Injection immunotherapy

A J Frew on behalf of a British Society for Allergy and Clinical Immunology Working Party

A working party of the British Society for Allergy and Clinical Immunology has reviewed the role of specific allergen immunotherapy in the treatment of allergic disease and produced a position statement summarising the available evidence for efficacy and safety. The working party recommends specific allergen immunotherapy for treating summer hay fever uncontrolled by conventional medication and for wasp and bee venom hypersensitivity. It is not recommended for asthma or for allergic rhinitis due to other allergens. For the recommended indications the risk:benefit ratio is acceptable provided patients are carefully selected; in particular, patients with asthma should be excluded as they are especially vulnerable to adverse reactions. Injections should be given only by doctors experienced in this form of treatment in a clinic where full resuscitative facilities are immediately available. Provided patients remain symptom free a 60 minute observation period after injection is sufficient to detect all serious adverse reactions.

The use of allergen injection immunotherapy to treat allergic disorders dates back to the early decades of the twentieth century, when Noon[1] and Freeman[2] at St Mary's Hospital, London, pioneered the use of pollen extracts to treat hay fever. Allergen immunotherapy was enthusiastically adopted in North America, where for many years it has been the treatment of choice for allergic rhinitis and asthma. In the United Kingdom, allergen immunotherapy never became as popular, and the practice of clinical allergy has largely remained an academic pursuit.

British allergists generally agree about the efficacy of allergen immunotherapy in seasonal allergic rhinitis, but doubt remains about its relative value in perennial allergic rhinitis and asthma. The fact that allergen immunotherapy has not been widely used to treat asthma in the United Kingdom is due in part to the fact that selective β agonists and inhaled corticosteroids became available here 15 years before they could be prescribed in the United States.

Background

Between 1950 and 1986 allergy injections were widely used in the United Kingdom, especially by general practitioners treating allergic rhinitis. In 1986 the Committee on the Safety of Medicines issued a report on deaths and adverse reactions associated with allergen immunotherapy, which appeared to be increasing in frequency.[3] The committee subsequently placed stringent restrictions on the practice of allergen immunotherapy and effectively curtailed its administration in general practice. In the absence of a system of hospital based allergy clinics, allergen immunotherapy in the United Kingdom was effectively abolished overnight. Elsewhere in Europe and in North America allergists noted the Committee on the Safety of Medicines' report but have continued their practice much as before.[4,5] Since 1986 interested groups in the United Kingdom and elsewhere have sought to ascertain the true risk:benefit ratios of allergen immunotherapy and to define more clearly the categories of patients for whom this form of treatment is appropriate. In October 1991 the British Society of Allergy and Clinical Immunology convened a working party to discuss these issues and to prepare a position paper reflecting expert opinion. A group of experts, including allergists, immunologists, clinical pharmacologists, general physicians, respiratory physicians, and paediatricians, participated in this project and this paper is a summary of our deliberations. The full report has been published in the August edition of *Clinical and Experimental Allergy*.[6] When necessary we consulted experts in Europe and North America, but the opinions and viewpoints expressed here are intended to reflect United Kingdom experience and clinical practice.

Aims of the working party

The working party's primary goal has been to optimise the management of patients with severe allergic disease. All reports published since 1986 regarding the efficacy and risks of allergen immunotherapy have been reviewed, together with unpublished data obtained from a survey of members of the British Society for Allergy and Clinical Immunology. Using these data, we have set out proposals for selecting patients to receive allergen immunotherapy and for preventing and minimising side effects. We conclude that allergen immunotherapy does have a place in selected patients and that the risk of adverse reactions can be contained by patient selection and the adoption of good clinical practices.

General considerations

In assessing the efficacy and place of allergen immunotherapy in managing allergic disease the important clinical questions are: Is allergen immunotherapy effective? Is it safe? How does it compare with existing available treatment? And can precise indications be defined for its use? We have also considered the criteria for patient selection, the type and dose of allergen used, protocols for induction and maintenance therapy and when to discontinue therapy, as well as how to manage any side effects.

It is important not to confuse allergen immunotherapy with certain unconventional and unproved forms of "allergy treatment" which also involve the administration of putative allergens by a variety of routes. These include neutralisation therapy, enzyme potentiated desensitisation, and oral immunotherapy, which have been claimed to be of benefit in a wide range of allergic and non-allergic diseases but are not supported by convincing trials using objective endpoints.[7,8]

Recent advances in our understanding of the mechanisms of allergic inflammation and immunological tolerance have suggested several alternative approaches to allergen immunotherapy. Several of these are currently under development, and, although it is too early to make formal judgments, we believe that improved and safer forms of allergen immunotherapy will probably be developed in the next decade.

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Seasonal and perennial allergic rhinitis

There have been several double blind placebo controlled trials of partially purified, standardised depot grass pollen extracts in patients with summer hay fever.[9-11] There is a lack of commercially available biologically standardised extracts of mould allergens.[12-14] Although there have been several studies in perennial allergic rhinitis associated with house dust mite allergy,[15-19] the symptoms of perennial rhinitis are heterogeneous and non-allergic factors are often implicated in its aetiology. Interpretation of these studies is complicated by differing selection criteria. Nevertheless, some good trials have been performed, although none have compared the benefits, side effects, cost, and duration of allergen immunotherapy with those of symptomatic treatment.

Overall, the working party concluded that allergen immunotherapy should be recommended in patients with seasonal allergic rhinitis who fail to respond to conventional pharmacological treatment with topical corticosteroids and antihistamines. Patients must be carefully selected and the contraindications respected (see box).[11] Induction courses should be completed in a specialist allergy centre, but maintenance treatment may reasonably be given in a non-specialist setting if doctors have had the appropriate training and resuscitative facilities are available. Although allergen immunotherapy for perennial allergic rhinitis due to house dust mite allergy does seem to be effective, further studies using standardised vaccines are needed to monitor safety and identify appropriate allergen immunotherapy protocols. In views of the greater potential for adverse side effects patients with co-existent chronic perennial asthma should be excluded.

Indications and contraindications for allergen immunotherapy for rhinoconjunctivitis

Indications

√ Evidence of IgE-mediated disease

√ Inability to avoid allergen

√ Inadequacy of drug therapy or intolerable side effects

√ Limited spectrum of allergen sensitivities (one or at the most two allergens)

√ Good likelihood of patient compliance

Contraindications

- **Non-availability of suitable allergen extracts**
- **Significant medical or immunological disease**
- **Multiple allergies**
- **Concurrent treatment with drugs likely to impair possible treatment for analphylaxis** (β blockers or other adrenergic blocking drugs)
- Insufficiently willing or motivated to attend regularly and complete the course

Not recommended for

□ **Children under 5 years**

□ **Pregnant women**

□ **Patients with a history of chronic perennial asthma (forced expiratory volume in 1 second or peak expiratory flow rate consistently less than 85% predicted)**

□ **Patients with severe dermatitis**

Allergen immunotherapy and asthma

The working party concluded that allergen immunotherapy remains a controversial form of treatment for asthma, largely because there have been few well controlled studies. Those studies which used a double blind, placebo controlled design and which included at least eight patients in each group were carefully reviewed. In general beneficial effects have been found in grass pollen asthma, but efficacy in adults with asthma sensitive to house dust mite, cats, or moulds is less certain, and comparative studies with conventional treatment have not been performed. In the 1986 Committee on the Safety of Medicines report asthma was the reason for treatment in 16 of the 17 fatal cases in which the indication for allergen immunotherapy was documented.[3] Other studies have reported systemic reaction rates of 5-35% in patients receiving allergen immunotherapy for asthma.[20] Thus, on the basis of uncertain efficacy and the potential for serious side effects we recommend that allergen immunotherapy is not indicated for the treatment of asthma.

Hymenoptera sensitivity

Every summer many people are stung by wasps and bees. In most cases this causes minor local inflammation which settles without treatment, but in a few people who are sensitised to antigens present in bee and wasp venom a sting may cause alarming symptoms and even death. About four such deaths occur in the United Kingdom each year, mainly in people aged over 40. Bee sting allergy is most often found in bee keepers, their relatives, and neighbours, while wasp allergy is sporadic.[21]

A history of severe systemic reactions induced by bee or wasp venom, including respiratory and cardiovascular symptoms, is one of the few absolute indications for allergen immunotherapy. The efficacy of immunotherapy using pure venom extracts is well established and there have been several good placebo controlled trials.[22-24] Treatment is usually given for three to five years. However, it is important to establish the presence of venom specific IgE antibodies before allergen immunotherapy is started. The indication for treatment is less certain in patients with milder symptoms, such as moderate urticaria, angio-oedema, mild asthma, nausea, and light headedness, following stings, even if venom specific IgE is present. The individual circumstances of such patients must be carefully considered, and allergen immunotherapy is usually given only if there are repeated reactions and continuing heavy exposure. Venom immunotherapy is not indicated in patients with mild forms of erythema, urticaria, angio-oedema, or large local reactions even if they have venom specific IgE antibody (see box).

Desensitisation for drug hypersensitivity

Adverse reactions to drugs are common in clinical practice, but only a small proportion of these—perhaps 10%—are caused by immunological mechanisms. The single most important feature in the management of a patient with a drug allergy is to avoid using the drug. Thus the issue of desensitisation arises only if it is essential to use a drug to which the patient is allergic because there is no alternative. In practice this situation is rare, but desensitisation is occasionally required for penicillin and insulin allergy and also for aspirin sensitivity (non-IgE mediated). Because these procedures carry a very real risk of severe adverse reactions patients need careful evaluation, and desensitisation is best conducted in specialised centres.

Desensitisation for other conditions

Allergen immunothrapy has been tried in various other conditions but has not been found helpful in non-allergic rhinitis/asthma, atopic dermatitis, chronic

urticaria, food hypersensitivity, or chemical hypersenstivities.[11] Although some trials have examined the efficacy of desensitisation for allergy to domestic animals,[25 26] these extracts cannot yet be recommended for routine use. If used on a "named patient basis" their safety should be carefully monitored for at least two hours after each injection.

Mechanisms for allergen immunotherapy

The mechanism by which allergen immunotherapy exerts its beneficial effect is still largely unclear. A variety of immunological changes have been described, but it remains uncertain which (if any) of these is responsible for relief of symptoms. For many years the main theory has been that allergen immunotherapy works by inducing the production of allergen specific IgG antibodies (so called blocking antibodies),[27-31] but this remains controversial. In the longer term there is altered regulation of IgE synthesis,[29 31] and recent work suggests changes in T cell cytokine profiles following allergen immunotherapy.[32]

Although an alteration in T cell reactivity seems a promising line of research in studying the mechanisms of desensitisation to airborne inhaled allergens, the mechanism in hymenoptera immunotherapy may well be different. Here the evidence for protective IgG antibodies is more persuasive. Nevertheless, in "rush immunotherapy" schedules patients can be desensitised to venom over one to five days without any associated changes in specific IgG or IgE concentrations.

Allergen standardisation

Accurate diagnosis of allergy and the safe treatment of patients by allergen immunotherapy requires the use of allergen extracts with consistent potency and composition. Early attempts to achieve consistency relied on crude weight to volume ratios or estimation of protein nitrogen content, but these methods proved unreliable. Allergen standardisation is now achieved by a variety of methods. Initial assessment of biological activity by skin prick testing is essential but assurance of constant composition and potency from batch to batch in routine manufacture is monitored by immunochemical methods such as crossed immunoelectrophoresis, sodium dodecyl sulphate polyacrylamide gel electrophoresis, and radioallergosorbent inhibition assays.[14]

Vaccines prepared from food, feathers, synthetic materials, bacterial extracts, enzymes, or occupational agents should not be used because there is no evidence of their efficacy. Vaccines prepared from multiple allergens are not recommended because of the significant likelihood that one component may degrade another (many allergens contain proteolytic enzymes).[14]

Methods of administration

There are three main types of extracts: aqueous, depot, and modified preparations. Aqueous allergen preparations can be easily standardised. Their main disadvantage is that because of their rapid absorption they have a much greater frequency of systemic side effects than depot preparations. Aqueous extracts are widely used in North America, but in Europe their use is largely restricted to venom immunotherapy. In depot preparations the allergen is bound to a carrier, such as aluminium hydroxide, from which it is slowly released. Depot extracts produce fewer adverse reactions than aqueous extracts and are widely used in Europe, particularly for inhaled allergens. Standardisation of depot preparations is more difficult than for aqueous preparations. In modified allergen extracts the allergenic proteins are partially denatured by chemical treatment with the goal of reducing the IgE binding potential (allergenicity) but retaining sufficient antigenicity to induce a beneficial immune response. These extracts have been field tested with some success but have not yet established themselves in the clinical mainstream.

Conventional allergen immunotherapy regimens consist of an initial or induction course of weekly or fortnightly subcutaneous injections, starting with a very low dose of allergen and gradually increasing to reach the maximum dose after about three months. Maintenance treatment is then given, usually monthly for three years. This duration is arbitrary, and current trends are towards longer periods of maintenance therapy. "Rush" induction schedules are sometimes used since conventional induction regimens are very time consuming. Patients need to be admitted to hospital for rush induction since the incidence of adverse reactions is significantly greater than for conventional regimens.[33] For seasonal allergens induction treatment should be started and completed out of the relevant pollen season, and maintenance doses should be reduced during periods of pollen exposure. For venom immunotherapy induction can be achieved in a single day ("ultra rush"): this regimen is better tolerated for wasp venom than for bee venom.

The "art" of the immunotherapist is in administering and monitoring the safety of allergen extracts. The working party recommends that injections should be given in a clinic, normally in hospital, where facilities for treating anaphylaxis and general resuscitation equipment are available. Patients should be involved in their management and educated in the potential side effects and the way that these should be managed. In our full document we describe the procedures required before each injection; which risk factors must be sought; when and whether to omit the next injection or modify the dose; the administration of the allergen injection; and routines to be followed after injection

Indications and contraindications for allergen immunotherapy for venom hypersensitivity

Indications

√ Anaphylaxis due to hymenoptera sting

√ Cardiac or respiratory distress after sting

√ Evidence of venom specific IgE

√ Likelihood of continued exposure to stings

√ Good likelihood of patient compliance

Contraindications

- Significant medical or immunological disease
- Concurrent treatment with drugs likely to impair possible treatment for anaphylaxis (β blockers or other adrenergic blocking drugs)
- Insufficiently willing or motivated to attend regularly and complete the course
- Pregnancy (never start course in pregnancy, but may continue maintenance course if indication is strong)

Not recommended for:

□ Children aged under 5 years

□ Patients with a history of chronic perennial asthma (forced expiratory volume in 1 second or peak expiratory flow rate consistently less than 85% predicted)

□ Patients with severe dermatitis

and after leaving hospital.[6] The dose and timing of each injection and patient selection are of paramount importance. Patients must be monitored carefully, particularly during the first 10 minutes after allergen injection, since most serious reactions will occur then. An important general principle is to treat anaphylaxis quickly, as this increases the likelihood of prompt resolution.

Adverse reactions to allergen immunotherapy

Injection immunotherapy can induce a variety of local and systemic side effects; these may be either immediate (occurring within minutes) or delayed (occurring up to 12 hours after injection).

The working party has made a thorough search for adverse reactions to allergen immunotherapy which have occurred since the Committee on the Safety of Medicines' update of 1986.[3] A survey of members of the British Society for Allergy and Clinical Immunology in February 1992 found that half of the United Kingdom based physician members of the society (27 out of 60) were currently treating patients by injection immunotherapy and that 10 were prospectively collecting data on adverse reactions. Detailed information was made available by seven of these clinicians. These data indicate that all serious adverse reactions to grass pollen and mites occurred within 30 minutes of injection, while a small proportion of serious side effects to venom injections occurred up to 45 minutes after injection. Anaphylactic reactions were rare but all such reactions started within 15-20 minutes of injection. Adverse reactions starting after 60 minutes were not life threatening and did not require specific intervention. Therefore the working party recommends that provided patients are carefully selected (people with asthma being specifically excluded) an observation period of 60 minutes after injection is enough to detect all serious side effects requiring treatment. In addition patients showing any signs of systemic adverse reaction should be detained beyond 60 minutes to ensure resolution of the reaction before they leave the clinic.

Summary of recommendations

(1) Specific allergen injection immunotherapy should be used on a routine basis only in (*a*) patients with seasonal allergic rhinitis (hay fever) who have failed to respond adequately to antiallergic drugs, and (*b*) patients with anaphylaxis due to wasp or bee venom hypersensitivity.

(2) Specific allergen immunotherapy should be administered only in hospitals or in specialised clinics. Adrenaline should always be immediately available and there should be easy access to resuscitative facilities. Attendant staff should be trained in resuscitative techniques.

(3) Patients should be kept under close supervision for the first 60 minutes after each injection. This period should be extended if the patient has any generalised symptoms, however mild.

(4) Severe or generalised delayed reactions should be recorded and reported to the Committee on the Safety of Medicines, with accurate details of timing, treatment, and response.

(5) Specific allergen immunotherapy is not recommended in chronic asthma. Also immunotherapy should not be used for treating mild seasonal asthma except as part of a carefully controlled research project. Immunotherapy is not recommended in non-allergic rhinitis, non-allergic asthma, atopic dermatitis, chronic urticaria, food hypersensitivity, and drug and chemical hypersensitivities.

(6) The use of allergen immunotherapy in children requires specialist assessment. Immunotherapy can be helpful, but as childhood allergic disease shows a natural tendency towards improvement appropriate patient selection is very important.

(7) Whole body extracts of stinging insects; allergen extracts prepared from foods, feathers, synthetic materials, bacterial extracts, and enzymes; and occupational allergens should not be used. Vaccines prepared from multiple allergens are not recommended.

(8) Extracts prepared from mould spores, animal danders, or house dust mites (*Dermatophagoides* spp) are also not recommended for routine use at present. Clinicians using these preparations on a named patient basis should continue to keep close supervision for two hours after each injection.

(9) All allergy extracts (for skin testing as well as intermediate products intended for immunotherapy) should be biologically standardised[11 14] and doctors should avoid changing from the products of one company to those of another during the course of treatment.

(10) These recommendations should be regularly revised and modified as necessary in the light of new information.

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Lesson of the Week

Acute airway obstruction after aspiration of boiling tea from teapot spout

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A child who has sucked hot tea directly from the spout of a teapot should be referred without delay for intubation.

Young children who suck hot tea from the spout of a teapot are at risk of acute airway obstruction, even though their immediate symptoms look mild.

Case report

A three year old boy was referred by his general practitioner to our paediatric ward, having sucked freshly made tea from the spout of a teapot three hours earlier. His mother had given him a cold drink immediately afterwards.

On admission he had a husky voice and was irritable, drooling saliva, and tolerating only sips of fluids and paracetamol syrup. His lips were erythematous, as was his soft palate, which had patches of flaking mucosa. There was no obvious oedema. His pulse rate was 90 beats/min, and he was not tachypnoeic. As initial appearances suggested only superficial burns to the mouth, and as his chest was clear on auscultation, a chest *x* ray examination was not performed.

Two and a half hours after admission he developed a temperature of 38·6°C and a tachycardia of 150 beats/min. His breathing was noisy, and opinions from an anaesthetist and ear, nose, and throat surgeon were sought urgently. He was fully conscious and appeared very quiet and calm. Although the upper airway sounded moist, he had no stridor or indrawing. Pulse oximetry showed an oxygen saturation of 93%, but he did not seem cyanosed. Because of the history of aspiration directly from a spout and the likelihood of imminent loss of the airway, arterial blood gas analysis was not performed because we feared that causing the child to cry could have produced sudden complete loss of the airway. He was instead transferred immediately to theatre, where a 4·0 mm plain orotracheal tube was passed under inhalational general anaesthesia. The epiglottis was grossly oedematous, completely obscuring the larynx, and there were full thickness burns to the soft palate and posterior pharyngeal wall.

A nasogastric tube was also passed, and he was transferred to the intensive care unit spontaneously breathing 30% oxygen via a continuous positive airway pressure circuit. He was sedated with an intravenous infusion of midazolam and given intravenous hydrocortisone and antibiotics. He was fed via the nasogastric tube.

The pharynx showed generalised oedema 24 hours later, but 48 hours after admission direct inspection showed a considerable reduction in inflammation and swelling. White slough was surgically removed from the soft palate, tonsils, and posterior pharyngeal wall. The vocal cords were only mildly erythematous. The trachea was extubated and the child returned to the intensive care unit, where humidified oxygen was continued. Twenty four hours later he was fully conscious and enjoying ice cream with no respiratory or swallowing difficulties. He was discharged five days after admission and followed up by the ear, nose, and throat department.

Comment

Two similar cases of aspiration of boiling tea from a spout have been described.[1,2] Five and a half hours after the aspiration the first child suffered complete respiratory obstruction and cardiac arrest, with subsequent irreparable brain damage. The second child was intubated urgently four and a half hours after aspiration. Both children had first been seen by their general practitioners, and had been prescribed paracetamol syrup and their parents reassured.

Our patient was admitted to the paediatric ward for observation but intubated urgently five and a half hours after the aspiration. There are two important points in the histories of all three children.

Firstly, the hot tea was sucked directly from the spout of the teapot. This directs a jet of water and steam at near boiling temperature on to the epiglottis and posterior pharyngeal wall but spares the lips and tongue, thus giving an outward appearance of only a mild erythematous reaction.

Secondly, although the injury in these cases appeared trivial at first, all three children required urgent intubation within four to five and a half hours after the aspiration. The intubations were made difficult by the presence of an enlarged oedematous epiglottis.

Any child who presents with a history of sucking hot tea from the spout of a teapot should be referred to an acute hospital without delay for assessment and intubation by senior anaesthetic staff.

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