

Perspective

Current standards and future directions in immunotherapy: perspectives on challenges and opportunities for the allergist

David I. Bernstein, MD*; Michael S. Blaiss, MD†; Linda S. Cox, MD‡; Ira Finegold, MD§; Bobby Q. Lanier, MD||; Harold S. Nelson, MD¶; and Dana V. Wallace, MD‡

INTRODUCTION

This year marks the 100th anniversary of immunotherapy and the publication of the third update of the Practice Parameters for Immunotherapy.¹ During the 2010 Annual Meeting of the American College of Allergy, Asthma and Immunotherapy (ACAAI), the ACAAI brought together a panel of nationally recognized experts to share their perspectives on these milestones and on the current and future practice of immunotherapy in the United States. The panelists discussed current standards for immunotherapy; the advent of sublingual immunotherapy (SLIT) in Europe and elsewhere, and its implications for potential future use in the United States; novel immunotherapy delivery methods, including intranasal, epicutaneous, and intralymphatic; and needed research and unanswered questions. This perspective looks at the opportunities and challenges that these issues present to the practicing allergist.

CURRENT STANDARDS OF CARE IN THE UNITED STATES

The new Practice Parameters expand the benefits of immunotherapy for more patients with the addition of 2 potential new indications, including atopic dermatitis in patients with

aeroallergen sensitivities and people with frequent and bothersome large local reactions to stinging insects. Another modification in the parameters that may increase the use of immunotherapy is that there no longer is an upper or lower age limit for the treatment, which should help dispel the belief of many allergists that, with the exception of life-threatening insect sting allergy, immunotherapy is contraindicated in children younger than 5 years. This paves the way for initiating therapy earlier as a strategy to prevent asthma. Although asthma prevention per se is not an indication for immunotherapy, it is a potential add-on benefit in children for whom immunotherapy is strongly indicated and who have a family history of allergy progressing to asthma. There also is good evidence that immunotherapy can reduce the future risk of polysensitization when administered to children allergic to only 1 aeroallergen.^{2,3}

There also is new evidence that subcutaneous immunotherapy (SCIT) is safer than ever. The results of the first year of an ongoing surveillance study⁴ reported no fatalities in nearly 16 million injections and only 0.1% of injections were associated with systemic reactions.

The accelerated build-up schedules of rush and cluster immunotherapy also provide opportunities for the allergist to expand therapy to more patients by offering the advantage of achieving therapeutic doses earlier. There is, however, concern about an increase in systemic reactions, especially with rush, even with intensive premedication. Although the incidence of systemic reactions relative to slow build-up regimens has yet to be determined with cluster, the technique enables clinicians to reach maintenance in as little as 4 weeks, compared with the 6 to 8 months that is the norm with conventional SCIT. This is an attractive modality for patients who do not have time for the frequent injection visits required by conventional buildup regimens and also can be cost-effective for payers, including patients with plans that require copay for each treatment day.

SUBLINGUAL IMMUNOTHERAPY

Although not yet approved by the Food and Drug Administration, there are a number of promising US clinical trials with SLIT completed or under way by 4 allergen extract

Affiliations: * Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio; † Department of Pediatrics and Medicine, University of Tennessee Health Science Center, Memphis, Tennessee; ‡ Department of Medicine, Nova Southeastern University, Fort Lauderdale, Florida; § Cook Institute of Allergy, St. Luke's Roosevelt Hospital, and Department of Medicine, Columbia University, New York, New York; || Department of Immunology, University of North Texas Health Science Center, Ft Worth, Texas; ¶ Department of Medicine, National Jewish Health and the University of Colorado School of Medicine, Denver, Colorado.

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manufacturers. The applications are currently limited to allergens for which there are standardized preparations, including grass, ragweed, cat, and house dust mite extracts, with most of the research to date focusing on grass allergen tablets. The promising results of these trials,^{5,6} combined with the evidence of efficacy and safety from Europe,⁷ where SLIT has been a part of clinical practice for more than 20 years, suggest that SLIT may be approved for use in the United States in the near future.

Although there are not many long-term studies with either SLIT or SCIT that have investigated the duration of efficacy, the collective literature⁷ suggests that SLIT has a persistent disease-modifying effect similar to what we have seen with SCIT. Data from research with the timothy grass allergen tablet^{5,6} demonstrated persistent improved symptoms and reduced medication use after 3 years of treatment for at least 2 years after treatment discontinuation. In 1 study,⁸ 3 to 5 years of treatment resulted in continuing remission for most patients for 6 to 7 years after treatment was discontinued. Of particular interest was, when there was a recurrence of symptoms, reinstituting SLIT resulted in a much more rapid response than initially, implying that it may require a small booster series of treatments to get patients back under control. There also are cost-effectiveness studies of this tablet in the United Kingdom that show significant savings compared with life-long medication use.⁹

Another issue that has been raised with SLIT is the frequency of dosing, with some regimens requiring daily administration. There are studies, however, looking at reducing treatment days with SLIT. One study,¹⁰ for example, found that instituting therapy with a 1-day buildup on the first day of grass pollen season and treating only through the season for an average of approximately 87 days per year for 3 years was as effective as daily grass tablets for 3 years. Furthermore, although the greatest benefit was seen in year 3, there was some benefit in years 1 and 2.

SLIT also shows promise in ameliorating the symptoms of asthma. In 1 large study⁵ that did not exclude asthmatic patients, there were no severe asthmatic responses, and although the study was not designed to look at asthma, it found that asthma symptoms were significantly reduced. Another study¹¹ that followed up grass allergic children in treated and untreated groups for 3 years specifically looked at asthma prevention as an end point. There was no difference between groups the first year, but by the second and third year there were virtually no additional cases of asthma in the actively treated group and continued development of asthma in the untreated group. Other studies^{2,3} also have shown that SLIT can prevent the development of new sensitivities in some patients.

Phase 1 and phase 2 studies with SLIT provide some good dose response data to aid the clinician in determining the optimum dose for both safety and efficacy. Except for the first 3 doses of SLIT, which were administered in the office setting during US clinical trials, the eventual home administration of this form of immunotherapy is more convenient and

is likely to be more acceptable to many children who resist "allergy shots."

What will US approval of SLIT mean for the nation's allergists? Some fear that, given the safety and efficacy profile of SLIT, the role of the allergist will be diminished as primary care physicians take over what will be seen as largely a pharmacologic therapy. Although the number of people in the United States with allergies continues to increase, the number of patients receiving SCIT has been consistent during the past 10 years. It is likely that SLIT will expand the use of immunotherapy to more patients who would benefit because of convenience. The important message is that allergen immunotherapy is the only type of allergy treatment with a disease-modifying effect. It is likely that the increased use of SLIT will also bring about an increased awareness of the importance of immunotherapy as a treatment option, whether it be SCIT or SLIT, and of obtaining an accurate diagnosis and a personalized treatment plan developed by the allergy specialist.

Although the overall safety profile for SLIT is very good, with no reported fatalities, local adverse effects, such as itching in the mouth and angioedema, are not uncommon. Patients, primary care physicians, and allergists must be reminded that despite its excellent safety profile, there have been a handful of systemic reactions reported with SLIT. Some of these episodes of anaphylaxis have been in patients who previously experienced severe reactions to SCIT. These troublesome and, at times, serious reactions have the potential to become more widespread as the population of patients treated with SLIT increases. The challenge for the future will be to identify the subset of patients who are most at risk and require ongoing care and treatment by an allergy specialist.

Adherence also is an issue in comparing SCIT with SLIT because of a marked difference in dosing intervals. With cluster immunotherapy, the dosing interval for SCIT is once or twice a week for 4 or 8 weeks and then monthly, whereas with SLIT dosing is much more frequent, often daily for a period of years. With SCIT, because patients come into the physician's office for injections, it is easier to monitor adherence. A recent study¹² from Italy using manufacturers' data on refills showed that adherence to SLIT decreased precipitously during a year to approximately 15%. A prospective Italian study¹³ found, however, that scheduling SLIT patients for office visits every 3 months significantly improved adherence.

Another question is how applicable a single grass allergen tablet will be in treating polysensitized patients, who represent the majority of individuals undergoing SCIT in the United States. Virtually all the controlled studies that have been performed with SLIT have been single-antigen studies, and there is no evidence yet that one can administer more than 2 allergen mixes sublingually and get the same result as with a single agent. Many European and US studies with SLIT included polyallergic patients and suggest that the polyallergic patient will respond to monotherapy to that particular allergen.

Another difficulty in comparing SCIT and SLIT is that most studies of multiple allergens with SCIT date back more than 20 years, and this issue is not currently under study. Most “evidence” on the effectiveness of multiple-allergen SCIT is based on clinical experience rather than on research studies. Idealistically, we would need some long-term, head-to-head, SCIT vs SLIT studies with multiple allergen extracts to provide a fair comparison.

NOVEL DELIVERY METHODS

In addition to SLIT, other novel delivery methods are being explored. Intranasal immunotherapy, for example, has been shown to be effective, but it is extremely difficult to control symptoms during administration. Intranasal might be a viable option if better allergoids were available but not with the current extracts.

Epicutaneous immunotherapy warrants further study based on 2 recent European studies^{14,15} that administered grass extract applied to a patch weekly for 12 weeks and left on for 24 hours in one group and 48 hours in the other. Both showed reasonably good response in the first year, and one showed continuing response in year 2 without further treatment.

Perhaps the most exciting new approach on the horizon is intralymphatic administration of allergen abstracts, a modality that has been explored by infectious disease professionals with expertise in vaccination science. Early animal data show a much greater immune response with a small amount of extract injected into the inguinal lymph node compared with significantly larger amounts injected subcutaneously. Results of the early research¹⁶ are extremely promising, with 3 injections at monthly intervals producing the equivalent of 36 months of SCIT with a carryover effect at least at the end of 3 years. The study showed that a milliliter of extract can be injected into 1 inguinal lymph node without pain, allowing multiple allergen dosing without added cost.

THE ROLE OF THE ALLERGIST

Regardless of the methods used for immunotherapy, the allergist has a number of important roles to play, especially in monitoring patients at risk for systemic reactions and in patient selection. It will be a great disservice to patients, for example, if they are started on SLIT or another form of immunotherapy based solely on results of serum specific IgE tests. Although skin tests and specific IgE tests identify sensitization, they do not establish a clinical diagnosis. Appropriate diagnosis and patient selection require not only in vivo and/or in vitro tests but also correlation with the patient's history and physical examination results to determine what the patient is allergic to and to choose the most efficacious treatment, including whether SLIT or SCIT is likely to have a favorable outcome. The allergist also has expertise in local and regional aerobiology, which is not part of primary care training. The allergist plays an important role in teaching patients how to avoid relevant allergens, treat their disease, and recognize potential treatment-related adverse events. Al-

lergists also are the physicians best trained to effectively treat anaphylaxis in the office setting should it occur.

With SLIT and other promising new approaches, immunotherapy will start to take its rightful place as the only disease-modifying treatment for allergic diseases. As more and more data emerge, people, especially those who before have resigned themselves to a lifetime of medication use, will begin to take notice. One informal review of marketing data from the major extract manufacturers found that, even as SLIT increased, there was no corresponding reduction in the use of SCIT.

We are also starting to get some impressive cost-effective data that show the value of SCIT. Recent studies^{17,18} in the Florida Medicaid population, for example, looked at 11 years of data in patients with new-onset rhinitis and found a 41% reduction in total health care costs in adults and a 52% reduction in children and adolescents with SCIT vs pharmacotherapy. Savings, which included pharmacy, outpatient, and inpatient costs, were seen beginning at 3 months and increased during an 18-month period.

We have completed the first 100 years of immunotherapy, and there is much ahead that has enormous potential to improve the lives of our patients. In addition to the more recent developments discussed in this perspective, we can expect even greater advances in immunotherapy. As with any form of therapy, our ultimate goal is the long-term benefit to patients. As physicians, we always should strive to do the job better, faster, and less expensively to benefit the greatest number of people for the longest period. With so many new options available or on the horizon, we have an exciting future ahead.

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Requests for reprints should be addressed to:

Dana V. Wallace, MD

Nova Southeastern University

2699 Stirling Rd, B305

Fort Lauderdale, FL 33312

E-mail: drdanawallace@gmail.com