

Allergen immunotherapy: does it work and, if so, how and for how long?

Douglas S Robinson

Allergy and Clinical Immunology, Imperial College School of Medicine at the National Heart and Lung Institute and St Mary's Hospital NHS Trust, London SW3 6LY, UK

Introductory article

Long term clinical efficacy of grass pollen immunotherapy

SR Durham, SM Walker, E-M Varga, MR Jacobson, F O'Brien, W Noble, SJ Till, QA Hamid, KT Nouri-Aria

Background. Pollen immunotherapy is effective in selected patients with IgE-mediated seasonal allergic rhinitis, although it is questionable whether there is long-term benefit after the discontinuation of treatment. **Methods.** We conducted a randomised, double-blind, placebo-controlled trial of the discontinuation of immunotherapy for grass pollen allergy in patients in whom three to four years of this treatment had previously been shown to be effective. During the three years of this trial, primary outcome measures were scores for seasonal symptoms and the use of rescue medication. Objective measures included the immediate conjunctival response and the immediate and late skin responses to allergen challenge. Cutaneous biopsy specimens obtained 24 hours after intradermal allergen challenge were examined for T cell infiltration and the presence of cytokine-producing T helper cells (Th2 cells) (as evidenced by the presence of interleukin-4 messenger RNA). A matched group of patients with hay fever who had not received immunotherapy was followed as a control for the natural course of the disease. **Results.** Scores for seasonal symptoms and the use of rescue antiallergic medication, which included short courses of prednisolone, remained low after the discontinuation of immunotherapy and there was no significant difference between patients who continued immunotherapy and those who discontinued it. Symptom scores in both treatment groups (median areas under the curve in 1995, 921 for continuation of immunotherapy and 504 for discontinuation of immunotherapy, $p=0.60$) were markedly lower than those in the group that had not received immunotherapy (median value in 1995, 2863). Although there was a tendency for immediate hypersensitivity to allergen to return late after discontinuation, there was sustained reduction in the late skin response and associated CD3+ T cell infiltration and interleukin-4 messenger RNA expression. **Conclusions.** Immunotherapy for grass pollen allergy for three to four years induces prolonged clinical remission accompanied by a persistent alteration in immunologic reactivity. (*N Engl J Med* 1999;341:468-75)

Allergen immunotherapy for grass pollen hay fever: indications and efficacy

Although allergen immunotherapy was first described nearly 100 years ago,¹ its use in clinical practice in the UK has a chequered history and it remains regarded by many as a fringe treatment of dubious benefit. This is in sharp contrast to practice in continental Europe and the USA, so who is right? Initially allergen immunotherapy, which entails subcutaneous injection of increasing doses of allergen extract to achieve a standardised monthly maintenance dose, involved giving crude allergen extracts and was given widely with varied protocols and often minimal supervision. The potential side effect of injecting allergen into any specifically IgE sensitised individual is anaphylaxis and,

despite controlled studies documenting efficacy for pollen hay fever,² the occurrence of serious side effects (and deaths) led to virtual proscription of this treatment in the UK by the Committee on Safety of Medicines in 1986.³ However, the science of allergy has moved on considerably to the point where many allergen proteins have been cloned and characterised at a molecular level, crystal structures solved for some, and IgE and T cell reactive epitopes carefully mapped.^{4,5} This scientific advance holds the prospect of engineered allergens with low IgE binding and the use of peptide fragments of allergen to reduce the potential for anaphylaxis. Does the evidence from trials of current immunotherapy suggest that such efforts are justified?

The introductory article by Durham and co-workers⁶

is one of a series following a carefully monitored cohort of patients with severe grass pollen hay fever since the late 1980s in work that sets standards of excellence in study design and has results in a series of seminal clinical and mechanistic reports.⁷⁻¹⁰ Initially they reported a one year treatment period using a modern alum absorbed, biologically standardised grass pollen extract to treat patients with severe hay fever symptoms uncontrolled by conventional anti-allergic treatment (such as topical nasal and intermittent systemic steroids, antihistamines, and cromoglycate eye drops).⁷ This work confirmed the dramatic clinical efficacy reported by Frankland and others in previous studies.² There were only two systemic reactions to treatment, both of which occurred within the first 20 minutes after injection and were rapidly reversed by adrenaline. Nonetheless, this emphasises that allergen immunotherapy (AIT) should be given in hospital by trained staff familiar with this treatment, with immediate resuscitation facilities to hand.¹¹ Seasonal rhinitis is often seen as a minor irritant by physicians and many would perhaps question the need for AIT for hay fever. In fact, the major quality of life (QOL) impact and health economic costs of seasonal rhinitis, which scores higher than angina on QOL questionnaires, have been documented¹² as have significant improvements in QOL scores after grass pollen immunotherapy.¹³ Patient preference assessment showed a clear preference for AIT. White *et al*¹⁴ recently surveyed control of seasonal rhinitis in a large primary care study. Even when 142 patients used optimal pharmacotherapy, only 38% reported good control of their hay fever symptoms. If only 10% of these patients were suitable for grass pollen immunotherapy, it would suggest that 5000–10 000 patients might benefit from such treatment in the UK, far beyond the capacity of current allergy services. Patient selection is vital for immunotherapy. Ideally, patients should have symptoms exclusively or largely attributable to one allergen (the specificity of allergens means that, for example, grass pollen immunotherapy will not control symptoms from tree pollen), not have chronic asthma (a contraindication in the UK but not the international guidelines), and not have other significant medical conditions that might interfere with immunotherapy, or that immunotherapy might affect – for example, β blocker treatment precludes resuscitation from anaphylaxis with adrenaline and is an absolute contraindication, and AIT should be used with caution in autoimmune disease.¹¹ Even given these careful selection criteria, it is likely that a large number of patients could benefit from grass pollen immunotherapy. At present there are no published studies of the health economics of AIT; this is a clear priority.

Immunotherapy for other allergens

The longest established indication for AIT in the UK is anaphylaxis to bee or wasp venom. This treatment is indicated in patients with a clear history of anaphylaxis (generalised systemic reactions including laryngeal oedema, asthma, collapse) or generalised urticaria if there is a high probability of re-sting – for example, bee keepers. The presence of venom specific IgE can be confirmed on skin prick testing or with radio-allergosorbent testing of serum (RAST). Trials involving sting challenge suggest that this treatment reduces the risk of anaphylaxis upon re-sting from around 50% to less than 5%.¹⁵

Double blind placebo controlled studies have also shown efficacy for AIT for other allergens including birch pollen,¹⁶ cat,^{17 18} and house dust mite rhinitis.^{19 20}

However, trial results are variable, and this may reflect the patient selection and the quality of the allergen extracts used. The heterogeneity of perennial rhinitis and difficulty in firmly attributing symptoms to a particular allergen make patient selection more difficult in perennial disease. In addition, chronic allergen exposure, as for house dust mite, may limit the total dose of allergen that can be given by AIT. It is estimated that 5–20 μ g of major allergen is required for efficacy,²¹ although the relative quantities of different allergen proteins (such as *Der p* 1–10 in house dust mite or *D pteronyssinus* extracts) in each extract can vary. At present in the UK AIT with allergens other than bee and wasp venom or grass pollen should be as part of controlled studies to define more clearly which patients would benefit from this treatment.

Immunotherapy for asthma

Although meta-analysis of a number of studies has suggested benefit from immunotherapy for asthma, the responses detected are variable and less useful for perennial asthma than seasonal asthma related, for example, to grass pollen allergy.^{22 23} Thus, immunotherapy for ragweed allergy achieved a significant but small improvement in lung function (peak flow rates), and an accompanying commentary suggested that better treatment responses could be achieved with inhaled corticosteroids or other conventional therapy for asthma.^{24 25} Although widely practised in other countries, immunotherapy for asthma is currently contraindicated in the UK.^{11 21} However, seasonal asthma due to grass pollen allergy is not a contraindication for AIT for severe hay fever, and grass pollen immunotherapy can reduce non-specific bronchial responsiveness and seasonal asthma symptoms.¹³ There is a clear need for comparative studies of AIT and other treatments for asthma, and to assess patient preference for treatment. Another possibility that needs exploration is whether AIT might modify the course of disease in asthma, rather than keeping inflammation under control (see below).

Other modes of immunotherapy

In an attempt to reduce the risk of anaphylaxis from conventional AIT (although this is less than one in 1000 injections in the allergy clinic setting¹¹), a number of alternative routes of administration or modification of allergens has been explored. Nasal immunotherapy involves giving doses of nasal allergen before the pollen season and, although it appears to alleviate seasonal symptoms, the side effects are such that benefit is questionable.²⁶ Oral immunotherapy has been disappointing, but sublingual dosing has been reported to confer symptomatic relief in randomised controlled studies.²⁷ These modes of administration have not been compared with more conventional subcutaneous injection.

AIT is thought to act by altering T cell reactivity (see below), but the potential for side effects results from binding to allergen specific IgE. A number of approaches have thus been taken to preserve T cell epitopes but reduce IgE binding. Allergoids are chemically altered allergen proteins which seem to be active in controlling symptoms²⁸ but have not yet been shown convincingly to reduce side effects from treatment. Since many allergens have been cloned and IgE binding epitopes defined, it is feasible to engineer recombinant molecules that lack or have reduced IgE binding. This has been done for house dust mite²⁹ and birch pollen proteins³⁰ and trials of

these vaccines are currently underway. Allergen proteins are processed by antigen presenting cells and complexed with MHC molecules to be presented to T cell receptors. Another approach to treatment is to generate peptides from allergen molecules that do not bind IgE, but do act on T cells. This approach was supported by animal models^{31 32} and proof of concept was provided by studies using peptides derived from the major cat allergen (*Fel d 1*).³³ These vaccines did show some symptomatic benefit, but at the expense of delayed asthmatic reactions and some early responses due to residual IgE binding. A potential problem with the peptide approach is the restriction by MHC haplotype which means that different patients have different MHC molecules and thus recognise different peptide fragments of the allergen.³⁴ Immunological models in animals suggest that tolerance may extend across different parts of the molecule. Trials of this approach are currently underway.

How does allergen immunotherapy work?

The current understanding of allergic disease is that it results from a Th2 T cell response driving both IgE synthesis and chronic eosinophilic inflammation.³⁵ It was suggested that AII induces blocking IgG₄ antibodies that block IgE interaction with allergen.³⁶ However, induction of IgG₄ does not correlate with clinical efficacy nor with onset of clinical response. Many studies have shown modulation of T cell responsiveness with variable inhibition of Th2 responses (IL-4 and IL-5) to allergen, and induction of more Th1-like responses with increased allergen induced interferon (IFN)- γ and IL-12.^{37 38} Thus, the concept of immune deviation (from Th2 towards Th1) has arisen and is discussed in the introductory article by Durham *et al*. Other work suggests the induction of IL-10 producing T cells.³⁹ There is much interest in this immunoregulatory cytokine which can inhibit both Th1 and Th2 proliferation and cytokine synthesis.⁴⁰ Regulatory T cells producing IL-10 have been described, termed Tr1, and it is possible that these cells are induced by immunotherapy.⁴¹ More recently it has been shown in mice that the T cell marker CD25 (the α chain of the IL-2 receptor), which is generally used as a marker of T cell activation, defines a sub-population of regulatory T cells.⁴² In this context it is of interest that Durham *et al* have previously described increased numbers of CD25+ cells in allergen induced late cutaneous reactions following AII.⁸ Defining the immunological mechanisms of AII should allow

optimisation of delivery, vaccines, and potential adjuvants for this therapy.

How long does allergen immunotherapy work for?

The study by Durham *et al* suggests that treatment for 3–4 years with grass pollen AII affords clinical benefit for at least a further three years. This is in line with other studies of AII, both of house dust mite and venom extracts.^{43 44} Other studies suggest that one year of treatment is not enough and that symptoms may recur within 2–3 years, and recent studies of venom immunotherapy suggest that 5 years of treatment is superior to 3 years.^{44 45} Most allergists treat for 3–5 years. The immunological changes described by Durham *et al* are in keeping with the sustained clinical benefit they observed, though it is of note that reactivity may begin to return by three years, so the longer term effects will need to be established. This treatment is generally given to young adults, and duration of benefit needs to be balanced against costs and the natural history of the disease, though spontaneous improvement of severe hay fever over time is unusual, particularly in patients whose rhinitis developed in adulthood and who have had symptoms for many years. Further knowledge of the mechanism of AII may help to define duration, although at present the duration of immunological memory is uncertain.

Can allergen immunotherapy alter the natural history of allergic disease?

Recent studies have defined allergen T cell responses in cord blood as early as 16 weeks gestation,⁴⁶ and Holt and others have suggested that allergen sensitisation occurs early in childhood.⁴⁷ A number of genes related to atopy and atopic disease have been defined, and risk factors for the development of atopy are well described.⁴⁸ If AII could modify the T cell response to allergen, it might offer the prospect of prevention of allergic sensitisation. Indeed, two studies of AII in children suggest that this is the case.^{49 50} Clearly, further work in this exciting area is required.

Conclusion

There is now clear evidence of clinical benefit from allergen immunotherapy for selected patients with severe

LEARNING POINTS

- * Allergen injection immunotherapy (AII) is effective for grass pollen hay fever not responding to conventional medical therapy and can result in a 50% reduction in symptoms, an 80% reduction in treatment requirement, and improved quality of life scores.
- * The clinical response persists for at least three years after a three year course of grass pollen AII.
- * Allergen immunotherapy for hay fever should only be given by experienced hospital allergy clinics.
- * AII for other allergens may be effective but requires more research.
- * Further comparative research is needed to define the role of AII in asthma.
- * Further studies are needed on cost effectiveness.

grass pollen hay fever. This study confirms long term benefit. Such treatment may be preferred by patients and may be cost effective in the long term control of this disabling disease.

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