Update review

Update on the current status of peptide immunotherapy

Mark Larché, PhD *Hamilton, Ontario, Canada*

The use of synthetic peptide fragments of allergen molecules holds promise for the delivery of effective immunotherapy without IgE-mediated adverse events. Early studies were associated with frequent induction of allergic symptoms after treatment, mostly related to activation of allergen-specific effector T cells with high doses of peptides. More recently, low doses of peptides have been shown to modify clinical and laboratory surrogates without inducing adverse events. Studies are ongoing to define the optimal dose, dose interval, and route of administration. Current results indicate that treatment with peptides modulates the immune response by reducing T_H2 responses to allergen and increasing IL-10 production and the activity of allergen-specific regulatory T cells. Further studies are required in larger numbers of subjects and with peptides derived from a variety of allergens. (J Allergy Clin Immunol 2007;119:906-9.)

Key words: *Epitope, immunologic tolerance, T cell, regulatory T cell, peptide, allergen, immunotherapy, IL-10*

Strategies to improve the safety of allergen immunotherapy have traditionally focused on reducing the allergenicity of the preparation administered to the patient. The use of peptide fragments, corresponding to T-cell epitopes, to induce immunologic tolerance has been reported in experimental models of both allergic and autoimmune disease.[1] By virtue of their size and relative lack of secondary and tertiary structure, peptides display reduced ability to cross-link allergen-specific IgE and activate IgE receptor–bearing cells. However, retention of T-cell epitopes allows targeting of allergen-specific T cells for the induction of tolerance. Translation of this approach to the clinic is ongoing, with a number of small clinical studies having been performed over the last decade. At present, 3 allergens have been targeted with this approach (Table I): the cat allergen Fel d 1, the bee venom allergen Api m 1 (phospholipase A_2), and the ragweed allergen Amb a 1 (clinical studies of the last have not been reported). Considerable objective evidence has accumulated demonstrating modulation of allergen-specific immune responses after peptide immunotherapy. Evidence supporting clinical benefit has been slower to accumulate, and definitive studies demonstrating reduced symptom scores and medication use combined with improvements in tolerability are still required.

The earliest clinical studies employed a combination of 2 peptides (Allervax Cat, ImmuLogic Corp., Waltham, Mass) from Fel d 1, administered subcutaneously in a variety of dosing regimens. In the first of these to be reported, peptides were administered at weekly intervals and in 3 dose cohorts (7.5 μg, 75 μg, and 750 μg).[2] After allergen exposure in a cat room, lung and nasal symptom scores were significantly improved in the higher dose cohorts. Despite the use of peptides that had been screened for reduced activity in basophil histamine release assays, numerous adverse events were documented occurring minutes to hours after peptide administration. Some adverse events may have been a result of the relatively long peptides used that may have harbored residual IgE reactivity; however, the majority of events probably occurred as a result of activation of allergen-specific effector T cells resulting in late asthmatic reactions.[3] The same peptides were evaluated in inhaled allergen challenge studies. A significant increase in PD_{20} was observed within cohorts receiving higher dose (total dose between 150 μg and 4500 μg) regimens, but this failed to achieve statistical significance when compared with placebo.[4]

In a double-blind, placebo-controlled parallel group study, peptides or placebo were administered by weekly subcutaneous injection (4 × 250 μg) to 42 subjects with cat-allergic rhinitis and/or asthma.[5] Treatment was associated with adverse events, primarily late-onset symptoms of rhinitis, asthma, and pruritus. No significant changes were observed in the primary outcome measure (change in wheal and flare reaction) or in late-phase skin responses to allergen challenge. PBMC cytokine secretion profiles did not differ between peptide-treated and placebo-treated subjects.

From the Department of Medicine, Division of Clinical Immunology and Allergy, Faculty of Health Sciences, McMaster University.

Supported by the Canada Research Chairs Programme, the Canadian Foundation for Innovation, and Asthma UK.

Disclosure of potential conflict of interest: M. Larché has consulting arrangements with, owns stock in, and has patent licensing arrangements with Circassia Holdings LTD.

Received for publication January 4, 2007; revised February 10, 2007; accepted for publication February 15, 2007.

Reprint requests: Mark Larché, PhD, Canada Research Chair in Allergy and Immune Tolerance, Professor, Department of Medicine, Division of Clinical Immunology and Allergy, Faculty of Health Sciences, McMaster University, HSC, Room 4H20, 1200 Main Street West, Hamilton, Ontario, L8N 3Z5, Canada. E-mail: larche@mcmaster.ca.

0091-6749/$32.00

doi:10.1016/j.jaci.2007.02.015

TABLE I. Clinical studies of peptide immunotherapy

First author	Allergen	No. of peptides and length	Total dose	Route	No. of subjects	Major outcome measures	Reference
Cat allergy							
Norman	Fel d 1	2 × 27	30-3000 μg	Subcutaneous	95	Improved symptom scores after cat room challenge	2
Simons	Fel d 1	2 × 27	1000 μg	Subcutaneous	42	No change in cutaneous allergen challenge	5
Pène	Fel d 1	2 × 27	15-4500 μg	Subcutaneous	31	Improved allergen PD_{20} compared with baseline	4
Maguire	Fel d 1	2 × 27	6000 μg	Subcutaneous	133	Improved FEV_1 in subjects with reduced baseline FEV_1	6
Oldfield	Fel d 1	12 × 16/17	5 μg	Intradermal	24	Reduced cutaneous late-phase reaction after allergen challenge	7
Oldfield	Fel d 1	12 × 16/17	90 μg	Intradermal	24	Reduced cutaneous early and late-phase reaction after allergen challenge, T_H1/T_H2 cytokines reduced, IL-10 increased	8
Alexander	Fel d 1	11 × 16/17	40.1 μg	Intradermal	8	Reduced airway hyperreactivity and cutaneous late-phase reaction after allergen challenge, increase in $CD4^+IFN\text{-}\gamma^+$ cells in skin after allergen challenge	9
Alexander	Fel d 1	12 × 16/17	131-341 μg	Intradermal	28	Improved nasal symptoms and late asthmatic reaction after allergen challenge	11
Bee venom allergy							
Müller	Api m 1	3: 11, 12, 18	397.1 μg	Subcutaneous	5	Improved tolerance of skin allergen challenge and partial protection from live sting challenge	13
Fellrath	Api m 1	3: 45, 53, 60	751.1-1551.1 μg	Subcutaneous	16	Increased allergen-specific IgG_4, increased IFN-γ and IL-10 in PBMCs	14
Tarzi	Api m 1	4 × 18	431.1 μg	Intradermal	12	Reduced cutaneous early and late-phase reaction after allergen challenge, T_H1/T_H2 cytokines reduced, IL-10 increased, transiently increased IgG_4	15

Modified with permission from Larché M. Peptide immunotherapy for allergic diseases. Allergy 2007;62:325-31.

Treatment with Allervax Cat was also associated with a significant clinical improvement in pulmonary function (FEV_1) in individuals with reduced baseline FEV_1.[6] Furthermore, a significant improvement in the subjective ability to tolerate cats was also observed through a visual analogue evaluation. Importantly, subjects recruited to this study had moderate to severe disease, with many demonstrating high IgE levels. Approximately 30% had failed previous whole allergen immunotherapy, and more than 40% of the group had asthma. Adverse events were common and consisted of occasional IgE-mediated acute reactions and more frequent late-onset symptoms of asthma. Approximately 20% of peptide-treated subjects developed late-onset symptoms after the first peptide administration, but the prevalence of these reactions decreased as dosing continued, indicating the induction of immunologic tolerance.

The incidence of late adverse events was related to both peptide dose and the severity of disease in the study group. Subjects with asthma appeared more likely to develop late-onset symptoms and particularly at higher peptide doses.[2,6] A weak relationship was also established between levels of allergen-specific serum IgE and the propensity to develop late reactions.[6] Some subjects developed *de novo* IgE specific for the treatment peptides, and this was associated in some cases with acute adverse events.[6]

Thus, early clinical experience established that peptide immunotherapy could modify immunologic markers, clinical surrogates, and subjective clinical outcomes in some studies. The development of peptide-specific IgE and the association of late adverse events with peptide dose and disease severity indicated that improved safety and tolerability may be achieved by using smaller peptides with reduced ability to elicit and interact with IgE (the Allervax Cat peptides were 27 amino acids in length, whereas an average CD4 T-cell epitope would be approximately 14 amino acids). Furthermore, evaluation of lower peptide doses in subjects with less severe disease was indicated.

A number of clinical studies have been performed more recently by using mixtures of shorter peptides from Fel d 1.[3,7-12] Peptides were administered intradermally to subjects with cat-allergic asthma. Dose-dependent