Immunotherapy – Vaccines For Allergic Diseases Adrian Young-Yuen Wu, BSc, MBChB, MRCP(UK), FHKCP, FHKAM(Med), DABIM, DABA&I

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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 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 these drugs do have side effects and their therapeutic benefits are short-lived. Moreover, many patients remain symptomatic on full therapeutic doses of anti-allergy drugs. Immunotherapy offers an alternative that gives persistent therapeutic benefits. Recent evidence also suggests that this form of treatment can prevent the progression of allergic diseases. In this article, we will review the evidence in support of the use of immunotherapy, 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 the 1950s that the first randomized placebo-controlled studies on immunotherapy were published. 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.

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.³ 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.

The most common causes of allergic rhinitis include seasonal allergens such as pollens from trees, grasses and weeds, and indoor allergens such as house dust mite, cockroaches, animal dander and moulds. A significant proportion of allergic rhinitis sufferers also develop ocular symptoms when exposed to allergens. The most effective drugs for treating allergic rhinitis are topical steroid sprays. The newest preparations have very low bioavailability and are therefore safe for long-term use. Antihistamines are also quite useful,

especially in controlling itch and sneezing, and are often used as rescue medications. However, allergic rhinitis is a chronic problem, and when these drugs are discontinued, symptoms usually return unless the source of allergen has been eliminated.

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 al⁴ 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.⁵ Another group of patients who had never been treated with immunotherapy was recruited as controls. For the subsequent 3 years, the efficacy of 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,⁶ subjects with allergic rhinoconjunctivitis and asthma due to cat exposure were treated with a cat dander extract or placebo. 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 study⁷ 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.

Haugaard et al⁸ performed a dose-response study of immunotherapy using a standardized mite extract. Seventy-three patients with asthma were treated with a maintenance dose of 0.7 μ g, 7 μ g or 21 μ g 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 μ g and 7 μ g 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 μ g.

The prophylactic role of allergen immunotherapy was first observed by Johnstone in 1957.⁹ 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 recently confirmed by the PAT study.¹⁰ In this study, 205 children were randomized to receive pollen immunotherapy or placebo. Eighty per cent 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.

Des-Roches et al¹¹ studied 22 children under 6 years of age monosensitized to house dust mites only and receiving a standardized mite extract. At the end of the 3-year treatment, 10 out of the 22 children did not develop any new sensitivities, whereas all 22 age-matched controls developed new sensitivities.

Immunotherapy for Asthma

Asthma is an inflammatory disease of the lower airways. While asthma is a heterogeneous disorder, allergic sensitization plays an important role, especially in early onset asthma. There has been a rapid increase in the incidence of asthma in developed nations over the past 20 years. The number of asthma cases in the US more than doubled between 1980 and 1998. Genetic factors and early life experiences greatly influence the risk of asthma; a child whose parents are asthmatic has a greater than 70% chance of developing asthma, and

more than 80% of childhood asthma is diagnosed before the age of 6. The incidence of asthma before puberty is greater in boys than in girls, whereas the reverse is true after puberty. A recent study¹² suggests that the rate of spontaneous remission is inversely correlated to the age of onset, from a rate of 60% in patients diagnosed before the age of 6 to less than 15% in patients diagnosed after age 20. Although asthma symptoms do remit in some patients, probably as a result of increase in lung function as children grow, BHR and allergic sensitization are often retained and asthma recurs in a proportion of these patients during adulthood. The likelihood of remission and recrudescence is linked to a complex interaction between genetic factors and environmental exposure such as allergens, cigarette smoke and infections. Asthmatic individuals experience twice the rate of decline in FEV₁ compared with non-asthmatic individuals, and smoking has an additive effect on this decline.

There has been a move in recent years to start anti-inflammatory treatment early in the course of asthma. Evidence suggests that early use of inhaled corticosteroids (ICS) can result in better lung function improvement and slowing of lung function decline.¹³ ICS are also very effective in symptom control, especially when an inhaled long acting β_2 -agonist is added. However, numerous studies have shown that asthma symptoms almost invariably recur after the withdrawal of ICS.¹⁴

There are many double-blind placebo-controlled trials on immunotherapy for asthma. While many of these have positive outcomes, some were negative studies. There may be many reasons why some studies failed to demonstrate efficacy. If the subjects are already on optimum drug treatment for asthma, the additional benefit seen with immunotherapy will be small and a large number of subjects will be needed to have sufficient statistical power to demonstrate a difference. Identifying subjects who will most likely benefit from immunotherapy is also important. Abramson¹⁵ published his first meta-analysis of immunotherapy for asthma in 1995. 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 FEV₁. He concluded that it would take an additional 33 negative studies to reduce the effect size to non-significance. He updated his analysis for the Cochrane Library¹⁶ in 1998 and the number of included studies was increased to 54. His conclusions were essentially the same.

In another update¹⁷ published in 1999, 62 studies published between 1954 and 1998 were included. 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. There was also significant reduction in medication requirement and BHR after immunotherapy. There was, however, no consistent improvement in peak flow rates. 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."

Immunotherapy for Insect Sting Allergy

Stings from insects of the order Hymenoptera, which include the honeybee (Apis), yellow-jacket, whitefaced hornet, yellow hornet (Vespula) and paper wasp (Polistes), are well known to produce severe lifethreatening anaphylaxis. In addition, patients can develop severe allergic reactions to the stings of the fire ant (Solenopsis) and the bites of the kissing bug (Triatoma).

In a prospective study of 320 randomly chosen adults,¹⁸ 3.3% had a history of systemic reaction to a hymenoptera sting, 17% had positive venom skin tests and 26% had serum IgE to venom. In another prospective study,¹⁹ out of 65 subjects with positive venom skin tests who were subsequently stung, 11 (17%) reported a systemic reaction. From the group of subjects with negative venom skin tests, 120 stings were reported and none resulted in systemic reactions. Therefore, subjects with negative venom skin tests have no risk of anaphylaxis from stings, and only a small proportion of subjects with positive skin tests are at risk of anaphylaxis from stings. However, patients with a history of anaphylaxis to insect venom have a high risk (74% in adults, 40% in children) of anaphylaxis with future stings.²⁰ Such patients should therefore take precautions to avoid being exposed to insect stings again and carry epinephrine that can be self-administered.

Stings are sometimes unavoidable, especially for people with outdoor occupations. Fortunately, venom immunotherapy is a very effective way of preventing insect sting anaphylaxis. In a prospective study,¹⁸ 74 patients with a history of severe systemic reactions after insect stings were treated for 5 years with venom immunotherapy. At the end of treatment, 28% of patients reverted to skin test negative status. Two to 4 years after immunotherapy ended, 56 to 67% of subjects became skin test negative. All patients underwent live sting challenges yearly for 3 years, and 8 out of 270 stings (3%) in 7 out of 74 patients (10%) had systemic symptoms, with only two reactions being clinically significant. Extended observations of the same group of patients²¹ for an additional 3 to 7 years revealed that the residual risk of systemic reactions after 5 to 6 years of immunotherapy is 5 to 10%. Most of these reactions are mild to moderate. Risk predictors for severe reactions include systemic reactions during immunotherapy, persistent strongly positive skin test reactions and severity of the pre-treatment reaction. For patients with these predictors, life-long treatment should be considered.

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 sensitivities will be more likely to benefit from immunotherapy. Immunotherapy for food allergies is hazardous and is not recommended. For insect sting allergies, immunotherapy is only indicated if patients manifest systemic reactions. Generalized cutaneous reactions in adults should also be treated. Patients who only develop large local reactions do not require treatment.

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. The majority of symptoms in a patient are usually attributable to a few 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.²²

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 Immunology²³ 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.

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 recent report of the combined use of an anti-IgE antibody with specific immunotherapy²⁵ 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 study²⁶ 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 WHO position paper²⁷ published in 1998 is a good source of information on the practical aspects of immunotherapy. The American Academy of Allergy, Asthma and Immunology also has up-to-date practice guidelines and templates for immunotherapy forms for the practicing allergist (www.aaaai.org).

Conclusion

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;1:1572-1574.
- 2. Cooke RA, Vander Veer A. Human sensitization. J Immunol 1916;1:201-305.
- 3. Kremer B, den Hartog HM, Jolles J. Relationship between allergic rhinitis, disturbed cognitive functions and psychological well-being. Clin Exp Allergy 2002;32:1310-1315.
- 4. 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;50:405-413.
- 5. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341:468-475.
- 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;27:860-867.
- 7. Hedlin G, Heilborn H, Lilja G, et al. Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. J Allergy Clin Immunol 1995;96:879-885.
- 8. 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;91:709-722.
- 9. Johnstone DE. Study of the role of antigen dosage in the treatment of pollinosis and pollen asthma. Am J Dis Child 1957;94:1.
- 10. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-256.

- 11. Des-Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997;99:450-453.
- 12. De Marco R, Locatelli F, Cerveri I, Bugiani M, Marinoni A, Giammanco G. Incidence and remission of asthma: a retrospective study on the natural history of asthma in Italy. J Allergy Clin Immunol 2002;110:228-235.
- 13. Selroos O, Pietinalho A, Lofroos AB, Riska H. Effect of early vs late intervention with inhaled corticosteroids in asthma. Chest 1995;108:1228-1234.
- 14. Haahtela T, Jarvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. N Engl J Med 1994;331:700-705.
- 15. 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;151:969-974.
- 16. Abramson MJ, Puy RM, Weiner JM. Allergen specific immunotherapy for asthma. (Cochrane Review) Cochrane Library, Issue 3, 1998. Oxford: Update software.
- 17. Abramson M, Puy R, Weiner J. Immunotherapy in asthma: an updated systematic review. Allergy 1999;54:1022-1041.
- Golden DBK, Addison BI, Gadde J, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Prospective observations on patients who discontinue venom immunotherapy. J Allergy Clin Immunol 1989;84:162-167.
- 19. Golden DB, Marsh DG, Freidhoff LR, et al. Natural history of Hymenoptera venom sensitivity in adults. J Allergy Clin Immunol 1997;100:760-766.
- 20. Reisman RE. Natural history of insect sting allergy: relationship of severity of symptoms of initial sting anaphylaxis to re-sting reactions. J Allergy Clin Immunol 1992;90:335-339.
- 21. Golden DBK, Kwiterovich KA, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Discontinuing venom immunotherapy: outcome after five years. J Allergy Clin Immunol 1996;97:579-587.
- 22. Laffer S, Valenta R, Vrtala S, 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;94:689-698.
- 23. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol 1987;79:660-677.
- 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;97:1207-1213.
- 25. Kuehr J, Brauburger J, Zielen S, 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;109:274-280.
- 26. Naclerio RM, Proud D, Moylan B, et al. A double-blind study of the discontinuation of ragweed immunotherapy. J Allergy Clin Immunol 1997;100:293-300.
- 27. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol 1998;102(4 Pt 1):558-562.

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