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Harold S Nelson

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Allergen immunotherapy: what's new, what's next?

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Harold S Nelson

National Jewish Health, 1400 Jackson Street, Denver, CO 80206, USA
Tel.: +1 303 398 1562
nelson@njhealth.org

Although three sublingual immunotherapy tablets have been approved in the USA and more are under study, it is not clear that sublingual immunotherapy tablets will answer the needs of many patients in the USA, and this is due to the limited number of allergens that will be offered. Alternatives that employ off-label, currently available extracts hold the greatest likelihood of entering the US allergy practice. Those approaches that employ recombinant technology to produce hypoallergenic products face a long and expensive pathway to approval. Which of the many approaches under study will make it to the market is presently not clear.

There have been no significant recent developments with subcutaneous immunotherapy (SCIT) in the USA. There have recently been a number of studies reporting some success with oral, sublingual and epicutaneous immunotherapy in patients with food allergy, but more work is needed to ensure the balance of efficacy outcomes with long-term safety before these approaches are applied in clinical practice [1]. What is new in the USA is the approval in April 2014 by the FDA of three tablet preparations for sublingual immunotherapy (SLIT). This opens the way for SLIT treatment of grass- and ragweed pollen-induced allergic rhinitis. SLIT tablets are under development for house dust mites, birch pollen and cat. This will leave, however, major gaps in the treatment of clinical allergies in the USA. A recent telephone survey of individuals with allergic rhinitis reported that the most frequent time for seasonal rhinitis in the USA was the early spring, prior to the grass pollen season indicating symptoms caused by a variety of tree pollens [2]. A birch SLIT tablet will have little impact on these spring symptoms as birch is not a major cause of allergy in the USA. Additionally, there are regional differences in exposures that are not addressed by the projected tablets, including western weeds such as sage and tumble weed and southern grasses such a Bermuda, Johnson and Bahia as well as allergy to dogs.

Many US physicians are using the aqueous extracts, approved for diagnosis and SCIT, for SLIT. There are problems with this practice; first is lack of studies on the appropriate dosing with these liquid extracts. Second is the assumption that the favorable results with SLIT monotherapy can be achieved with the administration of mixes of more than two allergen extracts, even though the only published study suggests that this may not be correct [3].

Despite its efficacy, SCIT has two drawbacks, many visits required to complete a course of therapy and potential for adverse reactions. Two methods employed in Europe address the frequency of visits and of reactions, especially during the build-up phase. These are the use of aluminum hydroxide to delay absorption from the injection site and treatment of the extract, usually with glutaraldehyde, to produce allergoids with decreased allergenicity (binding with specific IgE) but retained immunogenicity (stimulation of T cells). Recently, with two of these product lines the up-dosing with allergoids has been shortened to 2 or 3 injections [4],

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without any apparent effect on safety. Although significant clinical improvement has been shown in placebo-controlled studies with allergoids [5], the concept of allergoids has been challenged by studies showing that both allergenicity and immunogenicity are reduced in the process [6]. Whatever the truth of this debate, neither widespread use of aluminum hydroxide nor of allergoids is likely to be introduced into practice in the USA. Previous actions of the FDA on polymerized extracts and concerns regarding the safety of long-term administration of aluminum hydroxide will not encourage any pharmaceutical company to undertake the expensive development program that would be required for their approval.

If improvements in SCIT are stifled by the approval process and SLIT has definite shortcomings for the US market, where is the future of allergen immunotherapy in the USA likely to be? There are certainly many new approaches to allergen immunotherapy under active investigation, some in Phase III studies, others still limited to murine studies [7,8]. They may be divided into those approaches that employ the aqueous extracts currently approved in the USA and those involving modifications in the extracts, usually employing recombinant technology.

New approaches that utilize the aqueous extracts currently approved in the USA are attractive. They may involve off-label use, but may be able to avoid the expensive clinical trials required for FDA approval of a new drug. Under active investigation using currently available extracts are intralymphatic [9], epicutaneous [10] and intradermal [11]. In an open trial, 165 patients with grass pollen-induced rhinoconjunctivitis were randomized to receive a conventional 3-year course of SCIT requiring 54 injections with a cumulative allergen dose of 4,031,540 SQ units or, alternatively, three intralymphatic injection over 2 months with a cumulative dose of only 3000 SQ units. The 3-year outcomes were similar and the safety of intralymphatic was superior to conventional SCIT [9]. However, a randomized, placebo-controlled study of this approach failed to confirm the efficacy of intralymphatic immunotherapy [12], but the results were challenged because the injections were given at 2-week rather than 4-week intervals. ClinicalTrials.gov lists two ongoing studies of intralymphatic immunotherapy that may settle the controversy.

Epidermal delivery of allergen extract by placement of patches is said to have the advantages of greater efficiency and safety. Several clinical trials have been reported with clinical efficacy persisting into the second pollen season without any booster treatment. Although the results are promising, further research is needed to define the optimal regimen that balances clinical efficacy and safety, including method of preparation of the skin to enhance penetration, the allergen dose, the number of patches and the duration that each patch will remain in place [10]. Thirty grass-sensitized adults were given six intradermal injections of small amounts of grass pollen extract at 2-week intervals. By the end of the treatment, they had marked suppression of the late phase cutaneous reaction to grass pollen extract, but not to birch pollen extract indicating specificity of the treatment [11]. A clinical trial in patients with seasonal allergic rhinitis was scheduled for completion in August 2014, but the results have not yet been reported.

Alternatively, but also at much greater expenses, standard SCIT can be combined with a biological treatment to make it safer or more effective. Randomized controlled trials have shown that pretreatment with omalizumab increases the safety of both rush immunotherapy in ragweed allergic rhinitis and cluster immunotherapy in allergic asthma due to perennial allergens [13]. Underway are studies to determine if reduction in the Th2 responses, either with an IL-4 or a thymic stromal lymphopoietin inhibitor will enhance the effectiveness of SCIT.

Recombinant technology makes possible altering the structure of allergens [7,8]. Among the approaches that are under investigation designed to manipulate the major allergen to avoid reactivity with IgE but retain T-cell epitopes are: folding variants of Bet v1, hybrids of T-cell epitope-containing stretches of the five most important *Fagales* allergens, three contiguous overlapping peptides of Bet v1 and a mosaic protein derived from four cDNAs coding for Phl p 1 fragments. A different rationale underlies the generation of peptide-carrier fusion proteins that have been produced by bindings two nonallergenic Fel d 1-derived peptides [14], or hypoallergenic peptides from the four major allergens of timothy to hepatitis B virus-derived PreS domain. Administration of these proteins results in the generation of IgG antibodies that have been shown to inhibit the binding of allergic patients' IgE to the allergen.

Perhaps farthest along in clinical development are the Fel d 1-derived peptides described by Kay and Larche. These consist of 7 (13–17 amino acids) peptides that react with T-cell epitopes, do not react with specific IgE and bind to the most common HLA antigens. In an Environmental Exposure Chamber, 4 monthly intradermal injections of 6 nmols of peptides produced an improvement in nasal symptoms of approximately 30% over that with placebo that persisted 2 years after initiation of treatment [15]. A caveat regarding this result, however, is that only 51 of the initial 202 subjects were still available for the 2-year follow-up. A large Phase III study with these peptides has completed enrollment. Peptides derived from ragweed, cat and house dust mite are also undergoing study.

Another approach to immunotherapy is stimulation of the innate immune system to induce Treg and Th1 responses. Results with two preparations with this mechanism of action have recently been reported. A tyrosine adsorbed grass allergoid combined with the Toll-like-receptor-agonist MPL provided 13.4% improvement over placebo in a field trail [16], while a ragweed preparation provided 20% improvement over placebo in an environmental exposure chamber [17]. Neither of these results would suggest that these preparations will meet FDA requirements for approval. A Toll-like-receptor-agonist consisting of DNA with CpG motifs encapsulated in a virus-like particle without accompanying allergen was reported to have had beneficial effects on asthma outcomes in a steroid-taper

study [18]. However, on 14 April 2014 the company issued a press release reporting early termination of a large study in asthma due to failure to achieve improvement in asthma control [19]. There are two hurdles for any of these products to enter the US market in the future. The FDA has set a high bar for efficacy, 15% overall, but 10% separation of the 95% CI of the active product from the mean of the placebo. This requires that the drug be effective, but also have the financial backing to perform large and very expensive studies to narrow the confidence interval. Whether any of these developing products will meet these hurdles remains to be seen.

Financial & competing interests disclosure

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