

Immunotherapy for allergic disorders

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SYNOPSIS

Immunotherapy can be an effective and safe treatment for reducing allergic reactivity to a number of inhaled and injected allergens. It can be used for the treatment of problematic respiratory allergic disorders that are not responding well to environmental measures and drug treatment. Immunotherapy for hay fever or asthma is generally given by subcutaneous injection of increasing doses of an extract of the allergen to which the patient is sensitive. Injections should be given by experienced medical practitioners and resuscitation equipment must be readily available. The patient should be under observation for 30 to 45 minutes following each injection.

Index words: desensitisation, injections, rhinitis.

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Introduction

Immunotherapy for allergic disease is the administration of increasing amounts of the specific allergen to which the patient is known to be allergic. It has been used for the treatment of hay fever since 1911. The common allergic disorders treated with immunotherapy are hay fever and asthma. Numerous trials have shown immunotherapy to be effective, although some clinicians have emphasised its potential dangers. Allergen-specific immunotherapy is also used for treatment of bee-venom and wasp hypersensitivity to prevent anaphylactic reactions following stings.

The mechanism of action of immunotherapy has been debated for as long as it has been in use. Early researchers felt that it acted by either reduction in allergen-specific IgE or by induction of 'blocking' IgG antibodies. Whilst both of these serologic changes occur with immunotherapy, they generally do not occur for months or years, well after the beneficial effect of immunotherapy is evident. Furthermore, neither of these alterations in antibody concentrations correlates with the clinical efficacy of the immunotherapy. More recent research indicates that immunotherapy is likely to act by altering T cell reactivity to the specific allergen. This could be considered a form of high-dose tolerance, resulting in a reduction in the release of pro- (allergic) inflammatory cytokines. A reduction in cytokine release would also lead to a decrease in specific IgE, as antibody production is strictly T-cell dependent.

Common allergens

The major perennial allergens include the house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides*

farinae are the major species), pet hair and danders (particularly cat) and mould spore (particularly *alternaria* and *cladosporium*). Spore levels do show some seasonal variation in atmospheric concentration, being highest in the summer and autumn but, unlike pollens, significant levels are present throughout the year.

In Australia, and particularly in the southern states, seasonal hay fever and asthma are very common and generally due to grass pollen sensitivity. Clinical allergic disease due to tree and weed pollen sensitivity is certainly important in many areas of Europe (commonly birch and olive) and North America (commonly ragweed) but is less of a problem in Australia.

Indications for allergen-specific immunotherapy

In Australia the major use for allergen-specific immunotherapy is for the treatment of allergic respiratory diseases including hay fever and asthma. It is only one of a range of therapies for these conditions and should not be considered unless allergen avoidance strategies and drug treatments have been implemented and found to be inadequate. These approaches should always be continued even if immunotherapy is commenced.

It is critical to ensure that the allergen for which immunotherapy is being undertaken is relevant to the patient's clinical illness. This is frequently apparent from the correlation of allergen exposure and symptom development but, on occasions, allergen provocation tests may be necessary. Before treatment, the allergen, defined by the presence of specific IgE, must also be confirmed by either skin prick test and/or radioallergosorbent test (RAST).¹

The use of immunotherapy in the treatment of atopic dermatitis or eczema is controversial. Although it may be beneficial in occasional patients, there is also a risk of significantly aggravating the disease. Eczema frequently coexists in patients with respiratory allergic diseases and, if desensitisation is considered for the respiratory component, the state of their skin disease must be taken into consideration. It is certainly preferable not to commence immunotherapy unless the eczema is well controlled and the skin condition must be closely monitored during treatment.

Immunotherapy is not indicated for the treatment of food allergies and, in fact, a number of trials conducted overseas have been abandoned because of serious anaphylactic events. In general drug allergies are not treated by desensitisation although there are a few situations where this can be beneficial.

In patients who need to continue a medication for which no suitable alternative exists, a form of tolerance can be induced by giving increasing doses of the medication over a relatively short period of time. This form of therapy has been used most successfully for penicillins, but has also been used for a number of other medications including aspirin and allopurinol. The mechanism for the tolerance has not been clearly delineated and is likely to be different for different drugs. Moreover, it is almost certainly not the same as for the more traditional allergen-specific immunotherapy. Furthermore the state of non-responsiveness only lasts as long as the medication is continued.

Efficacy

For seasonal hay fever, immunotherapy is widely considered to be very effective with at least 80% of patients having a significant and prolonged response.^{2,3} Perennial hay fever is commonly due to house dust mite sensitivity and properly controlled studies have also shown that immunotherapy is beneficial, although not as much as it is for pollen desensitisation.

Immunotherapy for asthma is somewhat controversial and is certainly not regarded as conventional therapy by all physicians involved in the treatment of patients with asthma. Nevertheless there are a large number of well-powered, randomised, placebo-controlled trials showing beneficial effects. These include statistically significant reductions in symptoms and medication use with improvements in lung function and indices of bronchial hyperreactivity. The Cochrane Database contains a systematic review of immunotherapy for asthma. It includes 54 trials, using a number of different allergens, and shows that the effects were generally beneficial with a highly significant reduction in asthma symptoms and medication use. Immunotherapy also resulted in a significant reduction in allergen-specific bronchial hyperreactivity, with some reduction in non-specific bronchial hyperreactivity as well.⁴

Administration

It is preferable to undertake immunotherapy for only one or a limited number of allergens at a time. In Australia immunotherapy is usually given by subcutaneous injection in the outer upper arm with an increasing dose of the specific allergen to which the patient is sensitive. During the escalation phase of the course the injections are usually given at fortnightly intervals, but anywhere between weekly and every three weeks is as effective. After completion of the course, patients with perennial allergic sensitivity should go on to receive monthly maintenance therapy, again by subcutaneous injections. The optimal duration of the maintenance therapy is uncertain, but a World Health Organization position paper from June 1998 recommended between three and five years.

Opinions vary concerning immunotherapy for grass pollen sensitivity. Allergists practising in southern states of Australia generally advise that patients should receive pre-seasonal courses of immunotherapy during the autumn and winter for

three consecutive seasons, without maintenance injections. In more northern states the immunotherapy regimen is usually similar to that for perennial allergens, with a course at any time of the year followed by maintenance injections.

Immunotherapy can also be given by non-parenteral routes, including intranasal, sublingual or oral. The effectiveness of these routes has not been well established and they are not recommended.

Safety

As with all forms of treatment, it is essential that the administration of immunotherapy be as safe as possible. As the patients have high titres of specific IgE and are being given parenteral doses of allergens to which they are sensitive, the risk of a severe systemic reaction always needs to be kept in mind.

In 1986 a report was prepared by the UK Committee on Safety of Medicines because of concern over an increasing frequency of severe reactions including deaths.⁵ The report found that serious reactions to immunotherapy occurred at a rate of approximately 1 in 500. A number of problems were identified including poor selection of patients, inadequately trained operators, poorly standardised allergen extracts and lack of readily available resuscitation equipment. The report stipulated that immunotherapy should only be given where full resuscitation equipment was available and that patients should be observed for at least two hours after the injection. Although the waiting time was subsequently reduced to one hour in 1994, the effect of these restrictions was to markedly limit the use of immunotherapy in general practice in the UK.

The peak US body, the American Academy of Allergy, Asthma and Immunology (AAAAI), has reviewed the adverse events following immunotherapy on a number of occasions. One key study reported 24 fatalities associated with immunotherapy over a 25-year period.⁶ With rare exceptions, ultimately fatal reactions commenced within 25 minutes of administration of immunotherapy and usually much sooner. The current AAAAI Position Statement recommends a 20-minute waiting period for most patients, extending to 30 minutes for patients at potentially high risk, for example those with asthma or previous systemic reactions. In Australia five deaths were reported to the Adverse Drug Reactions Advisory Committee in a 21-year period. Four of these were in patients with asthma and in each of these a divergence from the recommended protocol had taken place.

The current recommendation from the Australasian Society of Clinical Immunology and Allergy is that the patient should be observed for at least 30 minutes following an immunotherapy injection, increasing to 45 minutes in higher risk patients. Resuscitation equipment must be immediately available and should include an intravenous giving set and fluids, parenteral adrenaline, corticosteroids and antihistamines, an oral airway and equipment for the administration of oxygen. A doctor with experience in administration of immunotherapy and resuscitation should be present at all times. Specialists should

check that these requirements are met before delegating the injections to general practitioners.

Conclusion

Allergen-specific immunotherapy can be a highly effective treatment for allergic respiratory diseases that are responding inadequately to more conventional therapies. Immunotherapy is most effective when given by the subcutaneous route with an increasing dose of the relevant allergen. The administering doctor should have experience in immunotherapy and resuscitation equipment must be readily available. The patient should be under observation for at least 30 minutes following each injection.

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REFERENCES

- O'Brien RM. Skin prick testing and *in vitro* assays for allergic sensitivity. *Aust Prescr* 2002;25:91-3.
- Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *Br Med J* 1991;302:265-9.
- 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.
- Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma (Cochrane Review). In: *The Cochrane Library*, Issue 2 2003. Oxford: Update Software.
- Committee on Safety of Medicines. CSM update: Desensitising vaccines. *Br Med J* 1986;293:948.
- Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 1987;79:660-77.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 95)

- Allergen-specific immunotherapy is an effective treatment for patients with food allergy.
- Allergen-specific immunotherapy can exacerbate eczema.

Book review

Hospital in the home

Michael Montalto. Melbourne: ArtWords Pty Ltd; 2002. 172 pages.

Price \$66 (including GST)

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Michael Montalto is the director of the Hospital in the Home at Edgeworth Hospital in Melbourne. It must be recognised that he is an advocate of a certain model of hospital in the home. For reasons that he briefly alludes to in this book, substitution of domestic for hospital care for patients who would otherwise 'require inpatient care by the nature of their medical or social condition', is far more advanced in Victoria than in other parts of Australia. For clinicians from these other areas, his book provides a short introduction to the topic, and a source of references for further reading. As I practise outside Victoria, I found the first two chapters the most interesting. These discuss factors supporting the emergence of alternatives to hospitalisation, the difficulties of organising randomised controlled clinical trials in this area, and organisational models of hospital in the home.

Chapters 3, 4 and 6 outline the frequently asked questions about hospital in the home – general clinical principles, patient selection and management, and the drugs and devices used. I may have missed something, but as a clinician in New South Wales the description of conditions that could be managed at home merely confirmed my suspicion that many of these programs deal with patients who would not be admitted to

hospital in other areas. Many general practitioners will manage uncomplicated deep venous thrombosis, pyelonephritis or pneumonia in the community. The Diabetes Education Centre in Newcastle, New South Wales, demonstrated more than 25 years ago that it is not necessary to admit people to hospital to start treatment with insulin, and in Leicester in the UK, even young children have been started on insulin as outpatients, for over forty years. The true advances have been the technological ones that allow long-term intravenous antibiotic therapy of conditions such as septic arthritis and bacterial endocarditis to take place outside the conventional hospital setting.

Chapters 5, 7 and 8 deal with cost, quality and ethical issues. It is always easy to criticise a non-expert writing in these areas, but I thought the chapter on ethics was lightweight and superficial. The final section in this chapter on identifying poor hospital in the home care was interesting, but for those who skim books it would have been better placed in the chapter on quality. I was also surprised that there was no recognition of the major criticism of cost analyses of hospital in the home, namely that while there may be some savings, these are only achieved if hospital in the home is substituted for hospital beds that are then closed. Publicity associated with the publication of the book suggested that hospital in the home was an alternative (less costly) way of meeting the need for increased hospital beds without building more hospitals. I could only find one sentence alluding to this, and those who like me were looking for some discussion of this idea will be disappointed.

These criticisms aside, this is a slim, readable introduction to an important development in health care.