Immunotherapy - Vaccines for allergic diseases

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ABSTRACT Allergic diseases are some of the most commonly encountered problems in clinical practice. Drugs such as corticosteroids and antihistamines can provide effective symptomatic relief, but do not alter the course of the disease. Specific immunotherapy (SIT) was first used to treat pollen allergy in 1911, and has since evolved into an effective treatment for allergic rhinitis and asthma. SIT has been shown in clinical studies to reduce symptoms and medication use in patients with allergic rhinitis and asthma. Recent studies also showed that the therapeutic benefit is long-lasting after the completion of three to five years of treatment. SIT can also effectively reduce the risk of developing asthma and new allergic sensitizations in children with allergic rhinitis.

KEY WORDS Allergic rhinitis; asthma; allergen; hayfever; desensitization; prevention

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Introduction

Allergic diseases are some of the most common diseases seen in clinical practice. The most common of these include allergic rhinoconjunctivitis, atopic asthma, atopic dermatitis, food allergies, drug allergies and insect sting allergies.

Successful treatment of allergic diseases depends on the correct identification of clinically relevant allergens. This is often accomplished with a detailed clinical and environmental history, aided by laboratory or skin tests to confirm sensitization and environmental allergen analysis. The importance of allergen avoidance or elimination cannot be over-emphasized. While complete elimination of allergen exposure is sometimes possible with animal and occupational allergens, it can be difficult or even impossible with other allergens. For example, one has little or no control over exposure to pollens in the air or venom from an insect sting. Anti-inflammatory drugs such as corticosteroids and antihistamines can offer significant symptomatic relief, but their therapeutic benefits are short-lived as they do not alter the natural course of the disease. Moreover, many patients remain symptomatic on full therapeutic doses of anti-allergy drugs. Allergen immunotherapy offers an alternative that gives persistent therapeutic benefits. Recent evidence also suggests that this form of treatment can prevent the progression of allergic rhinitis to asthma and the development of new allergic sensitivities. In this article, we will review the evidence in support of the use of immunotherapy in respiratory allergies, and discuss some practical considerations related to this form of treatment.

Historical perspective

The use of allergen extracts for the treatment of allergic diseases was first published in the Lancet in 1911 (1). The English physician Noon injected an aqueous extract of timothy grass pollen in incremental doses into hayfever patients and found that the dose of extract needed to elicit a conjunctival reaction was increased by 100-fold after treatment. Others soon confirmed his observations.

Robert A Cooke, a physician scientist in New York, developed the basic methods of allergen standardization and allergen immunotherapy that are still in use today. In his landmark paper published in 1916, Cooke described the inheritance pattern of allergy and concluded that "an unusual capacity for developing bioplastic reactivities to any foreign protein" can be transmitted to offspring (2).

It was not until 1954 that the first randomized placebo-controlled study on immunotherapy was published (3). Since that time, significant advances in allergen preparation, standardization, immunotherapy techniques, and understanding of the mechanism of immunotherapy have occurred. There have also been many more studies confirming the efficacy of immunotherapy in the treatment of insect sting allergies, allergic rhinoconjunctivitis and asthma.

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Immunotherapy for allergic rhinitis

Allergic rhinitis is a common medical problem. A recent telephone survey of over 2,000 Hong Kong residents revealed that 40% of them thought they had rhinitis. A random sampling of these rhinitis sufferers revealed that about 50% of them were atopic as defined by having one or more skin test reactions to a panel of common aeroallergens (unpublished). Rhinitis can be a debilitating problem; studies have shown that allergic rhinitis can lower patients' quality of life and impair learning (4). More importantly, a significantly higher proportion of children with allergic rhinitis will go on to develop asthma. In 2001, the WHO published new guidelines defining allergic rhinitis as a risk factor for asthma. In the most recent update (5), based on current evidence, the guidelines recommend the use of subcutaneous immunotherapy for both adults and children with allergic rhinitis caused by pollens and house dust mites. It also recommends the use of sublingual immunotherapy for adults with allergic rhinitis caused by pollens and house dust mites, but only for children whose disease is caused by pollens.

Immunotherapy for allergic rhinitis in patients with allergies to pollens, dust mites, cats, dogs and moulds has been shown to be effective in numerous double-blind placebo-controlled studies. Walker *et al.*(6) treated 40 patients with summer hayfever with a grass pollen extract. There was significant reduction in seasonal allergic symptoms and medication use in the actively treated patients as compared to placebo patients during the first allergy season. After 1 year, the placebo patients were started on active treatment and then followed for a further 3 years. Efficacy was maintained throughout the 3 to 4 years of treatment in all patients, although the initial decrease in skin test response was not maintained. At the end of the 4 years, half of the patients were withdrawn from immunotherapy, and the other half continued with treatment (7). Another group of patients who had never been treated with immunotherapy was recruited as controls. For the subsequent 3 years, the efficacy of immunotherapy was maintained in the patients who discontinued as well as in those who continued immunotherapy. This shows that after 3 to 4 years of immunotherapy, the efficacy of treatment persists for at least 3 years after discontinuation.

In Varney's study, subjects with allergic rhinoconjunctivitis and asthma due to cat exposure were treated with a cat dander extract or placebo (8). There was marked improvement in symptom score and peak flow rate following cat room visits in actively treated but not placebo patients after just 3 months of treatment. Hedlin's study showed that the therapeutic effects of cat immunotherapy persists for 5 years after termination of treatment with regards to cat exposure and non-specific hyper-responsiveness (9).

Haugaard *et al.*performed a dose-response study of immunotherapy using a standardized mite extract (10). Seventy-three patients with asthma were treated with a maintenance dose of 0.7, 7 or 21 μg of the major mite allergen Der P1, or placebo for 2 years. Outcome was assessed by allergen bronchial challenge, histamine bronchial challenge, allergen conjunctival challenge, symptom diary and skin tests. There was a ten-fold reduction in bronchial sensitivity to allergen and histamine challenge in the two high dose treatment groups compared to placebo after 12 months of treatment. Sensitivity to conjunctival challenge also improved by ten-fold in all three treatment groups after 12 months. These improvements were undiminished when the patients were challenged 6 years after the end of their treatment. Response to skin prick tests decreased during treatment, but returned to the initial status 6 years after treatment ended. There was no significant difference in efficacy between the 21 μg and 7 μg groups, but there was a significant increase in adverse reactions in the highest dose group. The authors concluded that the optimum maintenance dose for Der P1 is 7 μg.

A recent study addressing the optimum duration for immunotherapy showed that patients who underwent 5 years of subcutaneous immunotherapy had additional symptom score reduction when compared with patients who underwent 3 years of treatment (69.1% *vs.* 48% symptom reduction) (11). However, there was no difference in asthma score reduction between the two groups (79.9% *vs.* 80.9%). Therefore, 3 years of maintenance treatment might be sufficient for most patients undergoing subcutaneous immunotherapy.

The prophylactic role of allergen immunotherapy was first observed by Johnstone in 1957 (12). He noted that in a group of patients treated for ragweed-induced asthma, significantly more actively-treated children had a complete resolution of their asthma as compared to placebo controls. For those children treated for ragweed-induced rhinitis, none in the actively-treated group developed asthma during the 3 years of treatment as compared to 42% of controls. These findings were subsequently confirmed by the PAT study (13). In this study, 205 children with allergic rhinitis were randomized to receive pollen immunotherapy or placebo. 80% of the children were not asthmatic before treatment. There was a significant reduction in conjunctival sensitivity and bronchial hyper-responsiveness (BHR) in the active treatment group but not the placebo group after 1, 2 and 3 years of treatment. There was also a significant reduction in symptom score during allergy seasons. After 3 years of treatment, 60 out of 75 patients receiving active treatment and 40 out of 72 patients receiving placebo remained asthma-free, with a statistically significant odds ratio of 2.52. At 10-year follow-up (7 years after cessation of treatment), the asthma-free odds ratio remained at 2.5, and the difference in rhinitis and conjunctivitis symptom score between the two groups remained significant in favour of immunotherapy (14).

Pajno *et al.* studied 134 asthmatic children under eight years

of age monosensitized to house dust mites only and receiving a standardized mite extract or medication only for three years and then followed up for another three years (15). At the end of the 3-year follow-up, 52 out of the 69 children who received immunotherapy did not develop any new sensitivities, whereas only 18 out of 54 controls did not developed new sensitivities.

Immunotherapy for asthma

In a large multi-centre study of house dust mite immunotherapy in Chinese asthmatics, 129 subjects underwent 52 weeks of treatment with dust mite extract or placebo (16). Immunotherapy resulted in significantly reduced symptom and medication scores, and significantly improved self-evaluation score.

Another double-blind placebo-controlled study looked at the steroid-sparing effect of immunotherapy (17). Fifty-four adult asthmatics allergic to house dust mites underwent three years of treatment with subcutaneous immunotherapy or placebo. In patients with moderate persistent asthma, the median dose reduction in inhaled corticosteroid was significantly greater in immunotherapy than placebo patients (90% *vs.* 42%).

A recent study of sixty-five asthmatic children showed that house dust mite immunotherapy significantly reduced the requirement for inhaled corticosteroid (18). After two years of treatment, actively treated subjects reduced the daily dose of inhaled fluticasone proprionate from 330.3 to 151.5 μg, whereas the dose in the control group decreased from 290.6 to 206.3 μg, the difference being statistically significant.

Abramson published his first meta-analysis of immunotherapy for asthma in 1995 (19). Twenty double-blind placebo-controlled studies published between 1966 and 1990 met his criteria and were included. The overall odds ratio of symptom improvement was 3.2 and for reduction in BHR was 6.8, both statistically significant. When mite immunotherapy was separately analysed, the odds for symptom improvement was 2.7, reduction in medication was 4.2, and reduction in BHR was 13.7. The overall effect size was 0.71, corresponding to a mean improvement of 7.1% in FEV_1. He concluded that it would take an additional 33 negative studies to reduce the effect size to non-significance.

In his latest analysis for the Cochrane Library in 2010, 88 randomized controlled studies published between 1954 and 2005 were included (20). Immunotherapy for mite and pollens resulted in statistically significant improvement in symptom score, whereas there was no difference after cat, dog or multiple allergen extracts. Overall, it would take four patients being treated with immunotherapy to prevent one symptom deterioration. There was also significant reduction in medication requirement and BHR after immunotherapy. It was concluded that "immunotherapy for asthma can significantly reduce asthma symptoms and medication requirement", and "… Patients randomized to immunotherapy were significantly less likely to develop increased non-specific BHR, and there were modest improvement indices of non-specific BHR … Allergen immunotherapy significantly reduced allergen-specific BHR." The current WHO guidelines suggest the use of subcutaneous and sublingual immunotherapy for the treatment of asthma.

Practical considerations

Immunotherapy is a prolonged and expensive treatment option, but it is also the only one that has potential to prevent or alter the course of allergic diseases. The physician must therefore carefully assess whether patients are likely to benefit from this form of treatment.

In general, patients whose disease is adequately controlled by allergen avoidance and drugs do not require immunotherapy, but a point can be made for its preventive role in young children with allergic rhinitis and/or asthma. Children and young adults, patients early in the course of their allergic diseases, and those with fewer allergic sensitivities will be more likely to benefit from immunotherapy.

Choosing the correct allergens for treatment is of vital importance. Most clinical studies with positive results employed single allergens, but in reality, many patients are sensitized to multiple allergens. The practice of mixing numerous allergens into one mixture is unwise. Many of the allergens have enzymatic activities, especially moulds and mites, and will break down other allergens in the mixture. Furthermore, severe reactions to one allergen in the mixture will prevent other allergens from reaching their therapeutic dose. In fact, it is seldom necessary to treat with more than 2 or 3 allergens, which can be administered sequentially. A patient's symptoms are usually attributable to a few important allergens, with other sensitivities being of minor relevance. It is the job of the treating physician to correlate clinical symptoms with skin test results. Moreover, there is extensive cross-reactivity between certain allergens, and treating with one will effectively desensitize the patient to all of these cross-reacting allergens. For example, Phl p I, the major allergen from timothy grass, cross-reacts with allergens from eight other grass species (21).

One concern with immunotherapy is its potential to cause severe or even fatal systemic reactions. This concern was so great that the practice of immunotherapy was virtually abandoned in the UK in the 1980s. A study was conducted by the Committee on Allergen Standardization of the American Academy of Allergy, Asthma and Immunology (22) in 1983, in which a questionnaire on fatalities from skin testing and immunotherapy was sent out to 3,400 members. Forty-six fatalities were reported from 1945 to 1984. Of the 30 cases with sufficient data for analysis, half involved pollen vaccines. Risk factors identified include previous

systemic reactions, a high degree of sensitivity, the use of newly prepared vaccines, administration error, administration during pollen season, symptomatic asthma at the time of injection, and the concomitant use of β-blockers. Only two reactions occurred later than 30 minutes after injection. A more recent survey in 2006 covering the period from 1990 to 2001 calculated the incidence of near fatal reactions to be 5.4 per million injections (23). High pollen count and dosing errors were the two most important contributing factors to severe systemic reactions.

Adhering to strict practice guidelines can minimize the risk of severe reactions. In general, standardized allergens are preferred since there is less batch-to-batch variability and the amount of each allergen in the extract is known. Alum-absorbed extracts are released more slowly and might be safer than aqueous extracts. Patients with asthma should be monitored closely and the injection should be withheld if there is any sign of unstable asthma. Lung function should be monitored before and after each injection. All patients must be made to wait 20 to 30 minutes after each injection and should be advised not to exercise immediately after injection. Immunotherapy should only be administered in a medical facility equipped to treat anaphylaxis. Highly sensitive patients and patients with unstable asthma should perhaps be issued with self-injectible epinephrine. Premedication with antihistamines might reduce the risk of systemic reactions (24). The combined use of an anti-IgE antibody with specific immunotherapy (25) is an interesting concept and may reduce the risk of systemic reactions while improving efficacy at the same time. Large local reactions sometimes occur after injections; they usually respond to cold compresses and analgesics if symptomatic. If such reactions are larger than 4 cm in diameter or last longer than 24 hours, the dose of the next injection should be adjusted. Alum-absorbed extracts can also cause subcutaneous nodules, which usually disappear with time. Patients with atopic dermatitis may suffer a flare of their disease during immunotherapy. At this time, there is no evidence to support the use of immunotherapy for the treatment of atopic dermatitis.

The duration of treatment is a subject of debate. The advice given is generally 3 to 5 years. Several studies have shown long-term clinical benefit after 2 to 4 years of treatment. However, Naclerio's study (26) showed partial recrudescence of mediator response 1 year after the termination of a 3-year course of ragweed immunotherapy. The duration of treatment should therefore be tailored to each patient's needs and willingness to continue with treatment indefinitely. The allergen immunotherapy practice parameter published by the Joint Task Force on Practice Parameters is a good source of information on the practical aspects of immunotherapy (27). The American Academy of Allergy, Asthma and Immunology has up-to-date practice guidelines and templates for immunotherapy forms for the practicing allergist (www.aaaai.org).

Conclusions

Allergy is a global epidemic with rapidly increasing incidence in the developed world. Optimal management of allergic conditions requires proper diagnosis and treatment. Allergen avoidance and pharmacotherapy remain the mainstay of allergy treatment, but one should consider allergen immunotherapy if these modalities fail to achieve satisfactory disease control.

Immunotherapy is effective in controlling symptoms and reducing the requirement for medications. In addition, its therapeutic benefits persist long after the discontinuation of treatment and it can also prevent the development of new sensitivities and asthma. Successful immunotherapy depends on a good knowledge of local allergens and their cross-reactivities, as well as experience in managing risk. Newer forms of immunotherapy, including local immunotherapy, sublingual immunotherapy, peptide immunotherapy and DNA vaccination, have the potential of making immunotherapy safer and more effective.

References

1. Noon L. Prophylactic inoculation against hay fever. Lancet 1911;1:1572-4.
2. Cooke RA, Vander Veer A. Human sensitization. J Immunol 1916;1:201-305.
3. Frankland AW, Augustin R. Prophylaxis of summer hayfever and asthma: controlled trial comparing crude grass pollen extracts with isolated main protein component. Lancet 1954;1:1055.
4. Kremer B, den Hartog HM, Jolles J. Relationship between allergic rhinitis, disturbed cognitive functions and psychological well-being. Clin Exp Allergy 2002;32:1310-5.
5. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 2010;126:466-76.
6. Walker SM, Varney VA, Gaga M, Jacobson MR, Durham SR. Grass pollen immunotherapy: efficacy and safety during a 4-year follow-up study. Allergy 1995;50:405-13.
7. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341:468-75.
8. Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. Clin Exp Allergy 1997;27:860-7.
9. Hedlin G, Heilborn H, Lilja G, Norrlind K, Pegelow KO, Schou C, et al. Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. J Allergy Clin Immunol 1995;96:879-85.
10. Haugaard L, Dahl R, Jacobsen L. A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: clinical efficacy and side effects. J Allergy Clin Immunol 1993;91:709-22.
11. Tabar AI, Arroabarren E, Echechipía S, García BE, Martin S, Alvarez-Puebla

MJ. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. J Allergy Clin Immunol 2011;127:63-7.
12. Johnstone DE. Study of the role of antigen dosage in the treatment of pollinosis and pollen asthma. Am J Dis Child 1957;94:1-5.
13. Möller C, Dreborg S, Ferdousi HA, Halken S, Høst A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6.
14. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007:62:943-8.
15. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A 6-year follow-up study. Clin Exp Allergy 2001;31:1392-7.
16. Wang H, Lin X, Hao C, Zhang C, Sun B, Zheng J, et al. A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. Allergy 2006;61:191-7.
17. Blumberga G, Groes L, Haugaard L, Dahl R. Steroid-sparing effect of SC SQ-standardised specific immunotherapy in moderate and severe house dust mite allergic asthmatics. Allergy 2006;61:843-8.
18. Zielen S, Kardos P, Madonini E. Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: A randomized controlled trial. J Allergy Clin Immunol 2010;126:942-9.
19. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. Am J Respir Crit Care Med 1995;151:969-74.
20. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database Syst Rev 2010;(8):CD001186.
21. Laffer S, Valenta R, Vrtala S, Susani M, van Ree R, Kraft D, et al. Complementary DNA cloning of the major allergen Phl p I from timothy grass (Phleum pratense); recombinant Phl p I inhibits IgE binding to group I allergens from eight different grass species. J Allergy Clin Immunol 1994;94:689-98.
22. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol 1987;79:660-77.
23. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol 2006;117:169-75.
24. Nielsen L, Johnsen CR, Mosbech H, Poulsen LK, Malling HJ. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. J Allergy Clin Immunol 1996;97:1207-13.
25. Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von Berg A, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. J Allergy Clin Immunol 2002;109:274-80.
26. Naclerio RM, Proud D, Moylan B, Balcer S, Freidhoff L, Kagey-Sobotka A, et al. A double-blind study of the discontinuation of ragweed immunotherapy. J Allergy Clin Immunol 1997;100:293-300.
27. Cox LS, Nelson H, Lockey R, Calabria C, Chacko T, Fingegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127:S1-55.

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