T Cell Epitope-Based Allergy Vaccines

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Abstract Specific immunotherapy (SIT) with extracts containing intact allergen molecules is clinically efficacious, but associated with frequent adverse events related to the allergic sensitization of the patient. As a result, treatment is initiated in an incremental dose fashion which ultimately achieves a plateau (maintenance dose) that may be continued for several years. Reduction of allergic adverse events may allow safer and more rapid treatment Thus, many groups have developed and evaluated strategies to reduce allergenicity whilst maintaining immunogenicity, the latter being required to achieve specific modulation of the immune response. Peptide immunotherapy can be used to target T and/or B cells in an antigen-specific manner. To date, only approaches that target T cells have been clinically evaluated. Short, synthetic peptides representing immunodominant T cell epitopes of major allergens are able to modulate allergen-specific T cell responses in the absence of IgE cross linking and activation of effector cells. Here we review clinical and mechanistic studies associated with peptide immunotherapy targeting allergy to cats or to bee venom.

Contents

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1 Introduction

Specific allergen immunotherapy as a clinical intervention is approaching its centenary year. Since the inception of controlled clinical trials of this therapeutic modality in the 1950s it has been widely demonstrated to be clinically effective and to have a duration of action that substantially exceeds the treatment period (Durham et al. 1999). The latter is indicative of the induction of functional immunological tolerance, although the precise mechanisms underlying such a phenomenon remain incompletely understood. Despite lasting clinical efficacy, current clinical practice with whole allergen extracts requires an extended period of treatment, the generally accepted optimum period being 3 years. The lengthy treatment period is caused, at least in part, by dose limitations related to the frequent occurrence of predominantly IgE-mediated adverse events. Adverse events are manifested as allergic reactions to the treatment and range from mild local reactions to severe systemic reactions including anaphylactic shock. A number of strategies aimed at reducing the allergenicity of treatment preparations whilst maintaining immunogenicity, has been described. Physical modification of allergen molecules offers the prospect of reducing or eliminating IgE reactivity and thus, allergenicity. Such approaches have taken many forms including chemical modification, conjugation with synthetic bacterial DNA motifs, point mutations in native allergen gene sequences, and the use of allergen multimers, fragments, and peptides of various lengths. The use of soluble synthetic peptides for the treatment of allergic disease allows the delivery of T cell epitopes of the allergen in a tolerogenic form, whilst avoiding IgE-mediated allergic reactions. Synthetic peptides have been evaluated in both experimental animal models and in human clinical studies. Synthetic peptides are defined chemical entities and can be produced and standardized to levels impossible to achieve with allergen extracts. Furthermore, they are inexpensive to produce, easy to purify and are stable in lyophilized form.

Early indications that peptides may be used to modulate immune responses toward tolerant phenotypes came from in vitro studies investigating the effects of high-dose peptide presentation between T cells. Pure populations of $CD4^+$ helper T cell clones were pre-treated with supraoptimal concentrations of specific peptide and subsequently shown to be refractory to antigen stimulation (Lamb et al. 1983). As antigen presenting cells were not present in the cultures, presentation of peptide to T cell receptors likely occurred through binding to MHC class II molecules on T cells and recognition of antigen in a “non-professional” context. Subsequent studies have confirmed the ability of non-professional antigen presenting cells to induce T cell tolerance (Bal et al. 1990).

Experimental in vivo studies of peptide-induced tolerance have been reported in a number of disease areas including allergy, autoimmunity, and transplantation. Initial experiments demonstrated that it was possible to induce systemic tolerance to peptides administered in incomplete Freund's adjuvant during the neonatal period (Gammon et al. 1986; Clayton et al. 1989). Several studies have focused on prevention and treatment of experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (MS) (Critchfield et al. 1994) (Gaur et al. 1992; Metzler and Wraith 1993). Recently in a T cell receptor transgenic model of EAE, MBP peptides were administered via the intranasal route leading to protection from disease, which required deletion of effector T cells and the presence of IL-10 (Burkhart et al. 1999; Anderton et al. 1998). Peptide therapy has also been shown to be effective in murine models of experimental arthritis (Ku et al. 1993; Staines et al. 1996; Prakken et al. 1997), and in models of type I diabetes (Daniel and Wegmann 1996; Bockova et al. 1997; Tian et al. 1996).

A limited number of in vivo studies of peptide therapy have been performed in models of allergic disease. Mice primed with the major house dust mite allergen Der p 2 were treated with peptides containing immunodominant T cell epitopes from Der p 2. T cell and B cell (antibody) responses to the protein were down-regulated (Hoyne et al. 1993). The dominant T cell epitope of the birch pollen allergen Bet v 1 was administered prophylactically and therapeutically to CBA/J mice and inhibited T cell responses without a detectable effect on antibody production (Bauer et al. 1997). Prophylactic treatment of venom sensitized mice with peptides from the bee venom allergen Api m4, or the hornet venom allergen Dol m 5, reduced T and B cell responses to allergen challenge (King et al. 1998). In another study of insect venom allergy, mice sensitized to Api m 1 (phospholipase A_2; PLA_2) were treated with a mixture of three polypeptides spanning the entire molecule. Mice were protected from anaphylaxis. A significant reduction in specific IgE was observed together with an increase in allergen-specific IgG2a and a reduced Th2:Th1 ratio (von Garnier et al. 2000). Mice sensitized to the major cat allergen Fel d 1 were treated with two allergen-derived polypeptides that encompassed much of the sequence of Fel d 1 chain 1. Treatment resulted in decreased production of IL-2 and allergen-specific IgG, but no Th2-specific outcomes were reported (Briner et al. 1993). Most recently, Campbell and colleagues sensitized mice devoid of murine MHC class II and transgenic for the human MHC molecule HLA-DRB1*0101, with recombinant Fel d 1 and subsequently treated them with a single ultra-low dose (1 μg) of a Fel d 1 peptide previously shown to bind to HLA-DRB1*0101. Treatment ameliorated allergic airways disease and suppressed the systemic Th2 response to allergen. Tolerance induced by this single T cell epitope was found to cross over to other T cell epitopes of Fel d 1, indicative of the induction of linked epitope suppression. Tolerance in this model was shown to be IL-10 dependent (Campbell et al. 2009).

Little is known about the most effective dose for induction of tolerance through peptide therapy. In mice, tolerogenic peptide doses range from a few microgrammes (Chai et al. 2004) to milligrammes (Karin et al. 1994). By delivering T cell epitopes directly to dendritic cells in vivo, it has recently been shown that doses of little as

500 pg can induce tolerance in a murine model (Kretschmer et al. 2005). Fundamental differences may exist in the mechanisms of low and high-dose tolerance. High-dose protocols have been associated with clonal deletion and, to a lesser extent, anergy of antigen-specific cells (Critchfield et al. 1994; Karin et al. 1994; Kearney et al. 1994). Fewer studies of low dose tolerance have been performed, but both high and low dose models appear to be characterized by the induction of T cells with regulatory activity (Wraith et al. 2003, 2004; Apostolou and Von Boehmer 2004).

2 Clinical Studies

To date, translation of peptide immunotherapy into the clinical setting has focused on the treatment of cat allergy and bee venom allergy. The earliest studies employed two polypeptides from the major cat allergen Fel d 1, these peptides having previously been evaluated in a murine model of cat allergy described above. In a study by Norman and colleagues, an equimolar mixture of the peptides (27 amino acids each in length; IPC-1/IPC-2) or placebo, was given in four subcutaneous injections, over a period of 2 weeks, to 95 cat-allergic subjects (all with allergic rhinitis to cats and some with asthma) in three dose groups (7.5, 75 and 750 μg per injection) (Norman et al. 1996). Statistically significant, albeit modest, improvements in lung and nasal symptom scores were observed, but only in the high-dose group. A large placebo effect was observed in common with many allergen immunotherapy trials. Treatment was associated with a significant incidence of adverse events, which occurred a few minutes to several hours after peptide injection. Most frequently, subjects with a history of asthma reported chest tightness and wheezing several hours after peptide administration. This phenomenon was later investigated and shown to be attributable to isolated late asthmatic reactions following MHC-restricted activation of allergen (peptide)-specific T cells in the airways (Haselden et al. 1999). Mechanistic in vitro studies associated with the Norman study demonstrated reduced IL-4 production in peptide-specific T cell lines following therapy suggesting a decrease in allergen-specific Th2 responses (Marcotte et al. 1998).

Pène and colleagues evaluated the same peptides in an inhaled allergen challenge study. A reduction in allergen PD_{20} (provocative dose of inhaled allergen resulting in a 20% reduction in forced expiratory volume in one second; FEV_1) was seen in both high and medium (individual doses of 75 μg up to a total dose of 450 μg–medium dose and 4,500 μg–high dose) dose groups when compared to baseline, but not placebo (Pene et al. 1998). In mechanistic studies peripheral blood mononuclear cells were stimulated with cat allergen in vitro, before and after treatment, a reduction in IL-4 production was reported (in the high dose group), in agreement with earlier findings.

In contrast to these studies that reported some clinical benefit from therapy, a third trial found no clinical effect. In a double-blind, parallel group study, Simons and colleagues gave weekly (total of four) subcutaneous injections, of 250 μg of the peptide mixture or placebo, to 42 subjects with cat-allergic rhinitis and/or asthma

(Simons et al. 1996). Treatment was associated with late onset symptoms of rhinitis, asthma, and pruritis. No changes in early and late-phase skin responses to intradermal allergen challenge were observed. In associated mechanistic studies, PBMC cytokine secretion was not different between peptide-treated and placebo-treated subjects.

In the last reported study with IPC-1/IPC-2, 133 cat-allergic subjects were treated in a multi-center study design. Each subject received eight subcutaneous injections of 750 μg. The only positive clinical effect observed was a significant improvement in pulmonary function, which was seen only in individuals with reduced baseline FEV_1 (Maguire et al. 1999). Furthermore, improvements in pulmonary function were evident at only a single time point (3 weeks) after therapy. Frequent adverse events were reported during treatment, including some requiring epinephrine. In common with other studies using these peptides, late onset adverse reactions (isolated late asthmatic reactions) diminished with successive doses of peptide indicating that immunological tolerance was being induced to the peptides. The reduction in magnitude and frequency of adverse events through induction of peptide-specific tolerance was presumably related to the clinical benefits reported in this series of studies.

More recently, a series of clinical studies have been performed using mixtures of shorter peptides from Fel d 1 (Oldfield et al. 2001, 2002; Alexander et al. 2005; Smith et al. 2004; Verhoef et al. 2005). Cat-allergic asthmatic volunteers were challenged intradermally with whole cat dander allergen extract, before and after a single injection of 5 μg of each of twelve peptides in saline. The peptides encompassed approximately 80% of the Fel d 1 molecule and contained most of the major T cell epitopes (unpublished observations). Intradermal peptide injection significantly reduced the magnitude of the cutaneous late-phase reaction to allergen challenge given approximately 2–4 weeks after baseline measurements. In vitro mechanistic studies with PBMC demonstrated reduced allergen-specific proliferation and a reduction in both Th1 and Th2 cytokines (Oldfield et al. 2001).

The same mixture of 12 peptides was then evaluated in a double-blind, placebo-controlled clinical trial (Oldfield et al. 2002). Twenty four cat-allergic asthmatic subjects with moderate to severe asthma (PC20 as low as 0.1 mg/ml histamine) were treated with 4–5 injections of increasing dose (lowest dose 5 μg; highest dose 50 μg). Quality of life was evaluated by questionnaire (Global evaluation to cat exposure visual analogue scale). The primary outcome measure of the study was the size of the late-phase cutaneous reaction to intradermal challenge with allergen. Secondary outcome measures included the early-phase cutaneous reaction to allergen challenge, the allergen PD_{20} and the histamine PC_{20}. Baseline measurements were compared to two post-treatment follow-up evaluations; 4–8 weeks after therapy and 3–9 months after therapy. Subjects received a total of 90 μg of each of 12 peptides in divided incremental doses administered at 3–4 day intervals. A statistically significant reduction in the magnitude of both early (second follow-up only) and late-phase cutaneous reactions (both follow-up assessments) to intradermal challenge with allergen when compared to placebo was recorded. In mechanistic studies, reduced proliferative responses and reduced Th1 and Th2 cytokine production following culture with allergen were observed. The reductions

in pro-inflammatory cytokines were associated with an increase in production of IL-10. A recent publication (Campbell et al. 2009) also reported responses to individual peptides measured in PBMC samples from this study. The results showed that in addition to modulating the immune response to the vaccine peptides themselves, peptide therapy also modulated the immune response to non-injected peptides from the same allergen, indicative of intramolecular tolerance (also known as "linked epitope suppression"). Subjects treated with peptides felt significantly better able to tolerate exposure to cats after therapy although this improvement was not statistically significant when compared to the placebo group. No significant improvements were observed in PD_{20} or PC_{20}, however, the study was not powered to detect such changes. No immediate adverse events were reported in this study, but isolated late asthmatic reactions were expected (based on the dose of peptides employed) and recorded. Retrospective analysis of the incidence of these reactions and the induction of tolerance/improvement in outcomes, demonstrated that the induction of an isolated late asthmatic reaction was not required for the induction of tolerance.

In a related open-label study using a similar peptide preparation delivered at 2 week intervals and using a lower dosing regimen, a significant reduction in airway hyperreactivity (measured by PC_{20}) was observed (Alexander et al. 2005). Five incremental intradermal injections were given (0.1, 1.0, 5, 10, and 25 μg). A reduction in the cutaneous late-phase reaction to allergen challenge was also observed in common with other related studies. Immunohistochemistry of skin biopsy tissue obtained after allergen challenge revealed a significant increase in the number of $CD25^+$ cells and the number of $CD4^+$/IFN-γ^+ cells after peptide treatment, suggesting that recruitment of Th1 cells (and perhaps regulatory T cells) to the skin may be an important mechanism. No increase in IL-10^+ cells was observed in the skin but expression of TGFβ mRNA appeared to be increased but the cellular source of this cytokine could not be determined.

A related study aimed to investigate the effect of peptide immunotherapy on peripheral blood $CD4^+$ responses and $CD4^+CD25^+$ suppression of allergen-stimulated cultures in a double-blind, placebo-controlled trial (Smith et al. 2004). Proliferative responses and IL-13 production from PBMC cultured with allergen in vitro were significantly reduced following peptide therapy as in previous studies. The functional regulatory activity of $CD4^+CD25^+$ cells was assessed by mixing with autologous $CD4^+CD25^-$ cells. Peptide immunotherapy did not alter the suppressive activity of $CD4^+CD25^+$ cells in this study suggesting that naturally occurring regulatory T cells may not play a significant role in the immunological changes associated with peptide immunotherapy. Observations that may support this conclusion were made in a recent murine study which showed no increase in Fox p 3 + T cells in the lungs of mice after successful peptide therapy (Campbell et al. 2009).

A potential role of antigen-specific inducible regulatory T cells was addressed in a subsequent study by mixing $CD4^+$ T cells (containing the putative regulatory cells) with $CD4^-$ cells (Verhoef et al. 2005). Each population was labeled with a different fluorescent dye ($CD4^+$ were labeled red with PKH-26 and $CD4^-$ were labeled green with the cell cycle-tracking dye CFSE). In an autologous culture

system, $CD4^+$ cells from before and after peptide therapy were mixed with $CD4^-$ cells from before and after therapy, in all possible combinations. The results showed that antigen-specific proliferative responses of memory T cells were reduced following peptide immunotherapy compared to baseline samples and that $CD4^+$ cells isolated after treatment could suppress the proliferative response of baseline $CD4^-$ cells. These data suggest that peptide immunotherapy can induce a population of $CD4^+$ T cells with suppressive/regulatory activity.

3 Insect Venom Allergy

Subcutaneous whole allergen immunotherapy for insect venom allergy is highly effective although it requires a protracted treatment period. Systemic adverse events are common during treatment, encouraging the development of therapies with reduced allergenicity, such as the peptide approach. Five bee venom allergic subjects received incremental doses of three immunodominant peptides (an equimolar mixture) at weekly (Muller et al. 1998). Ten control subjects were treated with conventional bee venom immunotherapy to compare clinical outcomes and mechanisms. The cumulative peptide dose was 397.1 μg. One week after the last peptide injection, subjects were challenged subcutaneously with 10 μg of whole Api m 1. All five subjects tolerated the challenge without systemic allergic symptoms. One week later a wild bee sting challenge was performed. Three out of five tolerated this challenge without reaction, the remaining two subjects developed mild systemic allergic reactions. However, due to the variable nature of the allergic response to bee stings, it is likely that as many as half of these individuals would not have had a severe reaction to the sting challenge regardless of treatment. No change was observed in levels of allergen-specific serum IgE or IgG_4 during the course of peptide therapy. Interestingly, following subcutaneous challenge with the whole allergen 1 week after the last peptide injection, concentrations of both isotypes increased sharply, particularly IgG_4 and a month later serum levels of specific IgG_4 were higher than IgE.

Immunodominant T cell epitopes of Api m 1 and their MHC restriction elements were determined by Texier and colleagues, by direct binding of peptides to purified MHC class II molecules (Texier et al. 2000). Four peptides were identified, three of which were similar to those used previously for therapy by Müller and colleagues. Following a similar treatment regimen to Müller, Tarzi and colleagues performed a controlled, open-label, single-blind study of peptide therapy in subjects with mild bee venom allergy (Tarzi et al. 2005). The peptides were well tolerated and no adverse events were observed during treatment. In mechanistic studies, PBMC responses to purified allergen and whole bee venom were significantly reduced. Proliferative responses to treatment peptides were also reduced. Th2 cytokine production following culture with allergen was reduced, but IL-10 production was significantly increased, confirming earlier findings in subjects treated with cat peptides. Late-phase cutaneous reactions to both whole bee venom

and Api m 1 were significantly reduced following allergen challenge. Allergen-specific IgG, IgG_4 and IgE levels were measured using serum samples were collected before, during, and after treatment. A statistically significant, but transient, increase in allergen-specific IgG and IgG_4 during and after treatment was found. The functional significance of such an increase, which was considerably smaller in absolute terms than the response seen in whole allergen therapy, remains to be determined.

Using much larger peptides (long synthetic peptides; LSP) that encompassed the entire Api m 1 molecule, Fellrath and colleagues treated bee venom allergic subjects with a RUSH desensitization protocol (Fellrath et al. 2003). Patients received approximately 250 μg in incremental doses at 30 min intervals starting with 0.1 μg. Maintenance injections of 100 μg, or in some cases 300 μg, were given on days 4, 7, 14, 42 and 70. In the active treatment group a transient increase in T cell proliferation to the peptides was observed, together with an increase in IFNγ and IL-10 levels, but not Th2 cytokines. Allergen-specific IgG_4 but not IgE levels increased throughout the study period, similar to whole allergen therapy. Peptide-specific IgE was induced in some patients during the study. No significant change in skin sensitivity to intradermal allergen challenge was observed. Peptide therapy was generally well tolerated, however, local and disseminated erythema with hand (palm) pruritis was observed in two subjects.

4 Mechanisms of Peptide-Induced Tolerance

Peptide-induced tolerance following intradermal (systemic route) injection, is not replicated when peptides are administered via inhalation, despite the fact that both routes are equivalent in their ability to induce isolated late asthmatic reactions (Ali et al. 2004). Thus, T cell tolerance is likely to arise through systemic presentation of peptides (which in our own studies are delivered in saline, without adjuvant and at very low doses) to naïve T cells by non-professional APC (such as endothelial cells, epithelial cells etc.) and "steady-state" (quiescent) dendritic cells. All of these cell types are known to induce tolerogenic T cell responses (Steinman et al. 2003). Since the peptides are probably encountered in a non-inflammatory environment, the T cells probably make a "tolerant" response that leads to the expansion of existing allergen-specific regulatory T cells and de novo generation of more of these cells from the naïve T cell pool. When peptides are administered by intradermal injection, a significant amount of the injected dose is likely to pass rapidly into the systemic circulation through the capillary bed. Once in the circulation, peptides rapidly reach all tissues and bind to MHC class II molecules of the appropriate specificity. Relatively low plasma dose and high solubility may render peptides "tolerogenic". Recent studies have suggested that cross-linking of IgE on the surface of antigen presenting cells (for example, by allergen)

results in the activation of these cells and the release of cytokines which may have a pro-inflammatory outcome (Novak et al. 2001). In contrast, the small size of peptides does not allow them to crosslink adjacent IgE molecules and it follows, therefore, that peptides will elicit less inflammation than whole allergen. Thus, peptides may bind to MHC class II molecules on the cell surface without activating the cell. Previous studies have demonstrated the presence of a significant percentage of "empty" MHC class II molecules on the surface of immature and "steady state" dendritic cells (Santambrogio et al. 1999a). Empty MHC molecules are also associated with active HLA-DM, a chaperone and peptide editing protein, that loads exogenous peptides into empty MHC class II binding grooves (Santambrogio et al. 1999b). As a result, when peptide-loaded dendritic cells recycle through lymphoid tissue, they will present peptides to T cells whilst in a quiescent state resulting in a tolerogenic encounter.

5 Future Peptide Vaccine Design

In those allergens in which extensive T cell epitope mapping studies have been performed, it is clear that most allergens contain large numbers of T cell epitopes distributed throughout the molecule. Issues of solubility and formulation of a mixture of peptides for immunotherapy mean that peptide vaccines are unlikely to be able to accommodate all T cell epitopes in an allergen. Thus, critical choices must be made regarding which epitopes are the most important. The recent description of linked epitope suppression following peptide therapy in both human and murine systems provides an immunological basis for how a small number of selected T cell epitopes might confer tolerance to all epitopes in an allergen molecule (Campbell et al. 2009). In some cases lack of solubility of linear synthetic peptides precludes their presence in a vaccine, despite the fact that these sequences do exist as processed T cell epitopes in vivo. Ideally, peptides must have the ability to bind to diverse HLA types representing a broad cross section of the population. They must not selectively induce Th2 cytokines that may enhance Th2 responses in vivo. If the mechanisms underlying conventional immunotherapy are similar to that of peptide vaccination then induction of IFN-γ and IL-10 (and perhaps TGFβ) is desirable. In addition, peptide should not induce IgE antibody production but promote the generation of inhibitory IgG antibodies. These ideals may underlie the protective effect of high-dose natural exposure to cat allergens as reported by Woodfolk and colleagues (Carneiro et al. 2004). Cat-allergic subjects, whilst having high allergen-specific IgE levels, also produce IgG4 which appeared to protect from disease. This was described as a "modified Th2 response". Analysis of particular peptides from Fel d1 suggested the preferential induction of IL-10 (Reefer et al. 2004). Such peptides should be included in future clinical trials of cat peptide vaccination to enhance vaccine efficiency.

6 Summary

Several strategies to reduce the allergenicity of therapeutic preparations for the treatment of allergic diseases are under development. Short, synthetic peptides containing T cell epitopes of clinically important major allergens show markedly reduced ability to crosslink allergen-specific IgE. In a number of clinical studies, peptide treatment has been shown to modify surrogate markers of allergen exposure such as; cutaneous responses to allergen challenge, bronchial hyperreactivity (some studies), symptoms scores following nasal allergen challenge, quality of life, and the ability to tolerate natural allergen exposure. Mechanistic studies indicate that peptide therapy induces both immune deviation (Th2–Th1 response) and regulatory T cells capable of suppressing allergen-specific immune responses. Limited data is available on the effects of peptide therapy on humoral immune responses. There appears to substantially less allergen-specific IgG induced during peptide therapy (compared to conventional allergen extract immunotherapy). Treatment with bee venom peptides appears to induce allergen-specific IgG4, but this may be induced by exposure to whole allergen after treatment (in the context of IL-10-rich T cell help) rather than by direct exposure to treatment peptides. The reduced size of peptides and relative lack of conformational determinants are associated with reduced basophil activation and histamine release in vitro. Intradermal delivery of short peptides has demonstrated a substantial reduction in allergenicity compared to comparable molar doses of whole allergen. It is expected that this reduced allergenicity will translate into a reduced risk of IgE-mediated adverse events such as anaphylaxis. It remains to be seen whether the clinical response to peptide immunotherapy will be of equivalent efficacy to conventional treatment. Further peptide therapy studies and comparisons with existing therapy are anticipated.

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