Clinical reviews in allergy and immunology

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Immunotherapy: What lies beyond

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Activity Objectives

1. To review the rationale behind using novel immunotherapy approaches for the management of allergic diseases.
2. To review the therapeutic effects of human clinical trials using novel immunotherapy.

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Allergen immunotherapy has been used to treat allergic diseases, such as asthma, allergic rhinitis, and venom allergy, since first described over a century ago. The current standard of care in the United States involves subcutaneous administration of clinically relevant allergens for several months, building up to eventual monthly injections for typically 3 to 5 years. Recent advances have improved the safety and efficacy of immunotherapy. The addition of omalizumab or Toll-like receptor agonists to standard subcutaneous immunotherapy has proved beneficial. Altering the extract itself, either through chemical manipulation producing allergoids or directly producing recombinant proteins or significant peptides, has been evaluated with promising results. The use of different administration techniques, such as sublingual immunotherapy, is common in Europe and is on the immediate horizon in the United States. Other methods of administering allergen immunotherapy have been studied, including epicutaneous, intralymphatic, intranasal, and oral immunotherapy. In this review we focus on new types and routes of immunotherapy, exploring recent human clinical trial data. The promise of better immunotherapies appears closer than ever before, but much work is still needed to develop novel immunotherapies that induce immunologic tolerance and enhanced clinical efficacy and safety over that noted for subcutaneous allergen immunotherapy. (J Allergy Clin Immunol 2014;133:612-9.)

Key words: *Immunotherapy, allergy, asthma, omalizumab, allergens, recombinant, peptide, epicutaneous, intraepithelial, sublingual immunotherapy*

Allergen immunotherapy (AIT) was first described over a century ago and has continued as a mainstay in the treatment of allergic diseases, such as allergic rhinitis, asthma, and venom allergy.[1,2] In this review we will discuss the rationale behind using novel immunotherapy approaches for the management of allergic diseases. We will focus on those studies that are in human clinical trials and examine the therapeutic effects noted thus far.

It is important to note the purpose of new immunotherapies to understand the rationale behind their development. Ultimately, the intent of new immunotherapies is to provide better therapeutic options for patients by reprogramming the immune system to ignore insignificant threats without compromising its ability to respond to real threats. Effective immunotherapy should change a person's allergen-specific response from an allergic profile (T_H2) to a nonallergic profile (T_H1) through regulatory T cells to achieve this goal.[3] The regulatory T cells release IL-10, which induces IgG_4 and TGF-β, increasing IgA levels.

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Abbreviations used
AIT: Allergen immunotherapy
ILIT: Intralymphatic immunotherapy
MATA: Modified allergen tyrosine absorbate
MPL: Monophosphoryl lipid A
OIT: Oral immunotherapy
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
TLR: Toll-like receptor

Conventional subcutaneous immunotherapy (SCIT) requires 30 to 80 injections with high-dose allergen over 3 to 5 years. This is very time consuming and associated with allergic side effects, including anaphylaxis. Sublingual immunotherapy (SLIT) is more patient friendly (less severe side effects, no injection, and can be done at home), but the treatment duration is still long (several years) and typically requires daily dosing. Because of these disadvantages, it is estimated that less than 5% of all allergic patients who could conceivably be candidates for allergy immunotherapy actually undergo this treatment. Thus there is clearly a need for allergy immunotherapy that is more convenient, effective, and safer. In 2011, we wrote a review for the *Journal of Allergy and Clinical Immunology* describing potential future allergy immunotherapy treatments.[4] Since that time, there has been considerable progress in allergen extract modifications and additions to standard extracts (Fig 1). Subcutaneous administration is the current norm, but the future holds promise for other options, including SLIT and oral immunotherapy (OIT; Fig 2). Below we describe some of these strategies to improve traditional subcutaneous AIT.

OMALIZUMAB PLUS SCIT

The safety and efficacy of standard SCIT preparations can be improved with the addition of anti-IgE therapy or adjuvants. The use of anti-IgE antibody therapy (omalizumab) in addition to conventional SCIT has been evaluated in several trials. Omalizumab therapy alone decreases serum IgE levels and FcεRI receptor expression on mast cells, basophils, and dendritic cells.[5] The use of omalizumab before starting AIT improved the safety of SCIT by reducing systemic allergic reactions up to 5-fold, as did the use of epinephrine and prednisone in treating immunotherapy-induced anaphylaxis in patients with allergic rhinitis.[6] Pretreatment with omalizumab reduced systemic allergic reactions to cluster SCIT by 50% in asthmatic patients.[7] In addition to increased safety, allergic rhinitis symptoms were reduced in patients treated with a combination of omalizumab and SCIT compared with those treated with SCIT alone.[6,8,9] A more recent randomized, double-blind, placebo-controlled, multicenter trial used omalizumab or placebo in combination with standard SCIT (depigmented allergoid vaccine) for grass allergy.[10] The core study consisted of a 2-week run-in phase, a preseasonal 10-week treatment phase, and an 8-week seasonal maintenance treatment phase. During follow-up, all patients were treated with the depigmented allergoid vaccine (Depigoid; Laboratorios LETI Sl, Tres Cantos, Spain) only over the 2 subsequent years in 4-week intervals. During the first season, the combination of omalizumab plus SCIT reduced symptoms of both asthma and allergic rhinitis to a greater extent. However, the reduction of asthma and allergic rhinitis symptoms was not noted in subsequent seasons when patients were maintained on SCIT alone.

This approach has also been studied for food allergy. Eleven children with cow's milk allergy received 9 weeks of omalizumab and then underwent oral cow's milk desensitization.[11] Double-blind, placebo-controlled food challenges done 8 weeks after omalizumab were discontinued and showed that all 9 patients who reached a daily dose of 2000 mg tolerated more than 8000 mg/d.

Finally, there are case reports of omalizumab plus venom immunotherapy, but the data are limited, and most, but not all, reports favor improved safety with venom immunotherapy when using omalizumab as a pretreatment.

Taken together, these data suggest that pretreatment with omalizumab can add efficacy and safety to immunotherapy administered subcutaneously and orally. It is unclear how long one needs to treat with both therapies and whether one can stop omalizumab and still have improved safety and efficacy. Indeed, the study by Kopp et al[10] suggests the combination might need to continue for a prolonged period to see added therapeutic benefits.

ADJUVANTS

Aluminum salts (alums), such as aluminum hydroxide, are the most widely used adjuvants in SCIT worldwide. The proposed mechanism involves slower release of allergen from the injection site, increasing the duration of antigen presentation. The use of alum-based grass AIT has demonstrated improvements in symptoms and reductions in medication use, but no head-to-head comparisons with non–alum-based AIT have been performed.[12,13] In addition to aeroallergens, venom immunotherapy with alum-based extracts has been effective.[14] The most common adverse event with alum-based immunotherapy is increased discomfort at the injection site compared with non–alum-based preparations.

Toll-like receptors (TLRs) are innate immune receptors designed to induce regulatory T-cell responses in response to specific pathogens. The addition of TLR agonists to immunotherapy or their use by themselves has shown some benefits.

Monophosphoryl lipid A (MPL) is a detoxified derivative from *Salmonella* LPS that acts as a TLR4 agonist. Pollinex Quattro (Allergy Therapeutics, Worthing, West Sussex, Unites Kingdom) is a short pollen extract allergoid adsorbed onto L-tyrosine with the addition of MPL (modified allergen tyrosine absorbate [MATA] with MPL).[15] MATA MPL has been shown to reduce symptoms and medication use, increase allergen- specific IgG levels, and blunt seasonal increases in IgE levels. A large randomized, double-blind, placebo-controlled study evaluated more than 1000 patients with 4 preseason injections of MATA MPL grass immunotherapy.[16] During the peak grass season, patients treated with Pollinex had decreased symptom and medicine scores compared with those seen in the placebo group. Treatment seemed more effective for patients with more severe symptoms, those with symptoms for 35 years or more, and those in areas of high grass pollen counts. The concept of only having to administer 4 preseasonal injections is very attractive. US trials have been positive for a number of seasonal allergens, and phase III efficacy studies are underway.[17] MATA MPL is currently available for use in Europe.