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Does Allergen Immunotherapy Alter the Natural Course of Allergic Disorders?

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Contents

Abstract

Allergy in patients with atopy is caused by clinical adverse reactions to environmental antigen, which is often associated with allergen-specific immunoglobulin (Ig)E production. Since allergy reflects an inappropriate immunological reaction, a therapeutic approach related to immunology is likely to actively alter the natural course of allergic disorders. Allergen immunotherapy, known at various times as desensitisation or hyposensitisation, is very recently defined by the World Health Organization as therapeutic vaccines for allergic diseases.

At present, it has become a common clinical practice in selected patients for the treatment and prevention of the recurrence of allergic disorders caused by insect venoms and has proven to be effective in changing the course of allergic responses induced by grass and tree pollen, animal hair and dander, house dust mite and mold, as demonstrated by improvement in clinical symptoms, skin prick test and medication scores. Reported effects of allergen immunotherapy on the natural course of allergic disorders include (i) prevention of reaction following re-sting in insect venom allergy; (ii) prevention or decrease the rate of the natural progress of allergic rhinitis to asthma; and (iii) inhibition of new sensitisation in monosensitised children.

Many aspects of the immune responses associated with allergic disorders, including antibody production, cytokine secretion, T cell activation and local inflammatory reactions, are found to be significantly altered during and/or after

immunotherapy. Specifically, the ratio of allergen-specific IgG4 to IgG1 correlates well with positive clinical outcome caused by allergen immunotherapy in patients with pollen-allergy. Allergen immunotherapy affects the cytokine profile of allergen-specific T cells and switches T_H2 type immune responses in patients with atopy towards T_H0 or T_H1 type responses. Although the changes in the absolute value of T_H1 or T_H2 cytokines appear quite variable, the increase in the ratio of T_H1/T_H2 cytokines is very consistent among published reports, especially in the late stage of treatment.

Accumulating evidence indicates that appropriate immunotherapy prevents the onset of new sensitisation and prevents the progress of allergic rhinitis to asthma. Although the changes in B cell and T cell responses, especially IgG antibodies and T_H1/T_H2 cytokine production, may be the major mechanism underlying the clinical efficacy of allergen immunotherapy and the prevention of the development of allergic phenotypic changes, multiple mechanisms may be involved in the outcome of alteration of the natural course of allergic disorders.

Allergic disorders refer to clinical adverse reactions to environmental antigens (allergens), which are often associated with allergen-specific immunoglobulin (Ig)E production. The current practice for treatment and prophylaxis of allergic diseases consists of (i) environmental control; (ii) pharmacological management; (iii) public education; and, in selected cases, (iv) allergen immunotherapy. Although avoidance of allergens is the most effective means to prevent allergic reactions, it is often difficult to achieve, especially for inhalant allergens. Pharmacological management, using drugs such as topical corticosteroids, bronchodilators, antihistamines and other antagonists of vasoactive mediators released from mast cells and basophils has proven to be highly effective in the prevention and control of allergic symptoms, but it can not cure or alter the natural course of allergic diseases.

1. Rationale for Allergen Immunotherapy

Since allergy reflects an inappropriate immunological reaction, a therapeutic approach related to immunology is likely to actively alter the natural course of allergic disorders. The largely empirical development of allergen immunotherapy happened in an era with little knowledge of immunology. As early as 1911, Noon and Freeman[1,2] reported that serial subcutaneous injections with gradually increased doses of pollen extracts ameliorated the symptoms associated with grass pollen-induced allergic rhinitis. This therapeutic approach, known at various times as desensitisation or hyposensitisation and more commonly as allergen immunotherapy, is very recently defined by the World Health Organization as therapeutic vaccines for allergic diseases.[3]

In general, conventional allergen immunotherapy consists of the administration of slowly increasing quantities of antigen over an extended period of time, up to 3 to 5 years. Its aim is to induce a degree of clinical tolerance, or lowered sensitivity to the particular allergen, leading to a decrease in clinical symptoms and requirement for pharmacological medications. At present, allergen immunotherapy has become a common clinical practice in selected patients for the treatment and prevention of the recurrence of allergic disorders caused by insect venoms and inhalant allergens. In particular, venom immunotherapy has been accepted as the standard of care for Hymenoptera-induced systemic allergic reactions.[4] This article reviews recent progress in studying the efficacy of allergen immunotherapy and the mechanisms of this therapeutic approach with an emphasis on its influence on the natural course of allergic disorders.

2. Efficacy and Tolerability of Allergen Immunotherapy

Allergen immunotherapy has proven to be effec-

tive in changing the course of IgE-associated immediate hypersensitivity caused by a large number of allergens including, but not limited to, grass and tree pollen,[5-10] animal hair and dander,[11-14] insect venoms,[4,15,16] house dust mite (HDM)[17-19] and mold.[20,21] For most reports, the parameters examined include improvement in the clinical symptoms, skin prick test and medication scores. Typically, after it has been given for long enough, allergen immunotherapy decreases the frequency and duration of symptoms, improves the quality of life and, in some cases, diminishes the requirement for pharmacological medications in patients with allergies.

Venom and pollens (grass and tree) represent the most extensively tested allergens in immunotherapy. Venom immunotherapy shows more than 90% efficacy[4] and most double-blind, placebo-controlled studies using pollens show significant improvement in clinical symptoms. A study by Durham et al.[22] recently showed long term clinical efficacy of grass-pollen immunotherapy after the discontinuation of treatment in a randomised, double-blind, placebo-controlled trial. During the 3 years of this trial, scores for seasonal symptoms and medication and the late skin response remained low after the discontinuation of immunotherapy, and there was no significant difference between patients who continued immunotherapy and those who discontinued it. Malling[23] recently analysed more than 40 controlled rhinitis immunotherapy studies published since 1980 and found significantly better improvement in clinical symptoms in the active group than in the placebo group in 80% of the reported studies.

Similarly, clinically relevant efficacy was documented in 12 out of the 16 controlled asthma studies.[23] A meta-analysis of 20 randomised, placebo-controlled, double-blind clinical trials of allergen immunotherapy for asthma showed that the combined odds of symptomatic improvement were 3.2 [95% confidence interval (CI) 2.2 to 4.9] and the combined odds for reduction in bronchial hyperresponsiveness were 6.8 (95% CI 0.43 to 1.00), indicating that allergen immunotherapy is a useful treatment option in highly selected patients with allergic asthma.[24]

2.1 Effect on the Natural Course of Allergy

Reported effects of allergen immunotherapy on the natural course of allergy include (i) prevention of reaction following re-sting in insect venom allergic patients; (ii) prevention or decrease the rate of the natural progress of allergic rhinitis to asthma; and (iii) inhibition of new sensitisation in monosensitised children.

The best results showing the alteration of the natural course of allergy caused by allergen immunotherapy are documented in insect venom immunotherapy. One study[25] investigating the natural history of insect sting allergy revealed that 220 patients with a history of venom anaphylaxis had a reaction rate after the first re-sting of 56%, with adults having a higher incidence of reaction (74%) than children (40%). The rate of reaction appeared unrelated to time interval since the initial sting reaction and the severity of reaction after re-sting was correlated with that following initial sting. A similar rate (50 to 60%) of reaction caused by resting was observed in several other studies.[26-28]

The natural course of insect venom allergy can be efficiently blocked by venom immunotherapy. A well-controlled study comparing the efficiency of venom immunotherapy with placebo demonstrated remarkable efficacy of the therapy in decreasing the rate of allergic reaction to a deliberate sting challenge.[29] The allergic reaction rate in placebo group (12 patients) was 60%, which was similar to that shown in other studies, whereas the reaction was observed in only 5% of the 18 patients treated with venom immunotherapy following resting. Several other trials have also shown a high efficacy with venom immunotherapy with few failures, confirming the significant effectiveness of this therapy in altering the natural course of venom allergy.[30]

2.1.1 Long Term Effects

The long term effect following treatment represents the most typical alteration of the natural course of allergy caused by allergen immunother-

apy. Mosbech and Osterballe[31] reported that the clinical effect lasted for 6 years after termination of immunotherapy. In patients with asthma caused by allergy to animal dander, the effect of immunotherapy using cat or dog allergen extracts was found to persist for 5 years after termination of immunotherapy.[32] More recently, Jacobsen et al.[33] studied the long term effect of tree pollen extract immunotherapy by following up the symptom scores and skin tests in 36 patients in 6 years after a 3-year course of immunotherapy. The data showed that 86% of the patients with rhinitis and 68% of the patients with asthma maintained improvement after termination of the therapy. The skin sensitivity of the patients decreased significantly during therapy, and the skin reactions 6 years after the treatment were still significantly lower than the pretreatment levels.

One significant aspect of the long term effect of allergen immunotherapy is the prevention of the progress of allergic rhinitis to asthma. A link between allergic rhinitis and atopic asthma has been demonstrated in numerous epidemiological studies. It is reported that 25 to 43% of the patients experiencing rhinitis naturally develop asthma within 10 years,[34,35] whereas in the study by Jacobsen et al.,[33] none of the patients with allergic rhinitis developed asthma over a 6-year period following termination of immunotherapy. Similarly, a study carried out in multiple centres of European countries showed that the incidence of asthma is significantly reduced following three years of allergen immunotherapy in children.[36,37]

2.1.2 Effects in Children

Encouraging data demonstrating the effects of allergen immunotherapy on the natural course of allergy also come from a 3-year follow-up survey carried out by Des Roches et al.[38] showing prevention of the onset of new sensitivities in children with this therapy. The natural course of allergic sensitisation in children is a gradual development of sensitisation initially to food allergens followed by sensitisation to inhalant allergens.[39-46] Sensitivity to perennial allergens including HDM seems to appear at an earlier stage than sensitivity to seasonal allergens such as pollen.

The controlled study by Des Roches et al.[38] followed the development of new sensitisation in 22 children monosensitised to HDM receiving allergen immunotherapy and 22 control children with monosensitisation to HDM without immunotherapy. They found that all those not treated with allergen immunotherapy developed sensitisation to other allergens such as animal dander, *Alternaria* species or pollen, whereas 45% (10 of 22) of those in the actively treated group did not develop any new sensitivity ($p < 0.001$). This study suggests that allergen immunotherapy can alter the natural course of allergy in children monosensitised to an allergen by preventing the development of new sensitivities.

However, children with multiple sensitivities to allergens do not seem to respond to such immunotherapy. A double-blind, placebo-controlled trial of multiple-allergen immunotherapy in 121 children with asthma with polysensitivity to allergens showed no difference between the active and placebo group in clinical symptoms, medication, or peak flow rate over a two-year period of immunotherapy.[47] A reservation in interpreting the data is that the method of simultaneous multi-allergen injection (mix of allergens for injection) used in this study was different from the standard approach which delivers single antigen.

2.2 Tolerability

Despite the broadly observed efficacy in properly selected patients, allergen immunotherapy has from the beginning presented problems with adverse effects. Controlled trials demonstrate that the effectiveness of immunotherapy on allergen-induced symptom/medication score reduction are dose related, with large doses more likely to elicit clinical improvement but greatly increasing the risk of anaphylaxis.[48,49] Largely because of the increased use of standardised allergen extracts, recent data show that, in general, allergen immunotherapy is well tolerated with rare severe cases of adverse effects. Maintenance immunotherapy is associated with

fewer adverse events than the initial treatment or build-up period.

In a recent retrospective study in Turkey, which included 1506 patients receiving allergen immunotherapy over a 12 year period, there were 125 systemic reactions in 109 patients (1 per 1813 injections), of which 52.8% were of the skin only and less than 5% showed hypotension with respiratory symptoms and skin reactions.[50] Toubi et al.[51] followed-up the adverse reactions occurring in patients attending an allergy clinic and found that out of 280 immunotherapy-treated patients, 37 (13%) developed systemic reactions, of which 70% (26 of 37) occurred during the build-up phase and 30% (11 of 37) in the maintenance phase of treatment. Severe adverse reactions developed in 5% (2 of 37) of the patients.

An interesting study investigating patient satisfaction with allergen immunotherapy revealed a contrast of poor opinion and high satisfaction after treatment, suggesting that the true efficacy and patient tolerance of allergen immunotherapy are better than patients' expectations in clinical practice.[52]

3. Immunological Changes Following Allergen Immunotherapy

In addition to the alteration in developing clinical symptoms, the underlying adverse immunological reactions in allergic disorders are also found to be changed after allergen immunotherapy. Indeed, the change in immune responses is likely to be the mechanism underlying the clinical improvement induced by allergen immunotherapy. Many aspects of the immune responses associated with allergic disorders, including antibody production, cytokine secretion, T cell activation and local inflammatory reactions are found to be significantly altered during and/or after immunotherapy.

3.1 Antibody Responses

The first observed and a commonly measured parameter indicating immunological changes caused by immunotherapy is the striking rise in IgG or 'blocking antibodies',[53-55] which is postulated by some to prevent allergen from combining with mast cell- and basophil-bound IgE and degranulation of these cells.[56,57] Since allergen specific IgE is the most typical antibody associated with, and in many cases mediating, immediate hypersensitivity nearly all of the reported studies investigating allergen immunotherapy examined allergen specific IgE responses during or after the termination of immunotherapy.

Decreases in allergen-specific IgE responses are observed in some studies,[58-60] but more studies do not show significant alteration in IgE responses following allergen immunotherapy, even when significant improvement in clinical symptoms and medication scores are observed. In comparison, IgG antibodies (IgG1 and IgG4), almost without exception, are increased following allergen immunotherapy. IgG1 antibody titres often rise at the beginning of treatment but tend to decline at late phase, whereas IgG4 titres remain high even several years after the termination of immunotherapy.[18,60-62] In addition to the potential mechanism that excessive allergen-specific IgG could 'block' allergens binding to the mast cell- and basophil-bound IgE, IgG antibodies induced by allergen immunotherapy can inhibit the occurrence of serum-facilitated antigen presentation (S-FAP) at very low allergen concentrations. This leads to significantly higher allergen threshold concentrations required to induce T cell proliferation and cytokine production, and thus an allergic reaction.[63] Blocking antibodies, especially IgG4 could play a role in co-crosslinking mast cell IgE and IgG receptors, thereby inhibiting the signal transduction of high affinity IgE receptor (FcåRI) for mediator release.[64] Indeed, several studies correlate the decreased symptom score with a significant increase in allergen specific IgG4 titres.[65,66]

More recently, Gehlhar et al.[67] found that the ratio of allergen-specific IgG4 to IgG1, rather than IgG4 or IgG1 alone, correlates well with a positive clinical outcome after allergen immunotherapy in patients with pollen allergy. They argued that although the measurement of IgG4 titres has served as a 'gold standard' to assess the effectiveness of immunotherapy, the increase in IgG4 titres alone

only indicates that the immune system is responding to the treatment, and does not predict the outcome. A similar, earlier study which used crude *Phleum pratense* extracts comes to the same conclusion, again emphasising the predicative value of IgG4 : IgG1.[68] In support of this argument, some studies show a positive association between IgG4 titres and treatment failure, instead of improvement.[69,70]

3.2 Cytokine and T Cell Responses

Currently, the most intensively investigated areas in the immune regulation of allergic disorders and the immunological changes induced by allergen immunotherapy are cytokine and T cell responses. Although deletion of allergen-specific T cells and induction of anergy by allergen treatment could be a mechanism for the effect of allergen immunotherapy, immune deviation (a shift of cytokine production patterns by allergen-specific T cells) is more widely observed.[71,72]

It is now generally accepted that atopic allergy is associated with active T cell responses to common environmental allergens that are skewed towards T_H2 cytokine production, in contrast to the T_H1 skewed responses in normal individuals.[73,74] T_H2 cytokines especially interleukin (IL)-4, IL-5 and IL-13 have been found to be critical in the development of immediate hypersensitivity. IL-4 is essential for IgE switch and IL-13, in many cases, plays a similar role to IL-4. IL-5 is crucial for the respiratory tract eosinophilia observed in asthma and rhinitis and IL-13 appears important for bronchial mucus production.[75] Using gene knockout mice, we recently demonstrated that endogenous IL-10 plays a role in promoting bronchial eosinophilia and mucus production in an asthma-like model.[76] In contrast, T_H1 cytokines, particularly interferon (IFN)-γ, can inhibit IgE production and the function of T_H2 cells.[77]

Allergen immunotherapy affects the cytokine profile of allergen-specific T cells and switches T_H2-type immune responses in patients with atopy towards T_H0- or T_H1-type immune responses. When the changes in the absolute value of individual cytokines caused by immunotherapy are analysed, there have been some discrepancies among reported studies. Some studies find reduced IL-4 production without change in IFNγ secretion after allergen immunotherapy,[78,79] whereas others show an increase in IFNγ production.[80-82] The discrepancy may be due to the differences among the reported studies in: (i) the stimulus used for *in vitro* restimulation, i.e. polyclonal or allergen-specific; (ii) the duration of therapy and the time after therapy; and (iii) the mechanisms operating in different allergen-specific immunotherapy.

Although the changes in the absolute value of T_H1 or T_H2 cytokines were quite different, the increase in the ratio of T_H1 : T_H2 cytokines appears very consistent in published reports, especially in the late stage of treatment.[78,79,83-88] We reported that treatment with chemically modified ovalbumin (OA-POL) inhibited OVA-specific IgE responses in mice, which correlated with a shift of altered allergen specific T cell cytokine patterns towards T_H1 responses as demonstrated by a significant increase in the IFNγ : IL-4 ratio during or a long time after the treatment.[89,90] Benjaponpitak et al.[91] recently investigated the kinetics of change in cytokine patterns of peripheral CD4+ T cells in 6 patients with allergies during conventional allergen immunotherapy. They found that the ratio of allergen-specific IL-4 : IFNγ production by CD4+ T cells from 4 of the patients receiving immunotherapy greatly increased during the period when the dose of allergen was increasing, but decreased (therefore the IFNγ : IL-4 ratio increased) after high dose maintenance therapy was achieved. In addition, they found diminished late-phase skin reactions and allergen-specific IgE levels in responding (increase of IFNγ : IL-4 ratio), but not nonresponding, individuals over the course of immunotherapy.

Therefore, the T_H1 : T_H2 ratio, instead of T_H1 or T_H2 cytokine alone, may be a valid indication for the effectiveness of allergen immunotherapy when it is examined in the late stage of treatment. It should be noted, however, that the changes in antibody responses after allergen immunotherapy (increase of both IgG1 and IgG4 and decrease or no

change in IgE) responses can not be fully explained by either the value of these cytokines or their ratio because it has been demonstrated that IgG4 and IgE production is dependent on T_H2 cytokines such as IL-4 and IL-13 and is down-regulated by IFNγ,[92-95] whereas IgG1 expression is sometimes promoted by IFNγ in humans.[96]

Based on the understanding of the central role of helper T cells in the initiation and regulation of immune responses to allergens, current research is directed towards improving the efficacy of allergen immunotherapy by targeting T cell responses. In addition to improving efficacy, another potential advantage of targeting T cells in immunotherapy, such as using modified allergens which can induce immune deviation in T cell levels without binding to IgE, is to improve the tolerability of the therapy because the most important tolerability problems involving the standardised allergen immunotherapy are IgE-mediated events.

3.3 Other Immune Responses

In addition to T_H1/T_H2 cytokine patterns and antibody isotypes, the changes in immune responses are also observed in other aspects after allergen immunotherapy. One recent study[97] showed down-regulation of peripheral blood CD4+ and CD8+ T cell activation after 1-year of allergen immunotherapy in grass pollen-sensitive patients with asthma, demonstrated by reduction of the expression of 2 activation markers, CD25+ (the p55 IL-2 receptor) and human leucocyte antigen (HLA)-DR. A significant decrease in CD23+ expression on B cells was also observed in the study. When patients allergic to *Parietaria* pollen were treated with allergen immunotherapy, the concentration of tryptase (the most specific marker for mast cell activation and mediator release) in nasal lavage after provocation tests was significantly decreased, indicating a decrease in mast cell reactivity to the allergen.[98]

The blocking antibodies induced by allergen immunotherapy also play a role in inhibiting CD4+ T cell activation via a decrease in serum-facilitated allergen presentation (S-FAP), which is mediated by allergen-specific IgE. A recent study[63] shows that in patients allergic to birch pollen, allergen-specific CD4+ T cells are activated by extremely low allergen concentrations *in vivo* due to S-FAP. This S-FAP of birch pollen allergen can be inhibited by long term birch immunotherapy which induces blocking antibodies, resulting in decreased proliferation of T cells and IL-4, IL-5, IL-10 and IFNγ production by allergen-specific T cells, thus inhibiting allergen-induced late phase responses. The inhibition was noted at as early as 3 to 9 months after the start of allergen immunotherapy and was mediated by the IgG fraction of the sera from actively treated patients.

Allergen immunotherapy can significantly inhibit eosinophilic inflammation in the airways of patients with asthma. In addition to inhibiting T_H2 cytokine production which enhances eosinophilia, allergen immunotherapy is able to suppress the production of factors which induce eosinophil adhesion thus inhibiting eosinophil recruitment in allergic inflammation.[99] Moreover, alteration in chemokine production such as IL-8, RANTES (the growth factor Regulated on Activation, Normal T cell Expressed and Secreted) and monocyte chemoattractant protein 1 (MCP-1) is also observed at various stages of allergen immunotherapy.[100]

Taken together, it is possible that specific immunotherapy exerts its beneficial effect via multiple mechanisms with variations related to the nature of allergen, the approach of treatment (dose, time and the route) and the phase of pathological changes.

4. Conclusion

Allergen immunotherapy is the only active treatment approach that may alter the natural course of allergic disorders. Accumulating evidence indicates that appropriate immunotherapy prevents the onset of new sensitisation and prevents the progress of allergic rhinitis to asthma. Although the changes in B cell and T cell responses, especially IgG antibodies and T_H1/T_H2 cytokine production, may be the major mechanism underlying the clinical efficacy of allergen immunotherapy and the

prevention of the development of allergic phenotypic changes, multiple mechanisms may be involved in the outcome of alteration of the natural course of allergic disorders.

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