



Perspective

Current and future challenges of subcutaneous and sublingual allergy immunotherapy for allergists in the United States



Harold S. Nelson, MD

National Jewish Health, University of Colorado Denver School of Medicine, Denver, Colorado

ARTICLE INFO

Article history:

Received for publication November 15, 2017.

Received in revised form December 13, 2017.

Accepted for publication December 19, 2017.

Both subcutaneous and sublingual allergy immunotherapy (SCIT and SLIT, respectively) for inhalant allergens have proven efficacy for allergic rhinitis and allergic asthma, with limited support for efficacy in selected patients with atopic dermatitis.¹ Both SCIT and SLIT have been shown to modify the immunologic defect underlying the allergic respiratory diseases,² an effect that is clinically manifest by suppression of new sensitization in monosensitized patients, reduction in the development of asthma in those only having allergic rhinitis, and persistence of clinical improvement for years after an adequate course of treatment.¹ Effective and often less-effective doses have been determined for many standardized extracts for SCIT through randomized, double-blind trials.¹ With SLIT tablets, large, blinded, dose-ranging studies have been conducted with grass, ragweed, and house dust mite tablets, establishing, again, effective and less-effective doses. There remain, however, problems with both SCIT and SLIT that limit their use to a small percentage of those patients who would benefit from allergy immunotherapy (AIT) (Table 1). This study expands on these challenges.

SCIT Safety and Inconvenience

Injections of allergens to which the patient is sensitive can produce painful local and alarming and dangerous systemic reactions. Because of this potential for systemic reactions, injections must be given in a physician's office. Also, for the same reason, a course of SCIT requires frequent visits for initial build-up to a maintenance dose followed by less frequent visits for the 3 to 5 years of treatment required for lasting benefit. There are a number of strat-

Table 1

Challenges with Use of Current AIT

Subcutaneous:
1. Safety
2. Inconvenience:
a. Duration
b. Requirement for clinic visits for injections
Sublingual:
1. Duration
2. Undefined doses for liquid extracts in the United States
Both SCIT and SLIT:
1. Need for standardization, quality improvement, and dose determination of present unstandardized extracts
2. Establishing the efficacy of multiallergen mixtures
3. Development of less costly alternatives to randomized, double-blind, placebo-controlled trials to establish dosing and efficacy

Abbreviations: AIT, allergy immunotherapy; SCIT, subcutaneous allergy immunotherapy; SLIT, sublingual allergy immunotherapy.

egies being explored to improve safety and efficacy and shorten the period of treatment (Table 2).³ The status of intralymphatic AIT is uncertain, but epicutaneous administration appears promising, with reduction in symptoms during consecutive grass pollen seasons of 38% and 25% compared with placebo after just 6 weekly applications of patches prior to the first season.⁴ In Europe, there is increasing use of allergoids prepared from native extracts by treatment with aldehydes. This approach reduces the allergenicity while retaining immunogenicity and allowing rapidly escalating doses, but it does not shorten the course of treatment.³ Other recombinant approaches promise greatly shortened duration of treatment, but thus far none have clearly established efficacy and there have been some notable failures, as there have also been with agonists for the Toll-like receptors.³ There have been some encouraging reports on the combination of AIT with probiotics. The most impressive is one from China in which the addition of the probiotic *Clostridium butyricum* to 6 months of SCIT produced marked clinical and immunologic

Reprints: Harold S. Nelson, MD, National Jewish Health, University of Colorado Denver School of Medicine, 1400 Jackson Street, Denver, CO 80206; E-mail: nelson@njhealth.org.

Disclosures: Author has nothing to disclose.

<https://doi.org/10.1016/j.anaai.2017.12.013>

1081-1206/© 2018 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Table 2Strategies to Reduce Number of Injections and Increase the Safety and Efficacy of AIT²

1. Change to a more efficient route of administration: intralymphatic or epicutaneous
2. Increase the dose of allergen by reducing its allergenicity by: chemical modification, recombinant modification, or non-IgE-binding peptides
3. Use of a Th1 or Treg promoting TLR ligand: CpG oligonucleotides or MLP
4. Suppression of Th2 response: Th2-cytokine antagonists
5. Adjuvants: anti-IgE, vitamin D, or probiotics

Abbreviations: AIT, allergy immunotherapy; CpG, cytosine-phosphate-guanine; IgE, immunoglobulin E; MLP, monophosphoryl lipid A; Th, T helper; Treg, regulatory T cell; TLR, Toll-like receptor.

changes that persisted, without diminution, 6 months after treatment was stopped.⁵ The results with SCIT alone included less clinical improvement during treatment and no significant persistence after stopping.

SLIT Duration

Although SLIT is clearly safer than SCIT, to the extent that all but the first dose can be taken at home, it still requires at least 3 years of treatment to achieve persisting benefit.⁶ Perhaps because there is not the continuing reinforcement of clinic visits, patient adherence to 3 years of SLIT is very poor, and worse than that with SCIT.⁷

Dosing with Liquid Allergen Extracts in the United States

Only 3 SLIT tablets, short ragweed, grass, and house dust mite, are available, with birch and cedar SLIT tablets in phase III studies. Due to the expense of developing and obtaining registration for these products there will never be SLIT tablets for most of the allergens treated with AIT in the United States.

US FDA-approved liquid allergen extracts are indicated only for injection, not for sublingual use.⁸ There have been no adequate dose-response studies conducted with these extracts administered sublingually. One double-blind, placebo-controlled study conducted with short ragweed extract demonstrated comparable clinical efficacy to that of the approved SLIT ragweed tablet with a dose 4 times greater.⁹ It is not possible to draw on the European experience to determine effective liquid SLIT doses, as the SLIT extracts commercially available in Europe have been shown to have a widely varying content of major allergens and, presumably, of potency.¹⁰

Standardization and Improvement in Quality of Current Nonstandardized Extracts

In the United States, perhaps the most compelling need is for standardized fungal (mold) extracts. Mold allergy has been a major contributor to asthma epidemics and death.^{11,12} Immunotherapy with standardized *Alternaria* extract has been shown to be very effective in childhood asthma.¹³ However, the fungal extracts available in this country are of widely varying and probably low potency,¹⁴ and it is questionable whether similar efficacy can be obtained with them as described in the study by Kuna and colleagues.¹³

Additional problems arise with extracts of the aeroallergens incriminated in asthma in inner city children.¹⁵ There are limited data showing that glycerinated cockroach extract is of borderline potency, but information on the quantity and relevance of the allergens in commercial mouse and rat extracts is lacking. Once standardized, it will be important to conduct dose-ranging studies with all of these extracts to determine safe and effective doses.

Most dog dander extracts commercially available in the United States are too low in allergen content to allow for administration

of doses shown to be effective.¹⁶ Fortunately, there is one dog extract that has been shown to contain sufficient major allergen to allow adequate diagnosis and treatment of dog allergy.¹⁶

Most weed and tree pollens have not been standardized. Fortunately, the method of pollen extract preparation assures the production of a potent extract, although potency varies from batch to batch and manufacturer to manufacturer.

Establishing Efficacy of Multiallergen Mixtures for SCIT and SLIT

There have been 4 randomized, blinded studies of SCIT with mixtures of more than 2 allergen extracts that demonstrated clinical efficacy in allergic rhinitis and asthma.¹ In 2 studies conducted with ragweed and 1 with grass pollen extract, both the patients receiving active treatment and those receiving placebo were also receiving in their injections a mixture of other allergens to which they were sensitive (although numbers of these extracts were not provided in any study). In the fourth study, children with asthma received separate vials containing mixtures of those pollens, fungi, and danders to which they were sensitive, but house dust extract was given alone. Thus, it is uncertain in this study the extent to which efficacy could be attributed to the allergens delivered in mixtures. Most US allergists are satisfied with the clinical response they observe in their patients treated with multiallergen mixes and feel supported, if they are aware of them, by the aforementioned studies; however, authors of the European guidelines generally reject treatment with more than 2 extracts and, when they do administer 2 extracts, they are given separately.¹⁷ Therefore, there is a likely need for a well-designed study comparing placebo, a single allergen, and that same allergen, at the same concentration and dilution, in a multiallergen mixture.

The situation with multiallergen SLIT is quite different. Two studies have demonstrated efficacy of 2 allergens administered together sublingually.¹ There has been only 1 study of a true multiallergen mixture.¹⁸ In that placebo-controlled study, the same dose of Timothy grass extract was administered mixed with saline or with 9 other unrelated pollen extracts. The outcomes, titrated nasal allergen challenge, titrated skin prick test (SPT), and Timothy-specific immunoglobulin G4, were all significantly different from placebo in the Timothy monotherapy group, but only titrated SPTs differed significantly from placebo in the multiallergen group and then to much lesser a degree than in the monotherapy group.¹⁸

Establishing Less Costly Alternatives to Randomized, Double-Blind Clinical Trials

When a new allergenic product is proposed for either SCIT or SLIT, it is mandatory that large, randomized, placebo-controlled trials be conducted in patients undergoing natural exposure to that aeroallergen to establish not only efficacy but also safety. These trials are extremely expensive and are usually conducted only when the sponsor is in a position to financially benefit from approval of the product. In addition to expense, there are other problems with trials based on natural exposure, including: the variability of pollen seasons due to differences in weather patterns; an isolated season of exposure does not exist for many pollens, especially weeds in the western United States and trees in most regions of the country; and, for perennial allergens, it is often difficult to determine whether a patient's symptoms are attributable to a particular aeroallergen or to other allergens, or even nonallergic causes. For these reasons, it would be desirable to utilize a less-expensive method, one in which the relationship to the allergen of interest is unequivocal and could be conducted out of season. So far, 2 approaches have been used, the environmental exposure chamber (EEC) and the nasal

allergen challenge (NAC), neither of which has been accepted by the US FDA.

An example of the use of the EEC compared with field trials with natural exposure is available in the studies on the recently approved house dust mite (HDM) SLIT tablet. One hundred twenty-four subjects with allergic rhinoconjunctivitis, who experienced the requisite level of symptoms on baseline exposure to HDM allergen in the EEC, were randomized to 24 weeks of treatment with placebo or to 6 or 12 developmental units (DU) of SLIT HDM tablets.¹⁹ After 24 weeks, the improvement in total nasal symptom scores during repeat EEC exposure relative to placebo was 48.6% for the 12-DU tablet and 26.6% for the 6-DU tablet. These same doses were studied in 992 HDM allergic subjects with allergic rhinitis symptoms despite pharmacologic treatment in a field trial.²⁰ After 1 year of treatment, the reduction in total combined rhinitis score, relative to placebo, was 17.5% for the 6-DU and 18.0% for the 12-DU HDM SLIT tablets. Thus, the EEC provided a more clearly defined dose-response with just one eighth as many subjects in half the time.

Even more readily available and less costly than an EEC, which could cost in the neighborhood of \$2.5 million, is the titrated NAC to measure the response to immunotherapy. As early as 1988, Bousquet and colleagues demonstrated a high degree of correlation between the endpoint on titrated nasal challenge to grass and symptoms during natural grass pollen exposure.²¹ Titrated NAC can provide information on both the clinical and immunologic response to AIT.²² In a recent study, retrospective scores during the grass pollen season correlated with both the total nasal symptom score and change in peak nasal inspiratory flow responses to nasal challenge and, with just 14 patients in each group, showed highly significant differences in clinical and immunologic responses between allergic subjects who were AIT-naïve versus those actively receiving AIT.²² Thus, the nasal allergen challenge may provide convenient and inexpensive answers to many practical questions that remain in the practice of AIT.

Conclusions

There are formidable challenges facing allergists in the United States in the practice of AIT. Who should be addressing them? When the need is new products, SLIT tablets, allergoids, modified allergens, and peptides from recombinant technology, clearly these will be developed by companies with the resources to pay for the large studies required to establish safety and efficacy and who, if successful, will benefit from the sale of these new products. When it comes to improvement in the quality and standardization of liquid allergen extracts, it is the responsibility of the FDA, and ultimately Congress, to provide adequate funding to meet this need. There are other needs as well, where the responsibility is not as clear. New approaches that utilize presently available and relatively inexpensive products offer no incentive for industry to invest large amounts of money for their development. In this category, we have intralymphatic and epicutaneous AIT, and adjuvants, such as vitamin D and probiotics. There is even less incentive for industry to pursue determination of appropriate SLIT dosing with FDA-approved liquid allergen extracts, or for the study of efficacy of multiallergen mixes by either SCIT or SLIT. It seems that either the National Institutes

of Health or the 2 national allergy societies should step up to meet this need.

References

- [1] Nelson HS, Makatsori M, Calderon MA. Subcutaneous immunotherapy and sublingual immunotherapy: comparative efficacy, current and potential indications, and warnings—United States versus Europe. *Immunol Allergy Clin North Am*. 2016; 36:13–24.
- [2] Lawrence MG, Steinke JW, Borish L. Basic science for the clinician: mechanisms of sublingual and subcutaneous immunotherapy. *Ann Allergy Asthma Immunol*. 2016;117:138–142.
- [3] Nelson HS. Allergen immunotherapy now and in the future. *Allergy Asthma Proc*. 2016;37:268–272.
- [4] Senti G, von Moos S, Tay F, et al. Determinants of efficacy and safety in epicutaneous allergen immunotherapy: summary of three clinical trials. *Allergy*. 2015;70:707–710.
- [5] Xu Z, Yang L-T, Qiu S-Q, et al. Combination of specific allergen and probiotics induces specific regulatory B cells and enhances specific immunotherapy effect on allergic rhinitis. *Oncotarget*. 2016;23:54360–54369.
- [6] Scadding GW, Calderon MA, Shamji MH, et al. Effect of 2 years of treatment with sublingual grass pollen immunotherapy on nasal response to allergen challenge at 3 years among patients with moderate to severe seasonal allergic rhinitis: the GRASS randomized clinical trial. *JAMA*. 2017;317:615–625.
- [7] Kiel MA, Roder E, Gerth va Wijk R, et al. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. *J Allergy Clin Immunol*. 2013;132:353–360.
- [8] Greenhawt M, Oppenheimer J, Nelson M, et al. Sublingual immunotherapy: a focused allergen immunotherapy practice parameter update. *Ann Allergy Asthma Immunol*. 2017;118:276–282.
- [9] Creticos PS, Esch RE, Couroux P, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2014;133:751–758.
- [10] Larenas-Linnemann DE, Mosges R. Dosing of European sublingual immunotherapy maintenance solutions relative to monthly recommended dosing of subcutaneous immunotherapy. *Allergy Asthma Proc*. 2016;37:50–56.
- [11] Salvaggio J, Seabury J, Schoenhardt E. New Orleans asthma. V. Relationship between Charity Hospital asthma admission rates, semiquantitative pollen and fungal spore counts, and total particulate aerometric sampling data. *J Allergy Clin Immunol*. 1971;48:96.
- [12] O'Hollaren M, Yunginger JW, Offord KP, et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *New Engl J Med*. 1991;324:359–363.
- [13] Kuna P, Kaczmarek J, Kupczyk M. Efficacy and safety of immunotherapy for allergies to *Alternaria alternata* in children. *J Allergy Clin Immunol*. 2011;127:502–508.
- [14] Esch RE. Manufacturing and standardizing fungal allergen products. *J Allergy Clin Immunol*. 2004;113:210–215.
- [15] Ahluwalia SK, Peng RD, Breyse PN, et al. Mouse allergen is the major allergen of public health relevance in Baltimore City. *J Allergy Clin Immunol*. 2013; 132:830–835.
- [16] Smith DM, Coop CA. Dog allergen immunotherapy: past, present and future. *Ann Allergy Asthma Immunol*. 2016;116:188–193.
- [17] Zuberbier T, Bachert C, Bosquet PJ, et al. GA2LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. *Allergy*. 2010;65: 1525–1530.
- [18] Amar SM, Harbeck RJ, Sills M, et al. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. *J Allergy Clin Immunol*. 2009;124:150–156.
- [19] Nolte H, Maloney J, Nelson HS, et al. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. *J Allergy Clin Immunol*. 2015;135:1494–1501.
- [20] Demoly P, Emminger W, Rehm D, et al. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: results from a randomized double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol*. 2016;137:444–451, e8.
- [21] Bousquet J, Maasch H, Martinot B, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. II. Comparison between parameters assessing the efficacy of immunotherapy. *J Allergy Clin Immunol*. 1988;82:439–446.
- [22] Scadding GW, Eifan AO, Lao-Araya M, et al. Effect of grass pollen immunotherapy on clinical and local immune response to nasal allergen challenge. *Allergy*. 2015;70:689–696.