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Allergen Immunotherapy in the Prevention of Asthma

Chitra Dinakar; Jay M. Portnoy

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Abstract and Introduction

Abstract

Purpose of review: Asthma is a disease causing significant morbidity and mortality. In the recent past, there has been an explosion of pharmacotherapeutic options attempting to control the disease. Unfortunately, none of the current options offers the promise of prevention or a permanent cure. However, there appear to be exciting, new data emerging to support the hypothesis that the prevention or early treatment of allergic rhinitis, such as with the use of allergen immunotherapy, may help mitigate the severity of bronchial symptoms and even prevent the development of asthma. In this paper, we review recent research published proposing immunotherapy as a means of preventing the development of, or at least ameliorating, allergic asthma.

Recent findings: There is evidence that the upper and lower airways may be considered a single unit, with the nasal and bronchial mucosa having features in common. Epidemiological, pathophysiological and clinical studies have shown that they can be affected by similar inflammatory triggers, with interconnected mechanisms amplifying the inflammatory cascade. Allergic rhinitis is interrelated to, and is a risk factor for, the development of asthma. An evidence-based review validates the successful use of allergen immunotherapy in treating allergic rhinitis and asthma. There is promising evidence advocating its use in the prevention of clinical asthma.

Summary: This article explores current research pertaining to the use of immunomodulation, such as by using allergen immunotherapy, to ameliorate and prevent the development of allergic asthma.

Introduction

Asthma is the most common chronic disease of childhood, and it is associated with substantial morbidity and mortality. The prevalence has been increasing globally since the 1970s.^[1] This increase in morbidity has occurred during a time when asthma treatments have improved as a result of the development of highly effective medications and the publication of national and international guidelines for using them.^[2,3] The failure of these treatments to improve asthma morbidity is partly caused by a lack of adherence by providers^[4-6] and by patients.^[7] However, even if full adherence were achieved, none of the pharmacological interventions known today has been proved to alter the course of the disease. Therefore, once an individual has asthma, unless they are predisposed to improve naturally, it is likely that treatment will have to be given over a lifetime. There are no known treatments that can cure asthma. Even the most aggressive disease management programme has to be followed for the duration of the illness.

Because there are no medications that can cure asthma, any intervention that could prevent asthma from

occurring in the first place would be of immense benefit. It has long been recognized that the nasal and bronchial mucosa have similarities, and that dysfunction of the upper and lower airways frequently go hand in hand. Encapsulating this concept into a key idea 'allergic rhinitis and its impact on asthma' has helped consolidate the link between allergic rhinitis and asthma.^[8] It has helped focus research around the hypothesis that the upper and lower airways are a single unit with an interdependent relationship. It has also opened the door to the possibility that modulating the allergic response may aid in preventing the development of clinical asthma. Immunotherapy is the chief immunomodulating weapon in the armamentarium of the allergist, and has convincingly been shown to re-direct the immune system away from the allergic response. As a result of practical concerns pertaining to patient tolerance and comfort, particularly in young children for whom preventive approaches would apply, there have been attempts to try non-injectable forms of immunotherapy. This review will consider recent promising literature that suggests that the early treatment of the allergic individual with allergen immunotherapy may play a role in mitigating, or even preventing, the development of asthma.

The Link Between Allergic Rhinitis and Asthma

More than 70% of individuals with asthma report having nasal symptoms.^[9] Approximately one out of five individuals with allergic rhinitis develop asthma later in life,^[10] with 50% of them having seasonal bronchial hyperreactivity (BHR). Rhinitis frequently predates the onset of asthma, and those with allergic rhinitis and BHR are more likely to develop asthma.^[11]

Factors operating very early in life may be particularly important for the acquisition of childhood asthma and rhinitis, whereas the development of atopic sensitization and seasonal allergic rhinitis may also be affected by environmental factors occurring beyond infancy. In an Australian study,^[12] it was found that atopy acquired before the age of 6 years is an important predictive factor for asthma continuing into late childhood, whereas atopy acquired later was only strongly associated with seasonal allergic rhinitis.

A growing number of studies have shown that inflammation plays a critical role in the pathogenesis of asthma and rhinitis. The inflammatory infiltrate appears to be composed of eosinophils, mast cells, T lymphocytes and cells of the monocytic lineage, and may be found even outside the allergy season in the airways of patients with seasonal allergic rhinitis.^[13] The same pro-inflammatory mediators (histamine, cysteinyl-leukotrienes), T-helper type 2 cytokines (IL-4, IL-5, IL-13 and granulocyte-macrophage colony-stimulating factor),^[14] chemokines (regulated upon activation: normal T cell expressed/secreted and eotaxin) and adhesion molecules appear to be involved in the nasal and bronchial inflammation in rhinitis and asthma. However, differences may exist in the extent of the inflammatory indices, with eosinophilic inflammation and epithelial shedding being more pronounced in the bronchi than in the nose of the same patients suffering from asthma and rhinitis.^[15] In addition to allergic triggers,^[16] the inflammation may also be triggered by viruses such as respiratory syncytial virus.^[17]

Recent advances have been made in our knowledge of the molecular and genetic mechanisms that induce airway hyperreactivity. Studies have demonstrated the essential role of repeated allergen inhalation,^[18] natural killer pulmonary V(alpha)14i NKT cells,^[19] and CD28 co-stimulation,^[20] in regulating the development of allergen-induced airway hyperreactivity and structural changes resembling remodeling in mice. There is an increased understanding of the role played by IL-18 gene polymorphisms,^[21] epitopes of CD4 T cells,^[22] and a lack of importance of cytokines such as IL-5, IL-13,^[23] and CCR8^[24] in allergic sensitization and the development of allergic rhinitis.

Many patients with allergic rhinitis have increased bronchial sensitivity to methacholine or histamine.^[25] The responsiveness of the bronchial mucosa in asthma patients is approximately 50 times that of normal (non-allergic or non-asthmatic) individuals, whereas that of the nasal mucosa in allergic rhinitis is only two to eight times that of controls.^[26] Whereas the inflammatory process involved in BHR is similar in both conditions, the greater

degree of BHR seen in asthma may be a consequence of the anatomical differences between the upper versus the lower airways.

Exposure to the allergens early on in life and the development of IgE-mediated sensitization appears to pre-date clinical symptoms,^[27] both by direct, and second-hand, exposure.^[28] Early exposure to cat allergen concentrations greater than 1 µg/g dust increased substantially the risk for specific sensitization to Fel d 1 and wheeze without infection at the age of 2 years.^[28] Whereas high-level indoor allergen exposure has clearly been linked to a lower forced expiratory volume in 1 s, higher exhaled nitric oxide values and more severe airways reactivity, even low-level exposure to common indoor allergens was recently shown to be correlated with non-specific BHR in asthmatic individuals.^[29]

Allergen Avoidance

As allergies play such a significant role in triggering allergic rhinitis and asthma, it makes sense to try allergen avoidance measures as a first-line prevention strategy. The effectiveness of allergen avoidance in the treatment of asthma was first suggested by studies in which patients were moved to houses with low dust mite levels at high dry altitudes.^[30] To be a successful intervention, however, it is important to create a low allergen environment in patients' homes, and, unfortunately, the majority of single interventions have failed to achieve a sufficient reduction in allergen load to lead to a clinical improvement. A meta-analysis of appropriately controlled house mite avoidance trials^[31] suggested that this approach was not very successful by itself in the treatment of asthma. This attempt at meta-analysis raised several methodological concerns,^[32] such as the effect of grouping attempts at house dust mite avoidance together as if they were one treatment. Almost all current asthma and rhinitis guidelines^[33] advocate allergen avoidance, including house mites as an integral part of a management strategy.

Injection Immunotherapy is Effective Treatment for Allergic Rhinitis

As allergen avoidance is desirable but not always practical, the next logical preventive strategy would be to use approaches that would mitigate the response of the target organs to the offending allergens. One such approach would be to use immunomodulation treatments such as immunotherapy as a means of circumventing the allergic response. Allergen-specific immunotherapy has been shown to improve the symptoms of allergic diseases and is the only treatment currently available that may alter the natural course of the disease.^[34,35**,36-38]

The traditional method of giving immunotherapy has been via graded subcutaneous injections over a planned period of time. In 43 placebo-controlled, double-blind studies, subcutaneous specific immunotherapy was compared with placebo treatment. Immunotherapy resulted in a mean reduction in symptoms of 45%, compared with placebo. This is equivalent to, or even better than, the efficacy obtained with most drugs.^[39] In addition to symptomatic improvement, immunotherapy leads to a downregulation of the allergic phenotype with the additional induction of a T-helper type 1 cytokine profile. This immunoregulation and the global downregulation of the allergic inflammation in mucous membranes may contribute towards long-term clinical efficacy, reducing the progression of rhinitis to asthma, and preventing the development of new sensitizations.^[40]

Non-traditional Immunotherapy Works for Allergic Rhinitis

Traditional immunotherapy, although successful in improving symptoms, is inconvenient and painful. For that reason, there has been a great deal of interest in delivering immunotherapy via the sublingual, oral, and nasal routes. There is increasing evidence that both traditional and non-traditional immunotherapy results in the immediate and long-term improvement of symptoms (i.e. after immunotherapy has been stopped).^[41*,42-47] An evidence-based review of 22 trials evaluating the efficacy of sublingual immunotherapy (SLIT), compared with placebo involving 979 patients, showed that SLIT is a safe treatment that significantly reduces symptoms and

medication requirements in allergic rhinitis.^[48] The review included six trials of SLIT for house dust mite allergy, five for grass pollen, five for *Parietaria*, two for olive tree and one each for ragweed, cat, tree and cupressus. Long-term clinical improvement on immunotherapy has been demonstrated by studies suggesting that 3-4 years of grass immunotherapy results in clinical benefit and a decrease in late skin response to allergen challenge for at least 3 years^[49] and 6 years^[46] after stopping injections. An indication of the preventive role of immunotherapy is the observation that 8 years after the commencement of SLIT, only 61% of the initially pollen-monosensitized children had developed new sensitization to perennial allergens compared with 100% in the control group.^[46]

Sublingual-swallow immunotherapy should not be confused with low-dose sublingual therapy that has been given based on provocation neutralization testing or Rinkel-type skin testing.^[35**] The efficacy of such low-dose immunotherapy remains unproved at this time.

Traditional Immunotherapy Works in Asthma

An evidence-based review^[50] suggested that immunotherapy improves BHR and reduces asthma symptoms and the use of asthma medications. In that review, 75 trials were included, with a total of 3506 subjects (3188 with asthma). Randomized controlled trials using various forms of allergen immunotherapy and reporting at least one clinical outcome were selected. There were 36 trials on house dust mite allergy; 20 on pollen allergy; 10 on animal dander; two on *Cladosporium* mold allergy, one on latex and six trials looking at multiple allergens. There was a significant improvement in asthma symptom scores, and it would have been necessary to treat four patients with immunotherapy to prevent one from having asthma symptoms. Overall, it would have been necessary to treat five patients with immunotherapy to avoid one requiring increased medication. Allergen immunotherapy significantly reduced allergen-specific BHR, also with some reduction in non-specific BHR. There was no consistent effect on lung function. One trial found that the size of the benefit was possibly comparable to that of inhaled steroids.

Non-traditional Immunotherapy Works for Asthma

There appears to be increasing evidence that non-injectable forms of immunotherapy benefit asthma, and that clinical efficacy is maintained for 4-5 years after discontinuation. The clinical efficacy (improvement of symptoms and reduction of drug intake) of SLIT for both asthma and rhinitis has been assessed in detail for the most common allergens: house dust mites, grass pollen, *Parietaria*, birch pollen and olive tree. The mechanisms by which sublingual therapy improves asthma include the dendritic cells of oral mucosa acting as efficient antigen-presenting cells and producing IL-12, which directs the immune response towards a T-helper type 1 profile away from the IgE-T-helper type 2 profile, and the induction of immunological tolerance rather than immunoreactivity. The safety profile of SLIT, derived from clinical trials and postmarketing surveillance studies, has proved to be satisfactory in adults and children.^[51] In a prospective parallel group controlled study^[52] of 60 children (mean age 8.5 years) suffering from asthma/rhinitis and allergic to dust mites undergoing SLIT, a significant difference versus baseline was found for the presence of asthma, the use of asthma medications, and mean peak expiratory flow in the active group. Interestingly, specific IgE showed a near-significant increase only in the control group, and no change was seen as far as new sensitizations were concerned.

Evidence that Immunotherapy May Prevent Allergies and Asthma

Allergen immunotherapy works in many ways to reduce the symptoms of allergic rhinitis and asthma, although the relative value of each marker is still unclear. It would seem logical that similar immunomodulatory effects would have a preventive effect if started well before the onset of the disease. Immunotherapy inhibits the early and late nasal, bronchial, and cutaneous responses to allergen challenge. There are increases in antiallergen IgG (two- to 10-fold) and IgG4 (10-100-fold), a gradual decline in antiallergen IgE antibodies, and reduced numbers of nasal or bronchial mast cells, eosinophils, IgE-mediated basophil histamine releasability,^[53] and CD4

T-helper type 2 lymphocytes. Cytokine changes include reductions in serum IL-4, in-vitro lymphocyte-derived IL-4, the induction of IL-10⁺CD4⁺CD25⁺ T cells^[54] and IL-12, and a lack of an increase in IFN- γ or IL-2. There is a profound IgG and IgA antibody response with a downregulation of T-helper type 2 and possibly an upregulation of T-helper type 1 responses.^[55*] The use of topical, such as intranasal, rather than systemic, immunotherapy may be linked to IL-10 production,^[56] and may be beneficial in inducing airway tolerance in particular.^[57]

Evidence that Immunotherapy Prevents the Development of New Allergies

Immunotherapy has been identified as the only currently available immunological treatment that can control and prevent allergic illness.^[58] Allergic sensitization usually begins early in life, and symptoms often start within the first decade. It is recommended that specific immunotherapy be started as soon as the allergy has been diagnosed,^[59] because inflammation and remodeling of the airways in asthma indicates a poor prognosis for effective treatment with specific immunotherapy,^[60] and it appears to be less effective in older patients than in children.^[60]

To determine whether specific immunotherapy with standardized allergen vaccines could prevent the development of new sensitizations over a 3-year follow-up survey, a prospective non-randomized study was carried out in a population of asthmatic children aged under 6 years, whose only allergic sensitivity was to house dust mites.^[61] In that study, 22 children who were monosensitized to house dust mites and who were receiving specific immunotherapy with standardized allergen vaccines were compared with 22 children of the same age who were monosensitized to house dust mites and who were taken as controls. Approximately 45% of the children receiving specific immunotherapy did not develop new sensitivities compared with none in the control group. This study suggested that specific immunotherapy in patients monosensitized to house dust mites alters the natural course of allergy in preventing the development of new sensitizations. It was therefore proposed that specific immunotherapy should be started early in the disease process in order to modify the spontaneous long-term progress of the inflammation and disease.^[8,62]

Clinical Evidence that Immunotherapy Prevents Asthma

There is increasing global interest in conducting clinical trials aimed at determining whether specific immunotherapy with allergens might prevent the onset of asthma in individuals with allergic rhinitis, and accelerate the remission of asthma in children with allergic disease.^[63] Recent research has indicated that when specific immunotherapy is introduced to patients with only allergic rhinoconjunctivitis, the development of asthma may be halted. A study with several different allergens^[64] showed that 28% of children receiving specific immunotherapy developed asthma compared with 78% of placebo-treated children. Another study has hinted that pre-seasonal grass pollen immunotherapy may have a permanent beneficial effect on asthma.^[46] Six years after the discontinuation of treatment there was significant improvement in chest symptoms along with the symptoms of allergic rhinitis. Only 23% of patients with previous pollen-asthma who had received SLIT experienced pollen-associated lower respiratory tract symptoms compared with 70% in the control group.

The Preventive Allergy Treatment study in children with seasonal allergic rhinoconjunctivitis^[65**] has been instrumental in providing convincing encouraging evidence to support the hope that specific allergen immunotherapy may stop the development of asthma. From six pediatric allergy centers in Austria, Denmark, Finland, Germany and Sweden, 205 children aged 6-14 years (mean age 10.7 years) with grass or birch pollen allergy but without any other clinically important allergy were randomly assigned either to receive specific immunotherapy for 3 years or to an open control group. All subjects had moderate to severe hay fever symptoms, but at inclusion none reported asthma with a need for daily treatment. Symptomatic treatment was limited to loratadine, levocabastine, sodium cromoglycate, and nasal budesonide. Asthma was evaluated clinically and by peak flow. Methacholine bronchial provocation tests were carried out during the season(s) and

during the winter. Before the start of immunotherapy, 20% of the children had mild asthma symptoms during the pollen season(s). Among those without asthma, the actively treated children had significantly fewer asthma symptoms after 3 years as evaluated by clinical diagnosis. Methacholine bronchial provocation test results improved significantly in the active group.

A retrospective, multicenter study studying the long-term and preventive effects of allergen-specific sublingual-swallow immunotherapy^[66] showed that 80.8% of patients maintained their clinical benefit. Only 1% of non-asthma patients reported an onset of respiratory symptoms, and only 9.6% of patients undergoing new skin tests showed new sensitizations. The study suggested that SLIT can obtain long-term and preventive effects so far attributed to traditional injection immunotherapy.

Other Promising Options on the Horizon

There is promise that the institution of allergen avoidance measures early in life may decrease the sensitization rate to allergens.^[67] With the development and refinement of genetic engineering resulting in 'new and improved allergens', the use of CpG motifs in allergen immunotherapy,^[68-70] immunomodulation using our knowledge of molecular biology and genetics,^[69,71-74] and an explosion in the understanding of the basic cellular mechanisms involved in the allergic reaction,^[74] it appears very likely that we will be able to offer safer and more effective forms of immunotherapy and immunomodulation in the near future.

Conclusion

Asthma is a significant global problem, with an increasing impact on health and economic resources. None of the current pharmacotherapeutic options has been proved to alter the course of the disease. Immunotherapy has convincingly been shown to show a long-term improvement of allergic dysfunction in the upper (rhinitis) and lower airways (asthma). Recent research appears to be validating the hope that preventive immunotherapy (before the clinical onset of asthma) may help mitigate and prevent the development of clinical asthma. With advances being made in the nature and immunizing potential of allergens, alternative routes of immunotherapy, and the use of adjunctive immunomodulators to improve the quality of immunotherapy, the prevention of asthma may be an achievable goal in the near future.

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Reprint Address

Correspondence to Chitra Dinakar, MD, Children's Mercy Hospital, 2401 Gillham Road, Kansas City, MO 64108, USA Tel: +1 816 234 3097; fax: +1 816 346 1301; e-mail: cdinakar@cmh.edu

Abbreviation Notes

BHR, bronchial hyperreactivity; SLIT, sublingual immunotherapy

Chitra Dinakar and **Jay M. Portnoy**, Section of Allergy, Asthma and Immunology, The Children's Mercy Hospital, Kansas City, Missouri, USA
