Allergen immunotherapy (desensitisation) for allergic diseases

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Allergen immunotherapy (desensitisation) involves the repeated administration of allergen extracts to allergic individuals to induce a state of clinical and immunological tolerance. Traditionally, this has involved repeated subcutaneous injections of incremental doses of allergen over a period of 8–16 weeks followed by monthly 'maintenance' injections for 3–5 years. Modified approaches have included shorter and preseasonal regimens and alternative routes of administration, particularly the sublingual route.

Immunotherapy is indicated in patients with immunoglobulin (Ig) E-dependent disease and is particularly effective in patients with insect venom anaphylaxis and in those with severe seasonal allergic rhinitis unresponsive to anti-allergic drugs. The risk/benefit should be assessed in every case. In view of the remote risk of systemic side effects, immunotherapy should be prescribed and given only by trained and experienced individuals with access to resuscitative measures.[1]

Efficacy

Immunotherapy is effective in seasonal allergic rhinitis due to grass, tree and weed pollens. Most hayfever sufferers respond to treatment with intranasal steroids and/or antihistamines (Fig 1). However, a primary care-based study in Southern England found that 40% of treated hayfever sufferers remain inadequately controlled,[2] a proportion of whom would benefit from immunotherapy. In a recent UK multicentre trial of immunotherapy in 410 participants with documented uncontrolled hayfever and IgE sensitivity to grass pollen there was a dose-dependent reduction in symptoms and rescue medication compared with placebo during the pollen season and a sustained improvement in quality of life.[3] Although direct comparative studies with pharmacological treatments are needed, the mean reduction in symptoms of about 30% over placebo compares favourably with documented effect sizes of nasal corticosteroids (18%), antihistamines (7%) and leukotriene modifiers (5%) compared with placebo, as reported in a recent Cochrane meta-analysis.[4]

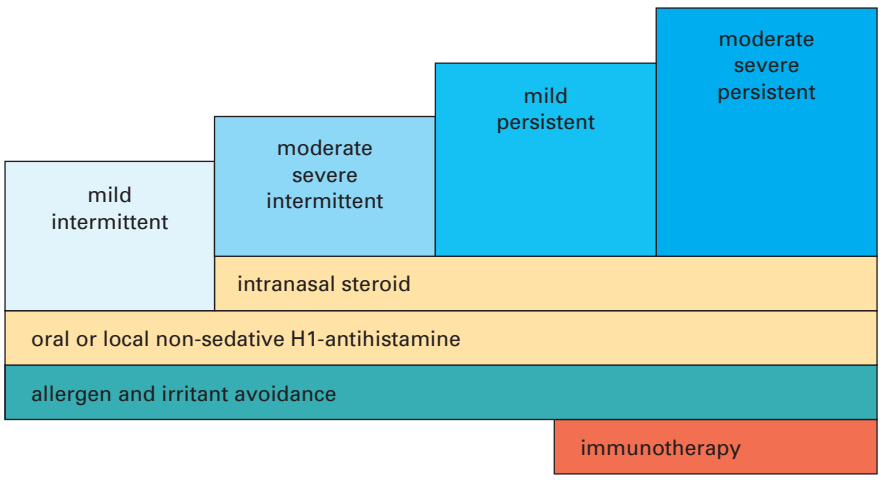

Fig 1. Treatment of allergic rhinitis, showing stepwise approach.

Desensitisation is also effective in patients with perennial allergy due to house dust mite and cats. Immunotherapy is not recommended for allergy to moulds, dogs and horses because of the lack of availability of well-characterised allergen extracts and the paucity of data from randomised controlled trials.[1] Immunotherapy is effective in allergic asthma,[5] although the risks in patients with asthma are increased. In contrast to elsewhere in Europe and the USA, chronic asthma is a contraindication within the UK.[6] Possible exceptions to this rule include:

- patients with severe seasonal rhinitis complicated by seasonal asthma who are asthma-free outside the pollen season
- individuals with asthma due to cats who are unable to avoid exposure.

Indications and contraindications for immunotherapy in rhinitis are given in Table 1, with levels of evidence in Table 2.

Insect venom allergy

Allergy to wasp and bee stings represents a spectrum, from local itching, redness and swelling through general urticaria to life-threatening anaphylaxis, which may involve any/all of the constellation of hypotension, cardiovascular collapse, angioedema and severe airflow obstruction, developing within minutes of a sting. All patients with general reactions following stings should be referred to an allergy specialist for IgE testing and further management. If venom allergy is confirmed, patients should receive advice on simple measures to reduce the likelihood of a further sting. All patients with general allergic reactions should be prescribed a self-injectable adrenaline device (epipen, anapen or similar) with instruction in its use.

Immunotherapy is not indicated for isolated local reactions because they are not associated with increased risk of progression to general allergic reactions. In patients with moderate/severe general reactions, careful consideration should be given to immunotherapy.[1] Venom immunotherapy is highly efficacious,

reducing the likelihood of a further systemic reaction by up to 95%, as shown by re-sting challenge.[7] There is long-term protection and a marked improvement in quality of life. Factors favouring immunotherapy include:

- severe reactions
- high risk of a further sting (eg bee keepers and their families)
- living remote from emergency medical assistance.

Long-term benefits

In contrast to treatment with anti-allergic drugs, immunotherapy has long-term benefit following discontinuation. A randomised placebo-controlled trial of withdrawal following 3–4 years' immunotherapy in subjects with severe hayfever gave prolonged benefit and suppression of immunologic markers which persisted for a further 3 years.[8] Similarly, venom immunotherapy afforded protection for five years following an adequate course of treatment.[9]

Immunotherapy reduced the onset of new sensitisations to other inhalant allergens in children with isolated mite allergy and pollen allergy, as determined by skin testing.[10] In pollen-sensitive children with allergic rhinitis, three years' immunotherapy produced a 2.5- to 3-fold reduction in the odds ratio for progression from rhinitis to physician-diagnosed asthma that persisted for at least five years.[11]

Mechanisms of allergen immunotherapy

Characteristic features of allergic inflammation include IgE production and the recruitment and activation of effector cells including mast cells, basophils and eosinophils. These events are under the regulation of a distinct subset of T lymphocytes, so-called T helper (TH2) cells, that preferentially produce the cytokines interleukin (IL)-4 (responsible for initiating IgE class-switching) and IL-5 (involved in eosinophil maturation, activation and survival).

Immunotherapy causes a transient increase in allergen-specific IgE ('Th2 priming'), followed by blunting of seasonal increases in IgE and an increase in allergen-specific IgG antibodies, particularly IgG4. The biologic relevance of these increases in IgG after immunotherapy has been questioned since there is a poor correlation with improvement in clinical symptoms. However, serum obtained after immunotherapy exhibits allergen-specific, IgG-dependent 'blocking' activity which includes inhibition of IgE-dependent basophil histamine release and IgE-facilitated antigen presentation and activation of T cells. In addition to alterations in antibody production, immunotherapy suppresses the recruitment and/or activation of effector cells at mucosal surfaces (reviewed in Ref 12).

Recent studies have shown that immunotherapy inhibits allergen-driven Th2 responses. These changes have been associated with immune deviation in favour of Th1 responses (with overpro-

Table 1. Immunotherapy for allergic rhinitis.

Indications	Contraindications
• IgE-mediated disease (positive SPT/RAST) • Inability to avoid allergen • Inadequacy of drug treatment • Limited spectrum of allergies (1 or 2) • Patients who understand risks and limitations of treatment	• Coexistent perennial asthma • Patients taking beta-blockers • Other medical/immunologic disease • Children under 5 years • Pregnancy • Patients unable to understand risks and limitations of treatment and/or to comply with immunotherapy protocol

RAST = radio-allergosorbent test; SPT = skin prick test.

Table 2. Levels of evidence for efficacy of immunotherapy in allergic rhinitis.

	Immunotherapy	
	Subcutaneous	Sublingual
Clinical efficacy in rhinitis	1a	1a
Prevention of new allergic sensitisations	2	2
Long-term clinical benefit after discontinuation	1b	2

Key Points

Allergen injection immunotherapy is highly effective in severe hayfever unresponsive to anti-allergic drugs and in insect venom anaphylaxis

Prophylactic effects include long-term benefit for up to five years following discontinuation, prevention of new allergic sensitisation and reduced progression from rhinitis to asthma

Mechanisms of immunotherapy involve suppression of T helper (TH2) T lymphocyte responses, by immune deviation in favour of Th1 responses and/or by inducing T regulatory responses

Biomarkers such as allergen-induced T cell production of interleukin-10 and functional assays of immunoglobulin G antibodies have potential as surrogate and/or predictive markers of the clinical response to immunotherapy

The most promising novel immunotherapy approach is currently the sublingual route which has been shown to be effective with a favourable safety profile

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duction of the cytokine interferon γ) and/or the emergence of a population of regulatory T cells which produce the inhibitory cytokines IL-10 and/or transforming growth factor (TGF)-β (Fig 2). Regulatory T cells may act directly to suppress allergen-specific Th2 responses (reviewed in Ref 13). Alternatively, IL-10 is a switch factor for IgG4 whereas TGF-β favours IgA production. Tests are ongoing to determine whether these alterations in T lymphocyte responses or changes in 'functional' measures of IgG are predictive of the clinical response to immunotherapy.

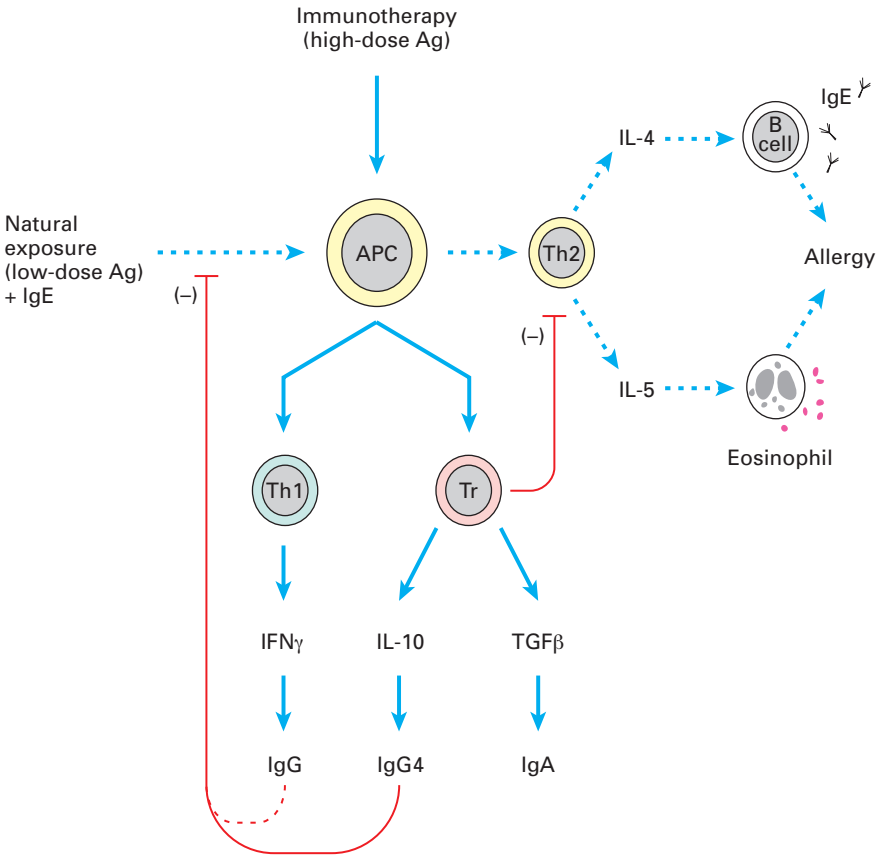

Fig 2. Mechanism of allergen immunotherapy. Ag = allergen; APC = antigen presenting cell; IFN = interferon; Ig = immunoglobulin; IL = interleukin; TGF = transforming growth factor; Th = T helper cell; Tr = T regulatory cells. Reproduced with kind permission from the *Journal of Clinical Investigation*.[13]

Safety and limitations

Allergen immunotherapy is effective but may result in occasional untoward side effects and rarely in the development of systemic allergic reactions. Local side effects of swelling and slight soreness several hours after injection are to be expected and, in general, are well tolerated and require no treatment. In 1986, following several deaths in the UK over the preceding 30 years, the Committee on Safety of Medicines made several recommendations.[6] The following should be observed:

1 In view of the rare occurrence of systemic side effects, immunotherapy should be given in specialist centres in the immediate presence of a physician and performed only by trained personnel experienced with immunotherapy protocols and familiar with the early recognition and treatment of anaphylaxis.[1]
2 There should be an observation area of sufficient size to allow supervision of patients for one hour following injections, adequate refrigerated storage facilities for vaccines and immediate access to adrenaline and other resuscitative measures.
3 Patients should be supplied with a telephone contact number in the event of the development of late reactions after discharge (these are usually self-limiting, occasionally requiring simple therapy with bronchodilators or antihistamines).

Detailed protocols and patient information sheets are available in published guidelines[1] and from the British Society of Allergy and Clinical Immunology (www.bsaci.org.uk).

Novel approaches

Injection immunotherapy, although effective, may be inconvenient and may involve some discomfort. Alternative routes have been developed, the most promising of which is the sublingual route in which allergen solution or allergen tablets are placed under the tongue for 1–2 minutes prior to ingestion.[14] Allergen is self-administered daily (or in some protocols three times weekly) either preseasonally or throughout the year. Many studies have confirmed the efficacy of this approach[15,16] although the overall effect size may be less than by the subcutaneous route. Local side effects include itching and slight swelling under the tongue which is in general well tolerated and self-limiting. There were no serious side effects in a recent meta-analysis.[16]

Other strategies include the use of small allergen fragments (peptides) which retain immunogenicity but are of insufficient length to cross-link IgE on the surface of mast cells, thereby reducing/eliminating the risk of inducing anaphylaxis.[17] The use of recombinant allergens might allow better standardisation and easier production of allergens for immunotherapy,[18] while mutated variants have potential for reduced allergenicity. Novel adjuvants in combination with allergen might enhance immunogenicity and reduce the allergen dose needed for efficacy and hence reduce the potential for side effects.[19] The combination of anti-IgE therapy with ragweed rush immunotherapy demonstrated

enhanced efficacy and an 80% reduction in systemic side effects compared with immunotherapy alone.[20]

At present, the conventional subcutaneous route remains the gold standard whereas the sublingual route represents the most promising novel approach.

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