Position Statement

Specific allergen immunotherapy for asthma

A Position Paper of the Thoracic Society of Australia and New Zealand and the Australasian Society of Clinical Immunology and Allergy

Specific allergen immunotherapy (desensitisation, hyposensitisation) is the technique of treating IgE-mediated disease with increasing doses of an allergen in order to decrease sensitivity to that allergen. First used early this century, 60 million patients annually are now treated with immunotherapy throughout the world.

The only absolute indication for immunotherapy is a life-threatening reaction after a Hymenoptera (bee or wasp) sting; all other indications are relative. Many randomised controlled trials have shown that hayfever caused by airborne pollens and house dust mite responds to this therapy.[1]

The use of specific allergen immunotherapy in asthma remains controversial. Despite this, the Thoracic Society of Australia and New Zealand and the Australasian Society of Clinical Immunology and Allergy believe that all strategies which may impact on the morbidity and mortality of asthma should be assessed. The cost-effectiveness of this therapy also needs to be addressed in the context of the total cost of asthma in Australia, the mid-estimate of which in 1991 was $652 million (National Asthma Campaign, 1992). We present an overview and do not cover all aspects of this subject. Interested readers are referred to recent reviews.[1-9]

Atopy, allergens and asthma

Allergy is best defined as an exaggerated response on exposure to an allergen following prior exposure, and mediated by an immune reaction involving IgE. The same clinical picture may result from non-immune mechanisms.

Atopy is an increased tendency to IgE-based sensitivity resulting in production of specific IgE antibody to common environmental allergens, such as house dust mite, pollens, moulds or animal danders. This sensitisation occurs in genetically predisposed people after exposure to low concentrations of allergen; cigarette smoke and viral infections may assist in the sensitisation process.

About 40% of the population is atopic, and about half of this group develop clinical disease ranging from trivial rhinitis to life-threatening asthma. After sensitisation, continuing exposure to allergens leads to a significant increase in the prevalence of asthma.[10] Ninety per cent of children and 80% of adults with asthma are atopic.[10] Once sensitisation has occurred, re-exposure to allergen is a risk factor for exacerbations of asthma.[11] Effective management of allergic asthma includes pharmacological therapy and allergen avoidance. For example, avoiding dust mite allergen can reduce symptoms and the need for medication.

Rationale for using immunotherapy for asthma

Asthma is an inflammatory disease characterised by the presence of cells such as eosinophils, mast cells, basophils, and CD25+ T lymphocytes in the airway walls. There is close interaction between these cells, because of the activity of cytokines which have a variety of communication and biological effector properties. Chemokines attract cells to the site of inflammation and cytokines activate them, resulting in inflammation and damage to the mucosa.[12] With chronicity of the process, secondary changes occur, such as thickening of basement membrane and fibrosis.[13]

An immunological reaction to allergen is the initiating event of airway inflammation in many cases of asthma.[14] Continued exposure to allergen results in chronic inflammation. Current therapy aims to suppress this inflammation with inhaled corticosteroids, sodium cromoglycate, or nedocromil sodium, all of which interfere with the cellular and cytokine interactions by diverse mechanisms, but do not address the initiating event in allergic asthma. By withdrawing the allergen or altering the immune response to allergen, it is theoretically possible to control the allergic trigger of asthma.

Immunological changes have been described after immunotherapy. These include an initial rise in specific serum IgE, followed by a fall, and a rise in specific IgG ("blocking antibody"). Specific IgG titres correlate poorly with the degree of protection. Immunotherapy leads to a reduction in mediator release from mast cells *in vitro*, alterations in lymphocyte subsets, and a downregulation of IL-4 production from T cells.[15] Several studies have shown a reduction in inflammation and a decrease in bronchial hyperresponsiveness after immunotherapy.[1,16,17]

There are strong theoretical arguments why immunotherapy should be used early in the course of the disease, before irreversible secondary changes such as fibrosis have occurred. Further, data are emerging to suggest that immunotherapy may also influence the progression of clinical disease.[3,7] Immunotherapy should not be regarded as an alternative to established forms of preventive therapy, as recommended by the National Asthma Campaign.[18] A systematic cost–benefit analysis of immunotherapy has not yet been undertaken.

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Clinical trials

There have been numerous randomised placebo-controlled double-blind trials of immunotherapy for asthma. Comparison of these trials is difficult, not only because of the inherent problems of trials involving asthma (such as standardisation of inclusion and outcome criteria), but also because of differences in allergen extracts and dosage regimens. A meta-analysis can address some of these difficulties, and has recently been applied to 20 randomised controlled trials of immunotherapy for asthma in both adults and children.[19] This meta-analysis found a clinically useful improvement from immunotherapy with house dust mite and with other allergens (see Box). It concluded that immunotherapy is a treatment option in highly selected patients (discussed more fully below) with allergic asthma.

The reviews cited in this position paper,[1-9] the meta-analysis[19] and further controlled studies published in the last five years[20-24] provide references to the most important trials of immunotherapy.

Odds ratios (95% confidence intervals) for improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy (from a meta-analysis by Abramson et al.)[19]

	House dust mite	Other allergens (pollens, moulds or animal dander)
Symptomatic improvement	2.7 (1.7–4.4)	4.8 (2.3–10.1)
Reduction in medication	4.2 (2.2–7.9)	—
Reduction in bronchial hyperresponsiveness	13.7 (3.8–50)	5.5 (2.8–10.7)

Allergen extracts and route of administration

Although several routes of allergen delivery have been used in immunotherapy, only subcutaneous injection has been studied in detail and shown to be effective. Giving allergen extract sublingually is not recommended as studies have failed to show long-term efficacy.[25] Trials with giving birch pollen orally appeared promising, but large doses were required and there was a high incidence of side effects. Further studies of oral immunotherapy using modified preparations are under way. Intranasal administration of pollen extracts resulted in an unacceptable level of side effects. Local bronchial immunotherapy with mite extract in patients with asthma has been studied in a controlled trial but failed to produce significant clinical improvement.[26]

Most allergen extracts used in Australia for immunotherapy of inhalant allergy are alum-precipitated. Such preparation slows the absorption of allergen, reducing the risk of serious anaphylaxis and providing sustained immune stimulation.

There is no reliable standardisation of biological activity for many allergen extracts used in Australia. Mass and concentration of active material are not useful guides to biological activity. The concentrations of the slow-release (alum-precipitated) preparations are expressed in "protein nitrogen units" and not biological activity. Aqueous preparations of some allergens, including *Dermatophagoides pteronyssinus*, are standardised against a WHO standard and are extremely potent. Their use in asthma should be restricted to specialist centres.

Adverse effects

Local reactions

Mild swelling and erythema at the site of the injection is to be expected. It may persist for 24 hours or more and is not a cause for concern. A more severe reaction over 50 mm in diameter is an indication for reduction in the subsequent dose.

Systemic reactions

These include sneezing, bronchospasm, urticaria and, in more severe cases, anaphylaxis with hypotension and collapse. They must always be regarded seriously. Although they usually occur within 30 minutes of the injection, they may be delayed for several hours with the use of alum-precipitated preparations. Recent data from the UK estimate that the incidence of severe systemic reactions was 1 in 500 injections,[1] but most occurred with aqueous extracts, and alum-precipitated extracts appeared to be much safer. The incidence of anaphylaxis with Allpyral (Bayer, Pymble, NSW), the alum-precipitated material available in Australia, was reported to be 1 in 27 854 courses of treatment, and of anaphylaxis and/or bronchospasm, 1 in 14 998 courses of treatment.[27]

The Committee on the Safety of Medicines, in the United Kingdom, reported in 1986 that in the 29 years from 1957 to 1986 during which 1 459 273 courses of treatment were given, there were 29 deaths from immunotherapy — 16 in patients where the indication for therapy was asthma.[27] Highly purified and potent aqueous extracts were involved in most of these deaths, and no deaths were reported with the Allpyral extract. Subsequent reports indicated a much lower incidence of anaphylaxis and deaths in France and the US,[28,29] where one major difference in practice is that treatment is administered by specialists with expertise in the area.

In Australia, five deaths from immunotherapy were reported to the Adverse Drug Reactions Advisory Committee in the 21 years from 1972 to 1993. Four were in patients with asthma, and in each case there was a divergence from recommended procedure.

Long term adverse effects

There is no increase in the prevalence of vasculitis, autoimmune disease or monoclonal gammopathies during or after immunotherapy.[30] Further, there is no evidence that long term worsening of asthma occurs with immunotherapy.

Practical aspects of administering immunotherapy

These guidelines relate to specific allergen immunotherapy for the treatment of asthma in patients with clinical manifestations and/or need for treatment of ongoing bronchial hyperreactivity.

The decision to prescribe immunotherapy is based on appropriate patient selection, appropriate antigen selection, and whether potential benefits outweigh associated risks. Only a practitioner or team with training and experience in the management of both asthma and immunotherapy should make the decision. Suitably qualified practitioners include thoracic physicians with training and expertise in allergy, or clinical immunologist/allergists with *training and expertise* in asthma. It is the responsibility of the supervising consultant to (a) decide whether a patient needs to be treated in a hospital, and (b) ensure that the medical practitioner giving immunotherapy receives written instructions on patient assessment and immunotherapy protocol.

Informed consent according to currently accepted guidelines must be obtained from patients before starting immunotherapy.

Immunotherapy should be given only by a medical practitioner familiar with immunotherapy, conversant with resuscitative procedures, and in a setting where the following *resuscitation equipment* is immediately available: adrenaline 1:1000 for intramuscular use (adrenaline is the drug of choice for the immediate management of systemic reactions to immunotherapy), oxygen, an inflatable bag and mask ventilator, a nebuliser and bronchodilator nebuliser solution, needles and tubing for intravenous access, intravenous fluids suitable for volume replacement, parenteral antihistamine, and parenteral corticosteroid. The practitioner and a second appropriately trained health care professional should be present during immunotherapy to assist if resuscitation is required.

Each patient requires an *individual dosage schedule* according to the degree of sensitivity and clinical reaction to the injections. The principle of therapy is to start with a small dose and gradually increase it as tolerated. Supervising consultants will have the training and experience necessary to determine the starting dose and appropriate schedule. Flexibility in dosage is essential and rigid adherence to predetermined dosage schedules is inappropriate.

Extracts should be stored in a refrigerator at 4°C, clearly marked with the patient's identifier(s) and replaced in the refrigerator immediately after use. Before injection, the extract should be examined visually and discarded if its appearance has changed. The contents of the bottle should be mixed well to avoid variation in dosage. When changing to a new batch of unstandardised extract (such as Allpyral), the first dose should be reduced by 25% to take account of possible variation in biological activity of the preparations. Each patient should have his or her own individual vial of extract — laws in some States forbid multiple use of vials for different patients.

Every patient should be *assessed clinically on each occasion before an injection is given*, with particular attention to stability of asthma as indicated by peak flow charts, intercurrent illness, reaction to the last injection and any change in medication.

Spirometry or peak flow meter readings must be taken before injection and, if more than 20% below the best recent recorded reading for that patient, the injection should not be given. The readings should be repeated 30 minutes after the injection and immediately any lower respiratory symptoms arise during the period of observation — a fall of 10% or more is an indication for reducing the dose of the next injection.

The medical practitioner must be responsible for selecting the dose and having it checked by a second health professional. Injections are given subcutaneously, a suitable site being the tissue overlying the triceps muscle group. After introducing the needle, and before starting the injection, the plunger should be withdrawn gently to ensure that the needle is not placed intravenously.

There is no consensus about the optimal time that a patient must remain under *observation*. However, we recommend 45 minutes, as serious reactions after that time are rare. Reactions may be delayed with alum-precipitated preparations but they are usually minor. Before discharge patients should be examined to record the size of the local reaction, ensure that there are no signs of a systemic reaction, and to repeat spirometry or peak flow readings. Patients must not engage in strenuous physical exercise or take hot baths or saunas for six hours after the injection.

Patients should *monitor their peak flow at home*; excessive variability would indicate a need for re-evaluation of asthma and immunotherapy.

A local swelling larger than 50 mm requires a reduction in dosage. Patients should be instructed to measure the diameter of any local reaction should it increase in size after leaving medical supervision, and report this before the next injection.

Some practitioners "cover" therapy by giving prophylactic antihistamines to reduce the local reactions. This practice may make it difficult to judge the effects of therapy, both locally and systemically, and to modify dosage accordingly. It may also block the initial manifestations of an anaphylactic reaction. Use of this practice is a matter of judgement, but if prophylactic drugs are used use must be consistent.

Injection schedules vary with individual patients, but the Allpyral preparations are administered every 1–2 weeks until a maintenance dose is reached. Maintenance injections are administered every 2–4 weeks. It should be re-emphasised that immunotherapy schedules are individualised and fixed schedules are not recommended, particularly when aqueous extracts, which are becoming more readily available in Australia, are used.

The *duration of therapy* for optimal management is unknown at present. With bee and wasp venom immunotherapy, there is evidence that five years of maintenance injections will provide long term protection in almost all patients. There is no corresponding evidence in inhalant allergy and practice varies. Dust mite injections are often continued for 2–3 years if there is a response, and preseasonal immunotherapy with grass pollen is repeated for 2–3 years.

Indications for immunotherapy

1. A history indicating that exposure to a particular allergen precipitates symptoms and contributes to illness.
2. Documented sensitisation to the clinically relevant aeroallergen (by skinprick or radioallergosorbic tests).
3. Future exposure to the allergen should be unavoidable or only partially reducible.
4. Asthma symptoms should be stable. However, the severity of asthma should not be an indication or contraindication for therapy, but would determine whether the injections should be given in a hospital (see contraindications and practical aspects).
5. Significant allergic upper airway or ocular disease strengthens the indication. Clinical experience suggests that adequate control of allergic rhinitis improves the management of asthma. The efficacy of immunotherapy in controlling the symptoms of allergic rhinitis has been established, but is not the subject of this report.
6. An effective allergen extract should be available. Efficacy has been established for grass pollen, ragweed pollen (North America), house dust mite, birch pollen and cat dander. There are uncontrolled studies on other aeroallergen extracts and the decision to attempt a therapeutic trial with a commercially available extract rests with the supervising consultant.
7. Patients or parents/guardians should be able to give informed consent.
8. Other, less tangible, factors, such as unwillingness of the patient to continue with indefinite drug therapy and the quality of life desired by the patient, as well as socioeconomic factors should be considered in the selection of patients for immunotherapy.

Contraindications for immunotherapy

Relative contraindications

1. If the FEV_1 (forced expiratory volume in one second) is less than 70% of predicted, then immunotherapy should not be initiated unless a consultant physician with training and expertise in the management of asthma and immunotherapy has established that the potential benefits outweigh any risks, and the administration environment is suitable (see practical aspects).
2. Unstable asthma, defined by nocturnal asthma, use of a bronchodilator more than three times a week (excluding exercise), peak flow variability of more than 20%, or a bronchodilator response greater than 20%, are relative contraindications to both initiating and continuing immunotherapy. Patients with unstable asthma should not be given immunotherapy outside of hospital.
3. Immunotherapy should not be initiated in patients with autoimmune disease or malignancy,[3] although there are data which indicate that it does not predispose to development of these conditions.[31]
4. Immunotherapy during pregnancy has not been associated with an increased risk of teratogenesis. Nevertheless, we recommend that immunotherapy not be given because of the risk to the fetus of a systemic allergic reaction.
5. Should bronchospasm to an immunotherapy dose occur, the therapy should be suspended pending careful assessment by the consultant to determine whether the risk of continuing with the treatment is justified.
6. Patients with eczema may notice a flare of their skin disease during immunotherapy and should be appropriately informed. A significant reduction in dosage may be required to allow the eczema to subside.
7. While immunotherapy for asthma appears to be more beneficial in children than adults, particularly in children with seasonal hay fever and mild coexistent asthma, clinicians should consider carefully whether immunotherapy is appropriate in children when asthma is the only indication.
8. ß-Blocker eye drops (asthma is a relative contraindication to the use of these).

Absolute contraindications

1. Concomitant administration of ß-blockers and immunotherapy is absolutely contraindicated because patients taking ß-blockers are at increased risk of anaphylaxis and respond poorly to resuscitation (note that the use of ß-blockers is contraindicated in bronchial asthma).
2. Clinicians with no training or experience in giving immunotherapy should not attempt this form of treatment.
3. Lack of adequate resuscitation facilities and equipment.
4. Previous anaphylactic reaction to immunotherapy.

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Obituary

Karl George Ball

MB BS, FRCOG, FRACOG

Karl George Ball was born at Peterborough, South Australia, on 12 December 1924 and died in Adelaide on 3 November 1996. He studied medicine at the University of Adelaide, graduating in 1946. After a short period in general practice, he trained in obstetrics and gynaecology at the Queen Victoria Hospital, Adelaide, and then at the Royal Hobart Hospital. With further studies at Radcliffe Infirmary (Oxford, United Kingdom), he attained membership of the Royal College of Obstetricians and Gynaecologists in 1954.

When he returned to Adelaide, he began specialist practice in North Terrace and had appointments at both the Royal Adelaide Hospital and the Queen Victoria Hospital. In 1969 the Queen Victoria changed from a purely maternity hospital and Karl was appointed its first visiting gynaecologist, a post he held until his retirement.

Karl was a highly respected clinician, who counted among his patients a number of his colleagues and his colleagues' wives. He was a forward-thinking and compassionate man, concerned as much with his patients' psychological well-being and quality of life as he was with their physical health.

On his return from Oxford, it was apparent that he was no scion of the conservative Adelaide medical establishment with an interest in preserving the status quo, but rather a broad-minded liberal (definitely "small-l"!) with a particular interest in the social consequences of health policy. He was a founding member of Family Planning South Australia and subsequently its President and Chairman (1979–1984), and he effectively campaigned for the modernisation of South Australian abortion law.

His slow manner of speech concealed an acute and lucid intellect. What he lacked in speed of delivery in debate and teaching, he more than made up for with his clarity of thought and irrefutable logic.

He enjoyed baseball (he had represented South Australia while an undergraduate) and golf, and was interested in the visual arts, wine, food and travel.

Karl is survived by his three sons, two of whom are medical practitioners — David, a radiation oncologist in Melbourne, and Andrew, a medical officer with the World Health Organization in Geneva — and by four grandchildren and one great-grandchild.

David L Ball