issue, report the results of an e-mail survey of more than 1700 allergists asking about incorrect injections administered in their offices. Almost 60% of respondents reported that in the last 5 years a patient had received an injection meant for another patient. Seventy-four percent of respondents stated that patients in their practices had received an incorrect amount of vaccine. These errors, all too common, resulted in a spectrum of adverse reactions, including local reactions, systemic reactions (some of which led to emergency department care, hospital admissions, or both), and a fatality.

Bernstein et al[4] conducted a 12-year survey of fatal reactions to allergen immunotherapy injections between 1990 and 2001. Their results reported in this issue of the Journal showed that the rate of fatalities per immunotherapy injection has not changed much over the last 15 years. They estimated that fatal reactions occurred at a rate of 1 per 2.5 million injections, with an average of 3.4 deaths per year. The vast majority of fatalities occurred in patients with asthma, most of who were poorly controlled. Interestingly, some of these reactions occurred at times greater than 30 minutes after the injections (ie, at a time exceeding the current recommended waiting time for allergy immunotherapy injections). They also noticed that there was either a substantial delay in starting epinephrine or that epinephrine was not administered at all in many of the fatalities.

*Abbreviations used*
AIC: Amb a 1 immunostimulatory oligodeoxynucleotide conjugate immunotherapy
SLIT: Sublingual immunotherapy

Many of the mistakes reported by Aaronson and Gandhi[3] and the fatalities reported by Bernstein et al[4] could probably have been prevented by strict adherence to the recently published immunotherapy practice guidelines.[5] Furthermore, the Academy's efforts to standardize immunotherapy forms and vial labeling will also likely decrease patient and dosing errors. However, the need for clinicians involved in the practice of immunotherapy to constantly assess their patients' current medical status, avoiding the administration of injections to inappropriate candidates, especially patients with poorly controlled asthma, cannot be overemphasized. Furthermore, the appropriate and timely administration of epinephrine to treat anaphylaxis is essential.

The current practice of immunotherapy has many other challenges. We still do not have standardized extracts for many important allergens. There is a lack of information about the efficacy and safety of mixing multiple allergens in a single vial-injection. The stability of mixes and the calculation of antigen content in these mixes have yet to be defined. Moreover, the most impressive data defining the immunologic changes and long-lasting immunotolerogenic effects of immunotherapy come from studies of single antigens. Yet in the United States most allergists use mixes of unstudied or inadequately studied allergens made specifically for individual patients or practices. We need to accurately define the number, scope, and antigenic content of mixes that would provide the best short-term and long-term therapeutic benefits for our patients.

Despite these and other shortcomings of the current practice of immunotherapy, it remains the only viable option for the prophylaxis of insect sting allergy. Furthermore, as summarized by Till et al[6] in their review

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published in this issue of the Journal, immunotherapy has a number of distinct advantages over other currently available treatments for allergic diseases. Immunotherapy is the only antigen-specific immunomodulatory treatment routinely available. It can provide long-term benefits and modify the natural history of allergic diseases, preventing the development of neosensitization and asthma in children. These benefits arguably justify the long-term commitment, expense in time and money, and risk of adverse reactions associated with immunotherapy.[2]

What underlies these impressive immunomodulatory effects of immunotherapy? The reviews by Norman[2] and Till et al[6] address this in detailed fashion.

It has long been known that immunotherapy blunts seasonal increases in IgE levels and results in increases in allergen-specific IgG levels (ie, blocking antibodies), especially IgG4. This results in decreased IgE-mediated histamine release and inhibition of IgE-mediated antigen presentation to T cells. Till et al[6] point out that examining the correlation between IgE levels and clinical response to treatment is probably too simplistic of an approach. Recent studies demonstrated the importance of also examining the affinity and specificity of IgG subsequent to immunotherapy. Indeed, the binding capacity of IgG4 increased whereas that for IgE decreased after long-term immunotherapy.[7]

In addition to the effects of immunotherapy on immunoglobulins, its effects on lymphocytes have been intensely studied. Some peripheral blood studies have indicated a shift in the balance of T-lymphocyte subsets away from a $T_H2$ phenotype and toward a $T_H1$ phenotype on the basis of preferential production of IFN-γ and decreased production of IL-4 and IL-5. However, these findings are not consistent, as pointed out by Till et al[6] and Norman.[2] What is consistent is the demonstration of increased allergen-specific IL-10 subsequent to immunotherapy. Moreover, IL-10 has also been shown to be increased in the respiratory mucosa. IL-10 is produced by a number of cells, including $T_H1$ cells, $T_H2$ cells, regulatory T cells, B cells, monocytes-macrophages, dendritic cells, mast cells, and eosinophils.[6] IL-10 has a number of biologic consequences that could be important in mediating the immunotolerogenic effects of immunotherapy.[8] These effects include modulation of IL-4–induced B-cell IgE production in favor of IgG4, inhibition of IgE-dependent mast cell activation, inhibition of human eosinophil cytokine production and survival, suppression of IL-5, and induction of antigen-specific anergy.[6]

In this issue of the Journal, Vissers et al[9] explore the putative therapeutic role of IL-10 in immunotherapy by using a mouse model of asthma. They found that immunotherapy decreased the development of airway eosinophilia and hyperresponsiveness coincident with reductions in allergen-specific IgE levels, $T_H2$ cytokine production, and the IL-5/IL-10 ratio in bronchoalveolar lavage fluid. These positive therapeutic effects were inhibited by mAb directed against IL-10 receptors, suggesting an essential role for IL-10. The major source of IL-10 appears to be T cells, and there is evidence to suggest that $CD4^+CD25^+$ cells are the prime origin.[2,6]

Both Till et al[6] and Norman[2] provided figures with their hypothetic views on how immunotherapy works. These paradigms are different than those proposed 5 years ago in Norman's original Journal article.[1] Indeed, the importance of IL-10, regulatory T cells, and dendritic cells as critical components in the therapeutic effects of immunotherapy will likely be a fruitful area of future research.

Most of the work describing the mechanisms of action of immunotherapy has been done with the subcutaneous route of administration. However, recent evidence also suggests that high-dose sublingual immunotherapy (SLIT) is an effective alternative. Last year, Canonica and Passalacqua[10] reviewed in the Journal noninjection routes for immunotherapy. They emphasized the potential need to find safer alternatives to traditional subcutaneous immunotherapy. They described the positive and negative aspects of oral, bronchial, nasal, and sublingual routes. Of these various alternatives, the sublingual route appears the most promising for both allergic rhinitis and asthma. Many controlled trials support the efficacy and safety of SLIT for both adults and children. Although a much greater amount of allergen (20 to 375 times) is needed to affect a clinical response, home self-administration might ultimately result in cost savings versus the subcutaneous route.[10] In a letter to the editor in this issue of the Journal, Lombardi et al[11] measured adherence in 86 subjects receiving SLIT. According to tablet counts performed by patients during telephone interviews, they estimated adherence rates of approximately 97%, a remarkably high rate for self-administered medication. However, there was no verification by the investigators, and we do not know whether patients took the tablets at the prescribed times. Nonetheless, these results are encouraging. Yet there is a lot to be examined before recommending this treatment as a replacement for subcutaneous immunotherapy. There are very limited data comparing SLIT with subcutaneous immunotherapy. We also do not know the long-term effects of SLIT or what immunologic changes are evoked by this form of therapy. For the patient who is sensitized to multiple clinically relevant allergens, SLIT might not be a viable option. Finally, although the safety profile appears good with SLIT, studies of the magnitude done by Bernstein et al[4] are ultimately needed to define the true risk/benefit ratio of SLIT in comparison with subcutaneous immunotherapy.

In this issue of the Journal, Hsu et al[12] expand on the concept of oral immunotherapy. In novel murine experiments they examined the effects of oral feeding of dust mite allergen expressed by a plant viral vector in squash. Dust mite–sensitized mice administered the recombinant mite allergen orally had both decreased specific IgE levels and allergen-induced airway inflammation. They conclude that genetically engineered allergen-specific dietary supplements could be used to deliver high doses of allergens and thereby result in an improved paradigm for oral immunotherapy. These intriguing early results are worthy of further examination

to define the mechanisms of action and clinical potential in human subjects.

What are some other alternative approaches to traditional subcutaneous immunotherapy under investigation? Both Norman[2] and Till et al[6] briefly discuss the therapeutic potential of recombinant and genetically modified allergen proteins, synthetic peptides representing T-cell epitopes, adjuvants such as 3-deacylated monophosphoryl lipid A, CpG linked to Amb a 1, and anti-IgE plus immunotherapy. All of these approaches have positive and negative attributes. Genetically altered allergen proteins and synthetic peptides might represent a safer form of immunotherapy, but it remains to be determined whether either will evoke a long-lasting immunotolerogenic response akin to that of traditional immunotherapy while having a better risk/benefit therapeutic ratio.

Recently approved by the US Food and Drug Administration for moderate-to-severe allergic asthma, the anti-IgE mAb omalizumab has also been shown to be effective for seasonal and perennial allergic rhinitis. Kuehr et al[13] showed that omalizumab added to immunotherapy provided an additional therapeutic advantage for children with seasonal allergic rhinitis. We have just completed a trial examining the protective effects of omalizumab on allergic reactions caused by rush immunotherapy. The preliminary results reported at the 2004 American Academy of Allergy, Asthma and Immunology meeting indicated that omalizumab had a protective effect on allergic-type reactions caused by both rush and maintenance immunotherapy. These results suggest that omalizumab pretreatment might represent an effective strategy to allow more rapid and higher doses of allergen immunotherapy. Whether omalizumab might also permit administration of immunotherapy to high-risk patients (eg patients with poorly controlled asthma), thus avoiding or preventing the systemic reactions and fatalities reported to occur in this group,[4] remains to be determined. Indeed, further studies are needed to elucidate the exact dosing and timing of this regimen, as well as whether it will result in improved clinical and immunologic outcomes.

In articles published in the February 2004[14] and current[15] issues of the Journal, the potential therapeutic role of Amb a 1 immunostimulatory oligodeoxynucleotide conjugate immunotherapy (AIC) is discussed. AIC is prepared by covalently linking the purified short ragweed pollen allergen Amb a 1 to immunostimulatory phosphorothioate oligodeoxyribonucleotide fragments rich in CpG motifs. CpG is a ligand for the Toll 9 receptor. In preclinical animal studies AIC has been demonstrated to downregulate the $T_H2$ response while promoting a $T_H1$ response to Amb a 1. Tulic et al[14] reported the results from 28 patients who received 6 escalating doses of AIC (0.06-12 μg) subcutaneously at weekly intervals immediately before the ragweed season. They found that not immediately but 4 to 5 months after dosing and seasonal ragweed exposure, AIC modified nasal allergen challenges by increasing local $T_H1$ cytokine production and decreasing $T_H2$ cytokine production and eosinophilia. Although there was no clinical improvement in the first ragweed season, there was a significant reduction in chest symptoms and a trend toward reduced nasal symptoms in the subsequent ragweed season with no further AIC treatment. Simons et al[15] used the same dosing regimen as Tulic et al[14] and studied the effects of AIC administered during the winter months on peripheral blood mononuclear responses. They found that ragweed-specific $T_H2$ responses were selectively redirected toward $T_H1$ responses both at 2 and 16 weeks after the last injection. This implies that AIC resulted in a prolonged immunomodulatory effect. Why Tulic et al[14] did not find a clinical benefit from AIC during the initial ragweed season is unclear given the results of Simons et al.[15]

This approach, albeit exciting and novel, has some limitations. By conjugating a single antigen to ISS, the beneficial effects are specific for Amb a 1 alone. Although mouse models suggest that ISS-antigen conjugates are therapeutically and immunologically better than ISSs admixed with a single antigen,[16] it would be of interest to study the effects of CpG admixed with multiple allergens (as done with traditional immunotherapy). Although CpG works least well in animal models when given as monotherapy, the effects of CpG administered either before or during a pollen season with natural high-dose exposure is also worthy of consideration. The prospect of invoking profound and long-lasting tolerance to allergens with much less intensive immunotherapy regimens makes this approach intriguing.

In 2 related articles published in this issue of the Journal, Cohen[17] and Dworetzky[18] review the lives and accomplishments of Francis Lowell and William Franklin. Lowell and Franklin challenged the allergy community in the early 1960s to perform double-blind, placebo-controlled studies of allergy immunotherapy and to be skeptical of anecdotal, uncontrolled results. Their seminal studies laid the foundation for the appropriate testing and use of immunotherapy. We should heed their timeless advice when prescribing allergen immunotherapy for our patients and follow evidence-based practice guidelines.[5] Indeed, this will, in the immediate future, likely result in an improvement in the risk/benefit ratio of immunotherapy. However, further improvement will be forthcoming as we learn more about the pathogenesis of allergic diseases and translate this knowledge into targeted therapy against critical pathophysiologic pathways. I am confident that new and better paradigms of immunotherapy regimens that lead to long-lasting allergen-specific tolerance and better clinical outcomes are the future!

## REFERENCES

1. Norman PS. Immunotherapy: past and present. J Allergy Clin Immunol 1998;102:1-10.
2. Norman PS. Immunotherapy 1999-2004. J Allergy Clin Immunol 2004; 113:1013-23.
3. Aaronson DW, Gandhi TK. Incorrect allergy injections: allergists' experiences and recommendations for prevention. J Allergy Clin Immunol 2004;113:1117-21.
4. Bernstein DI, Wanner M, Borish L, Liss GM, and the Immunotherapy Committee of the American Academy of Allergy, Asthma and

Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol 2004;113:1129-36.
5. Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 2003;90: 1-40.
6. Till SJ, Francis JN, Nouri-Aria K, Durham SR. Mechanisms of immunotherapy. J Allergy Clin Immunol 2004;113:1025-34.
7. Pierson-Mullany LK, Jackola D, Blumenthal M, Rosenberg A. Altered allergen binding capacities of Amb a 1-specific IgE and IgG4 from ragweed-sensitive patients receiving immunotherapy. Ann Allergy Asthma Immunol 2000;84:241-3.
8. Bellinghausen I, Knop J, Saloga J. The role of interleukin-10 in the regulation of allergic immune responses. Int Arch Allergy Immunol 2001;126:97-101.
9. Vissers JLM, van Esch BCAM, Hofman GA, Kapsenberg ML, Weller FR, van Oosterhout AJM. Allergen immunotherapy induces a suppressive memory response mediated by IL-10 in a mouse asthma model. J Allergy Clin Immunol 2004;113:1204-10.
10. Canonica GW, Passalacqua G. Noninjection routes for immunotherapy. J Allergy Clin Immunol 2003;111:437-48.
11. Lombardi C, Gani F, Landi M, Falagiani P, Bruno M, Canonica GW, et al. Quantitative assessment of the adherence to sublingual immunotherapy. J Allergy Clin Immunol 2004;113:1219-20.
12. Hsu C-H, Lin S-S, Liu F-L, Su W-C, Yeh S-D. Oral administration of a mite allergen expressed by zucchini yellow mosaic virus in cucurbit species downregulates allergen-induced airway inflammation and IgE synthesis. J Allergy Clin Immunol 2004;113:1084-90.
13. Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von Berg A, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. J Allergy Clin Immunol 2002;109:274-80.
14. Tulic MK, Fiset P-O, Christodoulopoulos P, Vaillancourt P, Desrosiers M, Lavigne F, et al. Amb a 1-immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response. J Allergy Clin Immunol 2004;113:235-41.
15. Simons FER, Shikishima Y, Van Nest G, Eiden JT, HayGlass KT. Selective immune redirection in humans with ragweed allergy by injecting Amb a 1 linked to immunostimulatory DNA. J Allergy Clin Immunol 2004;113:1136-43.
16. Shirota H, Sano K, Kikuchi T, Tamura G, Shirato K. Regulation of murine airway eosinophilia and TH2 cells by antigen-conjugated CpG oligodeoxynucleotides as a novel antigen-specific immunomodulator. J Immunol 2000;164:5575-82.
17. Cohen S. Lowell and Franklin on double-blind hyposensitization therapy for ragweed hay fever: the people. J Allergy Clin Immunol. In press 2004.
18. Dworetzky M. Lowell and Franklin on double-blind hyposensitization therapy for ragweed hay fever: the paper. J Allergy Clin Immunol 2004; 113:1233-5.

## Correction

With regard to the May 2004 article entitled "First-aid treatment of anaphylaxis to food: Focus on epinephrine" (2004;113:837-44): A serious dosage error appears in the section entitled "Epinephrine in the first-aid treatment of anaphylaxis." On page 837, in the fifth line of the subsection entitled "Evidence base for epinephrine use in anaphylaxis," the epinephrine dosage for children appears incorrectly as "a maximum of 0.3 mg/kg." **The correct maximum initial dose is 0.2 mg to 0.5 mg in adults; 0.01 mg/kg to *a maximum of 0.3 mg in children*.** The sentence should read as follows:

> Recommendations for epinephrine dosing in the first-aid, out-of-hospital treatment of anaphylaxis are based on anecdotal experience and may vary with regard to maximum initial dose (0.2 mg to 0.5 mg in adults; 0.01 mg/kg to a maximum of 0.3 mg in children), route of injection (subcutaneous vs. intramuscular), and interval between doses (5-30 minutes).[6-9]

The incorrect dosage was a major error on the part of the publisher. If implemented, the incorrect dosage could result in a fatal epinephrine overdose for a child.