

*Editorial***Tradition and innovation: Finding the right balance**Stephen R. Durham, MD *London, United Kingdom*

**Key words:** Allergen immunotherapy, subcutaneous, sublingual, peptide, recombinant allergens, T-regulatory cells

Allergen immunotherapy involves the repeated administration of allergen extracts to subjects with allergy and IgE-mediated disease. The aim is to improve their quality of life while reducing symptoms and the need for antiallergic medication on re-exposure to the relevant allergen.<sup>1</sup> The traditional approach involves the subcutaneous injection of incremental amounts of extracts of natural allergen sources at weekly intervals for several months followed by monthly maintenance injections for generally 3 to 5 years. The practice of immunotherapy was initiated in the United Kingdom almost 100 years ago.<sup>2</sup> Frankland and Augustin<sup>3</sup> published the first randomized controlled trial of grass pollen immunotherapy in 1954. There followed the landmark studies of Lowell and Franklin<sup>4</sup> in ragweed hayfever in the 1960s and the use of *Hymenoptera* venom, as opposed to whole insect body extract, for the successful treatment of insect anaphylaxis in 1978.<sup>5</sup> Since the 1980s, attempts have been made to standardize allergen extracts better by using both biological methods (by skin-testing patients with allergy or by *in vitro* inhibition assays) and, more recently, by estimation of the content of major allergens in extracts.<sup>1,6</sup>

Injection immunotherapy using traditional allergen extracts is of proven value in subjects with anaphylaxis caused by bee and wasp venom and in subjects with allergic rhinitis and bronchial asthma caused by inhaled allergens, although in patients with asthma, the benefit/risk ratio must be carefully assessed because the risks of

adverse systemic side effects are increased.<sup>1</sup> Immunotherapy is particularly indicated in subjects with a limited spectrum of allergies and in those who have failed to respond to usual antiallergic drugs. In contrast with pharmacotherapy, allergen injection immunotherapy has long-term benefits that may persist for at least 3 to 5 years after discontinuation. These include long-term remission of symptoms,<sup>7</sup> a decrease in the onset of new sensitizations,<sup>8</sup> and, in subjects with rhinitis alone, a reduction in the likelihood of progression of their disease from rhinitis to asthma.<sup>9</sup>

Despite the proven efficacy of the traditional approach, there are clear limitations. This is the basis for the current series of articles in the Journal by experts in the field: to evaluate critically the traditional approach while identifying the knowledge gaps and to understand better the mechanistic basis of immunotherapy that has and will continue to provide impetus for the development of novel approaches and biomarkers to predict the clinical response to therapy. These approaches include alternative routes of administration, particularly the sublingual route<sup>10,11</sup>; the use of novel adjuvants<sup>12</sup>; and the combination of allergen extracts with anti-IgE therapy<sup>13</sup> to reduce IgE-mediated side effects. Peptide immunotherapy<sup>14</sup> involves the use of short allergen peptides that maintain immunogenicity while avoiding IgE cross-linking, thereby reducing the risk of anaphylaxis. Finally, there is a review of recombinant allergens, the holy grail of standardization, for the production of allergens of known and reproducible composition.<sup>15</sup>

The efficacy of allergen injection immunotherapy for allergic respiratory disease has been confirmed in systematic reviews and meta-analyses for asthma<sup>16</sup> and (recently) for allergic rhinitis.<sup>17</sup> The benefit of high-dose over low-dose therapy was shown in a large, definitive, real world controlled trial of severe hayfever in 410 patients who had free access to best standard therapy (intranasal corticosteroid and antihistamines).<sup>18</sup> The study included subjects who were polysensitized, with or without seasonal asthma. Reductions in symptoms and use of medication were accompanied by substantial improvements in quality of life. Injection immunotherapy is effective for seasonal allergies (to grasses, trees, and weeds) and for perennial allergies (to cats and house dust mite). As Nelson<sup>19</sup> points out, evidence is scanty and far less convincing for molds, cockroach, and dog allergy, and only preliminary data are available for patients with atopic dermatitis and food allergies, such that immunotherapy is not currently

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Disclosure of potential conflict of interest: S. R. Durham has received grants from ALK-Abelló, GlaxoSmithKline, and UCB; is a member of the Allergy Panel Immune Tolerance Network; has served on the speakers' bureau for ALK-Abelló and GlaxoSmithKline; and has served as an expert witness for Schering-Plough.

Received for publication February 16, 2007; revised February 26, 2007; accepted for publication February 28, 2007.

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J Allergy Clin Immunol 2007;119:792-5.

0091-6749/\$32.00

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doi:10.1016/j.jaci.2007.02.034

**TABLE I.** Cochrane systematic meta-analyses<sup>17,25</sup> for subcutaneous and sublingual immunotherapy for allergic rhinitis: summary statistics (standardized mean differences [SMDs] and CIs) for principle outcomes

	Subcutaneous immunotherapy <sup>17</sup> SMD (95% CI)	Sublingual immunotherapy <sup>25</sup> SMD (95% CI)
Seasonal symptom scores	−0.73 (−0.97, −0.50)	−0.42 (−0.69, −0.15)
Seasonal medication scores	−0.57 (−0.82, −0.33)	−0.43 (−0.63, −0.23)

recommended in these circumstances.<sup>1</sup> Whereas cited evidence for prolonged effects of injection immunotherapy and inhibition of progression from rhinitis to asthma is based on randomized controlled trials,<sup>7,9</sup> that for prevention of new sensitizations is based on retrospective and/or nonrandomized studies,<sup>8,20,21</sup> and more robust data are required to confirm this important concept. A major unmet need is effective therapy for subjects with perennial asthma and multiple allergen sensitivities, the group that is least likely to benefit from immunotherapy<sup>22</sup> and in whom the risk of side effects is increased.

The sublingual route has emerged as an effective alternative to subcutaneous immunotherapy.<sup>10,11</sup> The indications are broadly similar, and where both treatments are available, patient preference becomes an important determinant of choice. Selection of patients for sublingual immunotherapy remains the remit of physicians trained and experienced in allergy and immunotherapy, whereas a more favorable safety profile makes this treatment suitable for home use and therefore more accessible to a broader range of patients. Optimal dosing and duration of sublingual immunotherapy needs to be determined for the different allergens. Two recent large randomized trials<sup>23,24</sup> have confirmed that at least for preseasonal/seasonal grass pollen sublingual immunotherapy, there is a clear dose-response relationship, and that greater than 8 weeks of preseasonal treatment is more effective than a shorter preseasonal course. It is unclear whether more prolonged therapy over years will require such high doses for efficacy.

Nelson<sup>19</sup> reviews the scanty evidence directly comparing the subcutaneous and sublingual approaches and tentatively concludes that improved safety of the sublingual route may be associated with reduced efficacy. Summary data from 2 recent meta-analyses<sup>17,25</sup> for the 2 routes of immunotherapy in subjects with allergic rhinitis are shown in Table I. Selection criteria for the studies were very similar, except that the analysis of subcutaneous immunotherapy (2871 participants) was confined to seasonal disease, whereas the review of sublingual immunotherapy (959 participants) included a minority of studies that used perennial allergens (house dust mite and cat). Compared with placebo, both routes were effective, whereas the standardized mean differences for both symptoms and rescue medication were greater for the subcutaneous route. There is overlap of the 95% CIs such that without more data, no firm conclusions can be drawn concerning the comparison of the 2 routes. The sublingual route has a good safety record, and adverse events have been largely confined to itching in the mouth and localized tongue swelling, which in general have been well tolerated. There are conflicting

results for studies of sublingual immunotherapy in children, and Pajno<sup>26</sup> rightly identifies the need for more data on the mechanism of sublingual immunotherapy and more convincing evidence for the possible long-term effects of sublingual immunotherapy.

Our current knowledge of the mechanisms of immunotherapy is summarized by Akdis and Akdis.<sup>27</sup> Immunotherapy suppresses the numbers and activation of effector cells including mast cells, basophils, and eosinophils in target organs (see summary<sup>28</sup>). There are increases in allergen specific IgG antibodies, particularly the IgG<sub>4</sub> isotype, with blunting of seasonal increases in allergen-specific IgE. These events occur as a consequence of modulation of the T-cell response to allergen, principally the emergence of a population of T-regulatory cells with potential to downregulate both T<sub>H</sub>2 and T<sub>H</sub>1 responses to allergen,<sup>29,30</sup> whereas immune deviation in favor of allergen-driven T<sub>H</sub>1 responses has also been reported.<sup>31,32</sup> These observations have prompted the development of novel adjuvants including T<sub>H</sub>1-deviating agents such as bacterial cell wall LPS derivatives (monophosphoryl lipid A)<sup>33</sup> and bacterial DNA cytosine p guanine-containing oligonucleotides.<sup>34</sup> The latter have recently been shown to have potential for inducing protolerogenic effects via dendritic cells and Toll-like receptor 9 engagement.<sup>35</sup>

T-cell epitope-containing peptides derived from allergens are able to modulate T-cell responses while having a reduced ability to cross-link IgE and hence a low potential for inducing anaphylaxis.<sup>14</sup> The first trial of peptide immunotherapy in subjects with cat allergy by Norman et al<sup>36</sup> demonstrated that the use of high doses and longer fragments of Fel d 1 was associated with some evidence of efficacy but unacceptable delayed side effects. Oldfield et al<sup>37</sup> have shown that lower doses given by the intradermal route may induce allergen-specific T-regulatory responses that are accompanied by alterations in surrogate markers including suppression of allergen-induced late responses, without eliciting adverse events. Further studies of clinical endpoints are in progress. An unanswered question is whether T-cell epitopes alone, in the absence of B-cell epitopes, are sufficient to induce long-term efficacy and disease remission.

Knowledge of the mechanisms of immunotherapy, in addition to prompting novel approaches, has given rise to novel assays/biomarkers that have potential to predict the clinical response to immunotherapy. Immunoreactive serum allergen-specific IgG and IgG<sub>4</sub> levels are elevated after immunotherapy but fail to predict clinical efficacy. Functional assays of serum blocking IgG activity as determined by suppression of FcεR1-dependent basophil histamine release<sup>38</sup> or inhibition of FcεR2 (CD 23)-dependent

binding of allergen-IgE complexes to B cells<sup>39</sup> may be surrogate and/or predictive of individual clinical responses. Assays of T-cell tolerance such as peripheral IL-10 production,<sup>40,41</sup> detection of peripheral allergen-specific T cells by use of tetramer technology,<sup>42</sup> and functional assays of the ability of T cells to downregulate allergen-specific T-cell responses<sup>43</sup> are currently under development. The potential for clinical markers of tolerance, including suppression of immediate and late-phase skin responses to predict the individual response to immunotherapy, should be critically evaluated. These novel assays should be evaluated in the context of large controlled trials to determine whether they may predict when to start, when to stop, and when to predict relapse and the need for a further course of immunotherapy.

Valenta and Niederberger<sup>15</sup> present a compelling case for the further development of recombinant allergens for diagnosis and immunotherapy. This approach overcomes the major obstacle of standardization of natural allergen extracts and allows the production in unlimited amounts of allergens of defined and consistent composition. Other advantages outlined include the avoidance of contaminants, the potential to adjust allergen potencies and ratios precisely for tailor-made therapy, and the availability of pure molecules for mechanistic studies and for development of bioassays for clinical monitoring. Options include use of mixtures of recombinant allergens or recombinant hybrids to substitute natural allergens and/or the development of recombinant hypoallergenic variants. There may be potential disadvantages of the recombinant approach such as issues surrounding the level of glycosylation or the accuracy of refolding of recombinant allergens that may unpredictably alter their biological properties. Furthermore, it is possible that contaminants in natural allergen products may potentially have an adjuvant effect that may be important for clinical efficacy. Currently, the clinical evidence base for use of recombinant allergens,<sup>44</sup> although encouraging (see reference,<sup>15</sup> Table I) is very limited, and further controlled trials are urgently needed.

In summary, allergen injection immunotherapy with conventional allergen extracts is highly effective for IgE-mediated disease and has long-term benefits that persist for years after its discontinuation. The sublingual route is emerging as an effective alternative suitable for home administration. A greater understanding of mechanisms of immunotherapy has led to novel approaches and lends promise for the development of biomarkers to monitor the clinical response to therapy. The place of novel adjuvants, modified natural allergens, peptide immunotherapy, and recombinant allergens and their hypoallergenic variants will depend on the outcome of focused, adequately powered, and well designed clinical trials. Meanwhile, conventional allergen extracts via the subcutaneous route remain the gold standard for comparison.

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