

The role of immunotherapy in pediatric allergic disease

Gunilla Hedlin, MD

Knowledge of the mechanisms of immunotherapy has increased substantially in recent years. The development of better extracts for both injection immunotherapy and local immunotherapy continues, and techniques for the production of recombinant allergens and peptides will be important for future vaccines. Immunotherapy with conventional commercially available extracts is best documented in childhood pollen allergy and is useful in children with severe hay fever symptoms or seasonal asthma. Immunotherapy for perennial allergy has so far been most beneficial in dust mite- and cat-allergic children with asthma. Dust mite therapy is most efficacious in children with isolated dust mite allergy. Appropriate environmental measures should, however, precede immunotherapy when possible. Recent data indicate that immunotherapy has no additional benefit in children with multiple allergies and asthma who receive optimal pharmacotherapy. It is therefore preferable that immunotherapy be combined with anti-inflammatory drug therapy in most children with asthma. For safety reasons, it is important that immunotherapy be administered by physicians well acquainted with standardized extracts in a clinic or hospital where treatment for systemic reactions is available. Long-term treatment for 3 to 5 years results in a more sustained effect than short-term therapy.

Department of Pediatrics B 57, Karolinska Institute, Huddinge University Hospital, S-141 86 Stockholm, Sweden.

Current Opinion in Otolaryngology & Head and Neck Surgery 1996, 4:67-72

Abbreviations

BHR bronchial hyperreactivity
cDNA complementary DNA
LAR late allergen response
mRNA messenger RNA

This paper was previously published in *Current Opinion in Pediatrics* 1995, 7:676-682.

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ISSN 1068-9508

Immunotherapy in children with rhinitis and asthma caused by specific allergies is a well-documented and efficacious treatment. The best results have so far been reported from studies of tree, grass, and ragweed pollen allergies [1••,2,3•,4,5] and from studies of dust mite and cat allergy [1••,6]. Several key questions about immunotherapy remain, however, including how it affects the overall severity of disease, particularly asthma, whether it prevents the development of asthma in children with allergic rhinitis, and whether it has a preventative effect on asthma deterioration. These three questions are not as readily answered as the question of the short-term effect of immunotherapy on specific allergies.

Because pharmacology has improved with the introduction of topical steroids and nonsedating antihistamines, symptom control can be achieved in most children without immunotherapy. The indications for immunotherapy have to be evaluated accordingly. In this reevaluation, both short-term and long-term effects of immunotherapy have to be considered. In reviewing immunotherapy studies published or presented during the past year, there was a predominance of studies performed in adults. However, because a previous study comparing responses to immunotherapy in children and adults has shown the treatment effect to be comparable in different age groups [5], the adult studies should also be of interest to the pediatrician and are therefore included here.

Mechanisms of immunotherapy

A number of investigators have contributed during the past 2 years with new insights into the mechanisms of immunotherapy [7-9,10••]. Most importantly, Varney *et al.* [7] and Durham [10••] performed studies on cells from peripheral blood and from biopsies of the skin and nasal mucosa before and after immunotherapy with grass pollen extracts. These studies have shed new light on the effects of immunotherapy, showing that with grass pollen immunotherapy in patients with severe hay fever, there is an inhibition of the late allergen response (LAR) in both the skin [7] and nasal mucosa [10••]. This effect on the LAR is associated with a decrease in recruitment of T lymphocytes and activated eosinophils. By *in situ* hybridization techniques, a "switch" of the T-cell response from a Th2-type to a Th1-type could be demonstrated by local increases in interferon gamma messenger RNA (mRNA) expression. Finally, an increase in the mRNA expression of the macrophage-derived interleukin-12 was found [10••]. In summary, these effects at the cellular level in tissue could lead to inhibition of IgE synthesis by decreased local interleukin-4 production,

attenuation of eosinophil activation by decreased interleukin-5 production, stimulation of a local interleukin-12-driven Th1 response, increased interferon gamma production, and decreased eosinophil infiltration. Through these mechanisms, both the immediate and late (inflammatory) allergic responses could be abated by immunotherapy (Fig. 1).

Immunotherapy for asthma

An extensive review of the efficacy of immunotherapy in asthma was recently published by Bousquet and Michel [1•]. They report from studies of their own that children improved more than adults during dust mite immunotherapy, particularly those who were allergic only to mites. Furthermore, they report that the improvement from mite immunotherapy was greater in the children who had normal or close to normal lung function. A number of studies have examined the effect of immunotherapy on the late-phase reaction and have shown the LAR to be attenuated by mite immunotherapy [1•]. The effects on nonspecific bronchial hyperreactivity have been contradictory, however, with both beneficial effects [11] and lack of effect [1•] being seen in different studies.

Immunotherapy for animal allergy is best documented with cat extracts. In a 3-year-long study by our group, we demonstrated that immunotherapy for cat allergy in children with mild to moderate asthma has effects not only on cat sensitivity in the airways but also on nonspecific bronchial hyperreactivity (BHR) [6]. In a more recent study, we treated children with moderate asthma with inhaled steroids and pollen-cat or pollen-placebo immunotherapy and again confirmed the beneficial effect of cat immunotherapy on both BHR and specific allergy to cat [12•]. However, the treatment with inhaled steroids made the difference between the groups less striking. Furthermore, very few children could stop steroid treatment, and the overall dose reduction was not significant in either group.

The most interesting study of immunotherapy in asthma was recently presented by the group at Johns Hopkins

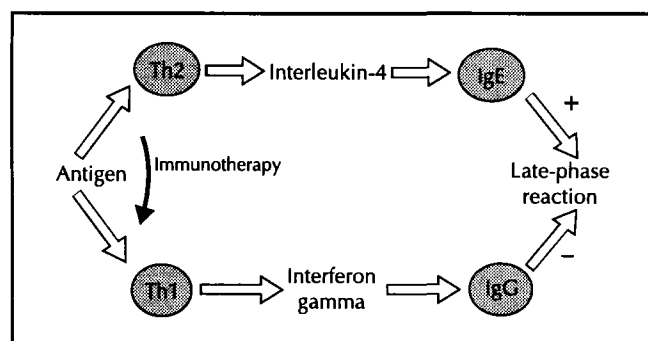


Fig. 1. Immunotherapy promotes Th1-type responses, which may inhibit interleukin-4-induced IgE synthesis and favor IgG production. (From Durham [10•]; with permission.)

University [13,14••,15]. The target group was children with moderate to severe asthma and multiple allergies who had their pharmacotherapy optimized during a long run-in period, whereafter they were randomly assigned to receive placebo immunotherapy or immunotherapy with up to seven different allergens (except animals), depending on their allergy pattern by skin test and radioallergen sorbent test. Each child then received immunotherapy for 2 years. About 50% of the children were taking inhaled steroids in addition to immunotherapy. The study was disappointing in that immunotherapy did not affect the severity of the disease, as measured either by medication requirements or by methacholine bronchial challenge.

Immunotherapy for rhinitis or hay fever

There is no doubt about the efficacy of immunotherapy in pollen allergy with symptoms of rhinoconjunctivitis [16]. The results of a 4-year trial of grass pollen immunotherapy in adults with severe grass pollen allergy were recently published, which further confirmed the efficacy of immunotherapy [3•]. Positive effects of immunotherapy on BHR induced by the pollen season have been reported previously [17].

A number of newly published studies have dealt with the use of local or oral immunotherapy [18,19•], which would be a particularly appealing way of administering immunotherapy to children [20]. However, so far the enthusiasm has been tempered by the fact that 10 to 100 times more allergen is needed to achieve results comparable to those from injection therapy. Sublingual administration is still under investigation, and standardization of extracts is so far not satisfactory [21]. With development of techniques for production of recombinant allergens, a new era in the field of local immunotherapy may arise [20].

Insect-allergy immunotherapy

The debate about who should receive venom immunotherapy was back on the agenda recently [22•]. The debate was initiated by a study on the natural course of systemic and local reactions to venom. Hauk *et al.* [23•] reported that in sting challenges in children with a history of mild to moderate reactions, almost all children had similar, milder, or no reaction at all to either of two stings. The authors of both papers conclude that immunotherapy is seldom needed in children other than those who have experienced a life-threatening sting reaction with hypotension or symptoms involving the airways.

Safety of immunotherapy

One of the crucial problems with immunotherapy concerns the risk of systemic reactions. Numerous approaches have been tried to diminish the risk of side effects [24,25••]. Conventional immunotherapy should be administered by physicians well acquainted with the

treatment of severe allergic reactions in a hospital or clinic setting where prompt treatment can be initiated. The opinion of the American Academy of Allergy and Immunology is that immunotherapy should never be given at home. Compliance with therapy may also be better if the patient receives the injections in an allergist's office [26]. A report of systemic reactions in children receiving immunotherapy was presented by Buscincio *et al.* [27]. The authors concluded that severe reactions are extremely rare in children with airway allergies. Tinkelman *et al.* [28] reported a prospective study of systemic reactions in children and adults receiving immunotherapy. Others have reported that systemic side effects during venom immunotherapy are also rare, although the reported frequency varies in different reports from almost none to 20% of the subjects [29]. Overall, the safety of immunotherapy is satisfactory if all precautions recommended by the American Academy of Allergy and Immunology are followed. Local immunotherapy has proven to be generally safe in studies to date [20], whereas the risk of systemic side effects with peptide immunotherapy is still being studied.

New approaches to immunotherapy

Allergen peptides

Allergens contain multiple epitopes, and the epitopes recognized by different individuals may vary. When the allergen is recognized by an antigen presenting cell, it is processed to form immunogenic peptide fragments. These peptide fragments, in association with MHC molecules, are then presented to and recognized by specific T-cell receptors. Full activation of the T cell then leads to the synthesis of lymphokines, proliferation of T cells, and activation of B cells, resulting in production and secretion of specific IgE antibodies. T cells can become unresponsive to stimulation by an allergen if the allergen is administered under conditions in which T-cell activation is incomplete. The aim of the research in peptide immunotherapy is to isolate the T cell-reactive epitopes of the allergen without the structure that is required for IgE binding [30•,31]. So far, T cell-reactive epitopes have been determined for the major allergens of grass pollen, ragweed, dust mite, cat [32], and bee venom. Studies are now in progress with peptides of *Fel d* I, the major cat allergen, which have thus far been promising with minimal side effects [33]. The approach is appealing, particularly for pediatric application, because treatment with T cell-reactive peptides from allergens that down-regulate T cell function without IgE binding activity would reduce the risk of side effects. If this mode of therapy proves successful, the ultimate goals would be immunotherapy without risk of allergic reactions and sustained effect with much shorter treatment duration.

Recombinant allergens

Recombinant allergens make it possible to improve characterization of the molecular and biologic features of aller-

gens, thereby allowing for the production of pure allergens for immunotherapy [34•]. Complete complementary DNA (cDNA)-cloned and sequenced allergens currently include ragweed (*Amb* I, II, and V) and cat (*Fel d* I). The method of cloning cDNA involves the isolation of mRNA from the organism and then transcription of the mRNA into cDNA by the retroviral enzyme reverse transcriptase. Allergen cDNA clones can then be identified by different methods. The advantage of recombinant allergens would be that they increase the possibility of individualizing allergen extract production. By recombinant allergen techniques, the unique proteins to which a patient is sensitized could be identified. A further possibility would be to chemically modify recombinant allergens to make them less allergenic. Attempts are currently being made with methods that were previously used in conventional allergen immunotherapy, such as formaldehyde polymerization and pegylation. Finally, the production of recombinant allergens might decrease the cost of pure allergen, which could contribute to the development of improved extracts, especially for local immunotherapy, because higher doses of allergen are required compared with injection therapy. Figure 2 summarizes the current trends in allergen biotechnology.

Local immunotherapy

During the past decade, several studies of local immunotherapy have been presented with conflicting results. The problems with local immunotherapy are somewhat similar to the problems with injection immunotherapy before characterization and standardization of allergen extracts became possible. Lack of standardization of the extracts is still a problem that could be one of the explanations of the disparate results. Another problem is the question of optimal dose, *ie*, the dose required to elicit the proper immunologic effect without local or systemic side effects. Recent studies in children and adults have been performed with pollen and dust mite extracts using both nasal and sublingual routes [20]. Efficacy using the sublingual route has been most questionable [21]. To the pediatrician, local immunotherapy would be an appealing treatment option that could make it possible to intervene in the development of specific allergies at an earlier age than with injection immunotherapy. Bousquet and Michel (Unpublished data) have hypothesized from experience of studies of their own that immunotherapy in children younger than 6 years of age could contribute to the prevention of development of new sensitizations. Injection therapy in children younger than 6 years of age has to be prescribed with great caution due to the risk for systemic side effects and psychologic trauma, but the possibility of using local immunotherapy would sidestep this restriction [35].

Preventative immunotherapy

A still open question is whether immunotherapy can prevent the development of asthma in children with allergic

rhinitis or sensitization to new allergens. A recent study of asthma prevention by immunotherapy was initiated in children with pollen-induced rhinitis. The first results of this so-called *PAT study* (Preventive Allergy Treatment study, conducted by ALK Denmark in collaboration with European allergists) were reported recently at the Congress of the European Academy of Allergology and Clinical Immunology in Madrid (1995) [36]. At this stage of the study, after 1 year with pollen immunotherapy, there was a trend toward more children in the open control group having developed asthma (15 of 35) than in the immunotherapy group (6 of 36). In a French study of children 2 to 6 years of age receiving immunotherapy for a single allergy, no new sensitizations occurred during a 3-year period, whereas in children not receiving immunotherapy, all had developed new specific allergies (Bousquet *et al.*, Unpublished data) [20]. However, as discussed previously, it is still highly questionable to use injection immunotherapy in children younger than 6 or 7 years of age.

Immunotherapy for food allergies

No new studies of immunotherapy for food allergies have been published, nor have there been any interesting results presented at recent meetings. The immunotherapy study by Oppenheimer *et al.* [37] of peanut-allergic subjects is still the best controlled and most relevant food-allergy immunotherapy study. This study showed a reduction in peanut sensitivity with immunotherapy but was limited by the risk of severe systemic side effects.

Long-term effects of immunotherapy

In view of the many controlled studies of immunotherapy, there are surprisingly few follow-up studies of the

duration of the effect of therapy after injections have been stopped. Bousquet and Michel [1••] followed up on patients who received immunotherapy for different lengths of time. The authors found the effect to last for 3 years or more when immunotherapy had been administered for at least 3 years. Four to 5 years after a 3-year course of immunotherapy for cat and dog allergy, we [38] reevaluated the 32 patients who completed 3 years of treatment. We found that specific allergy to cat and dog had increased, as measured by bronchial challenge. However, the patients' subjective evaluation of symptoms on exposure to the animals had not changed and in some cases even improved further. Most important, BHR evaluated by histamine bronchial challenge had remained stable, and asthma was still mild. A possible interpretation of these results is that the effect on the LAR remained, but the immediate reaction relapsed to some extent. In venom immunotherapy studies, protection against reactions with sting challenges has also been reported 5 years after stopping a 5-year course of immunotherapy [39]. From these three follow-up studies, one could conclude that immunotherapy should be used for 3 to 5 years to induce effects that are sustained for 5 years or more.

Natural history of specific allergy in asthma and rhinitis

A cohort of Swedish children with asthma and specific allergies was followed up for 15 years from a median 9 years of age to 24 years of age [40]. Most children with mild asthma and half of those with moderate asthma had improved, whereas very few with severe asthma had changed. At the start of the study, the most common allergies were to pollen and animal dander. In the majority of children, the specific allergies remained into adulthood.

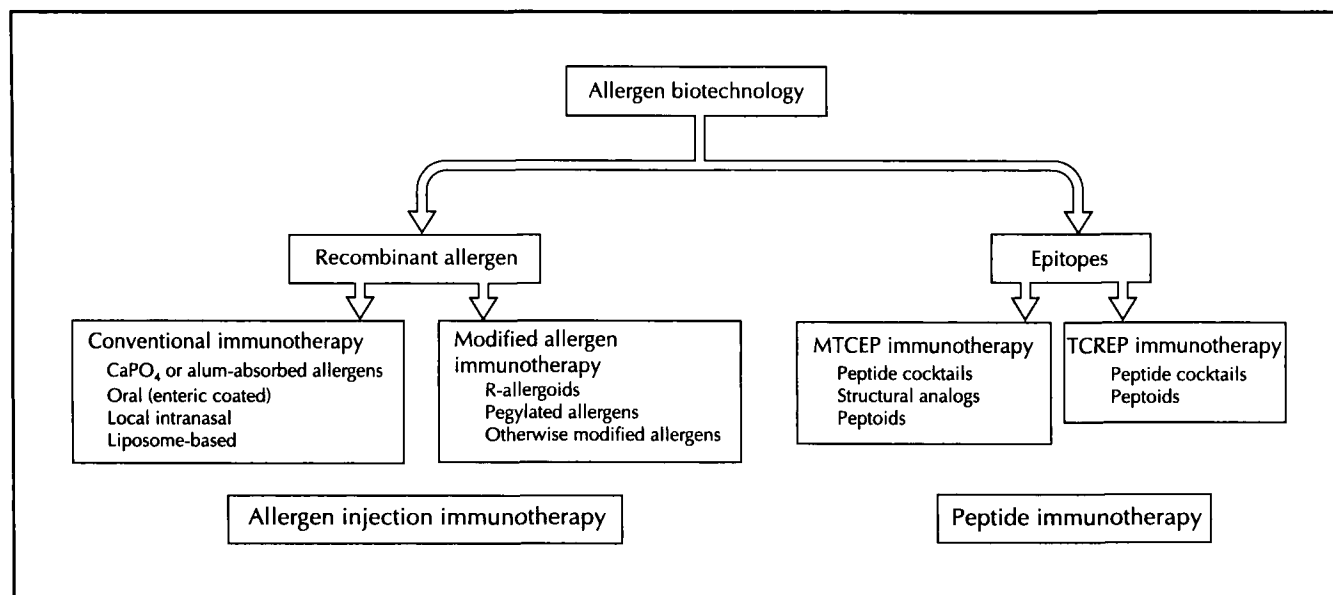


Fig. 2. Potential application of recombinant allergens and epitopes. MTCEP—minimal T-cell epitope peptide; TCREP—T-cell receptor epitope peptide. (From Mohapatra *et al.* [30••]; with permission.)

There was a very low remission rate for pollen and animal dander allergy. A Finish cohort of children with allergic rhinitis was followed up for 8 to 11 years [41]. Rhinitis symptoms persisted in 90% of the children, although they were mild in 40% at follow-up. Asthma had developed in 19%, mostly in those with perennial allergies, *ie*, to dust mite or animals. These two follow-up studies illustrate that the remission rate is low in children with asthma or rhinitis caused by specific allergies.

Conclusions

We have now come closer to understanding the mechanisms of immunotherapy through studies of cellular events in the skin and nasal mucosa during allergic reactions before and after treatment with immunotherapy. These studies provide a more convincing rationale for the induction of allergic tolerance through immunotherapy. The standardized extracts that are now available allow for more consistent treatment, thereby increasing both efficacy and safety (Table 1).

Recent studies indicate immunotherapy to be best suited for pollen allergy, particularly in children with severe allergic rhinitis. In asthma, immunotherapy seems to be most successful in mild and moderate disease caused by dominant allergies to dust mites and cats, whereas immunotherapy for severe asthma or asthma caused by multiple allergies has little effect on disease severity. Inhaled steroids are needed in many children with asthma in addition to immunotherapy. The fact, however, that cessation of steroid therapy in childhood asthma often results in increasing BHR and deterioration of lung function could point to a combination of immunotherapy and (low-dose) inhaled steroids or other anti-inflammatory drugs as the treatment of choice when asthma is caused by dust mite or cat allergy [42]. Avoidance of cats and other furred pets is necessary but not sufficient in some children, because pets are abundant and indirect exposure is impossible to avoid. Dog immunotherapy is less efficacious than cat immunotherapy [6], and better extracts are

needed before dog immunotherapy can be recommended. Venom immunotherapy should be offered to children who have experienced severe sting reactions resulting in airway symptoms or signs of hypotension.

The future of immunotherapy seems promising in view of the possible development of recombinant allergens for local or injection therapy and peptide extracts with effects directed to T-cell receptors, decreasing the risk of systemic reactions. The ongoing increase in the prevalence of specific allergies in children further underlines the need for safe and simple ways of performing immunotherapy. Finally, in a paper last year by Holt [43••], a different approach for prevention of asthma and atopic diseases during early childhood was proposed. The intention of the suggested strategy would be prevention of sensitization, which would be the ideal solution to the problem of childhood allergic disease.

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Table 1

Indications for immunotherapy with allergens

Allergen	Condition			
	Asthma	Rhinitis	Hay fever	Anaphylaxis
Pollen	Yes*	Yes	Yes	
Dust mite	Yes†	Yes		
Cat	Yes†	No		
Dog	Seldom	No		
Mold	Seldom	No		
Venom	Yes			Yes

*Mild, moderate, and severe asthma. †Mild and moderate asthma. ‡Moderate asthma.

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