The Journal of Laryngology & Otology
October 2005, Vol. **119,** pp. 799–805

Immunotherapy for allergic rhinitis – a United Kingdom survey and short review

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Abstract

Allergic rhinitis (AR) is a common condition which is treated using different modalities, including immunotherapy. The aim of this study was to survey the current management strategies among ENT consultants in the UK in treating AR, and their views on immunotherapy. The study design was a postal questionnaire survey and the setting a university teaching hospital. Participants were consultant members of the British Association of Otolaryngologists – Head and Neck Surgeons (BAO-HNS). The main outcome measures were common treatment modalities adopted by the survey group to treat AR, and the number of consultants practising immunotherapy. The majority (81.1 per cent) of the consultants surveyed practise medical therapy with or without surgery. Immunotherapy is advised by 26 per cent of ENT consultants, but only 6.6 per cent currently administer immunotherapy.

Keywords: Allergic Rhinitis; Immunotherapy; Questionnaires; United Kingdom

Introduction

Allergic rhinitis (AR) accounts for a considerable proportion of patients presenting to the ENT outpatient department, the majority of whom are initially treated by their general practitioner before referral. Standard management includes allergen avoidance, intranasal corticosteroid sprays, non-sedating antihistamines, chromones, decongestants and surgical intervention. Immunotherapy is another management option, which is not commonly used in the UK and is available only in a few centres across the country. Limited access and the potential risk of anaphylaxis are likely to be the main reasons why immunotherapy is not particularly favoured.

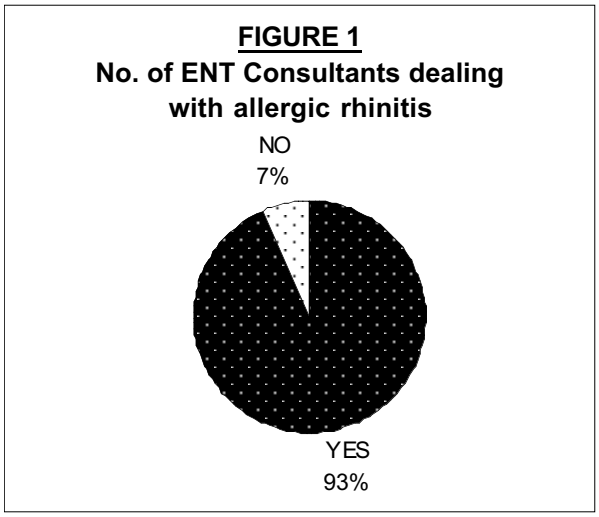

FIG. 1
Number of ENT consultants dealing with allergic rhinitis.

Materials and methods

A postal questionnaire survey was conducted among the consultant members of the British Association of Otolaryngologists – Head and Neck Surgeons (BAO-HNS). The questionnaire was sent to 565 consultants in the UK (Appendix 1).

Results

A total of 565 questionnaires was sent, from which 314 replies were received – a 55.6 per cent response rate. Replies from consultants who do not treat AR ($n = 8$) and incomplete replies ($n = 2$) were excluded from the study, leaving 304 replies to be analysed. Of the consultants who replied, 93.3 per cent deal with AR patients (Figure 1); 23.8 per cent of these feel that 10–14 per cent of their patients are diagnosed with AR. Medical therapy with or without surgery is practised by the majority of the consultants (247; 81.1 per cent). Immunotherapy was advised by 79 (26 per cent) (Figure 2).

After medical therapy has failed, 76 (25 per cent)

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Accepted for publication: 8 May 2005

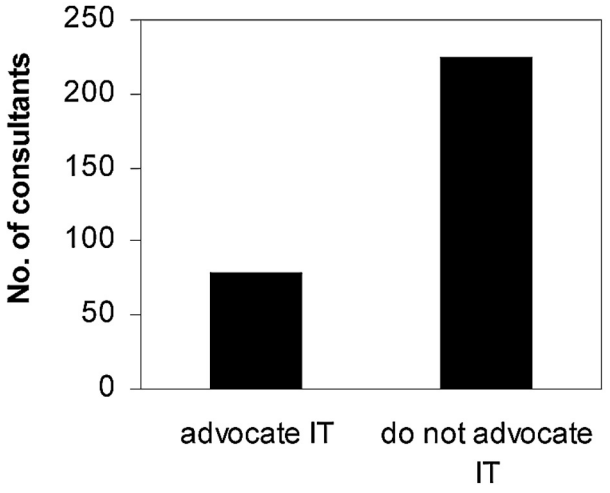

FIG. 2
Consultants advocating / not advocating immunotherapy.

advise immunotherapy. Only 18 (6.6 per cent) currently practise immunotherapy themselves; 72 (23.8 per cent) refer their patients to other centres for immunotherapy. One hundred and eleven (39 per cent) feel immunotherapy should be readily available at their hospitals, whereas 79 (26 per cent) think it should only be available in tertiary referral centres. Reasons for not using immunotherapy are illustrated in Figure 3.

Discussion

AR is common, and it is estimated that a third of atopic patients will develop symptoms of allergic disease at some stage.[1] The term 'atopy' refers to a genetic predisposition to produce IgE antibodies in response to minute amounts of environmental protein allergens. Non-atopic individuals can produce IgE, but do so only transiently. In atopic individuals the ongoing IgE production leads to the development of clinical disorders such as atopic dermatitis or eczema, asthma and allergic rhinitis. AR can be defined as the 'inflammation of the mucous membranes in the nose caused by an allergic reaction'. It can be either seasonal or perennial. Seasonal AR occurs during the seasons of airborne pollens, particularly grass, rye, birch and ragweed.

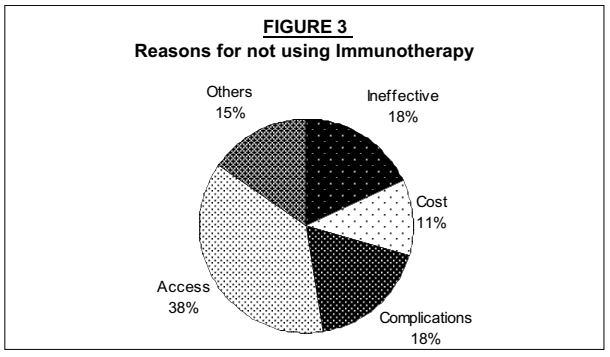

FIG. 3
Reasons for not using immunotherapy.

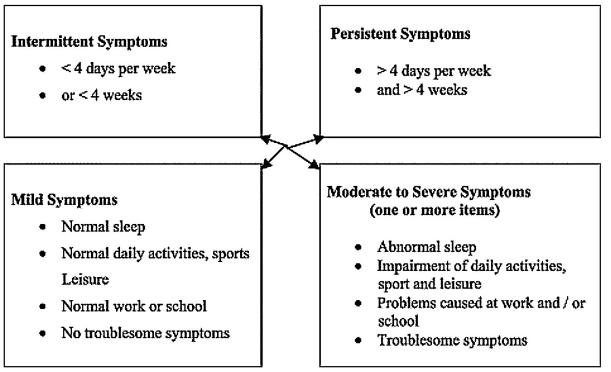

FIG .4
Classification of rhinitis according to ARIA guidelines.

Grass pollen is the most common cause of pollinosis worldwide, affecting over 95 per cent of seasonal AR patients in the UK. Perennial AR occurs throughout the year, triggered by indoor allergens such as house-dust mites, house pets, cockroaches and moulds.

The prevalence of AR has increased in western and westernised countries in the past 30–40 years.[2] It usually starts in childhood, at an average age of 10 years. Genetic make-up, allergen exposure, and possibly exposure to adjuvants that facilitate allergic sensitization play a major role in the development of the disease and its severity. It is often responsible for frequent absence or poor performance at work and school.

AR has significant co-morbid associations. These include asthma, eczema, otitis media with effusion, sinusitis, pharyngitis and disordered sleep. The most significant known link, however, is between AR and asthma.[3]

AR represents a global health issue, affecting 10–25 per cent of the world's population. Recognition of this led to the publication of the World Health Organization's guidelines on allergic rhinitis and its impact on asthma (ARIA),[4] the first set of evidence-based guidelines to be produced. In the ARIA document, rhinitis is classified as either 'intermittent' or 'persistent' (Figure 4). This classification recognizes AR as a global issue because it is applicable worldwide, whereas 'seasonal' and 'perennial' apply only to countries where there are seasons. The severity of AR is also classified as 'mild' or 'moderate–severe'.

ARIA also produced guidelines to treat AR based on disease severity and classification. The basic treatment plan according to the ARIA guidelines is shown in Figure 5. The evidence level for each treatment modality is shown in Figure 6. It is worth noting that allergen identification and avoidance forms an important first stage in the stepwise treatment approach, as shown in Figure 5, and immunotherapy is suggested as the final option.

The following sections of this paper focus on immunotherapy for AR and discuss some of the salient aspects of this treatment modality.

The history of allergy makes interesting reading. In 1872, Wyman in the United States suggested 'pollen' as the likely cause of symptoms in AR.

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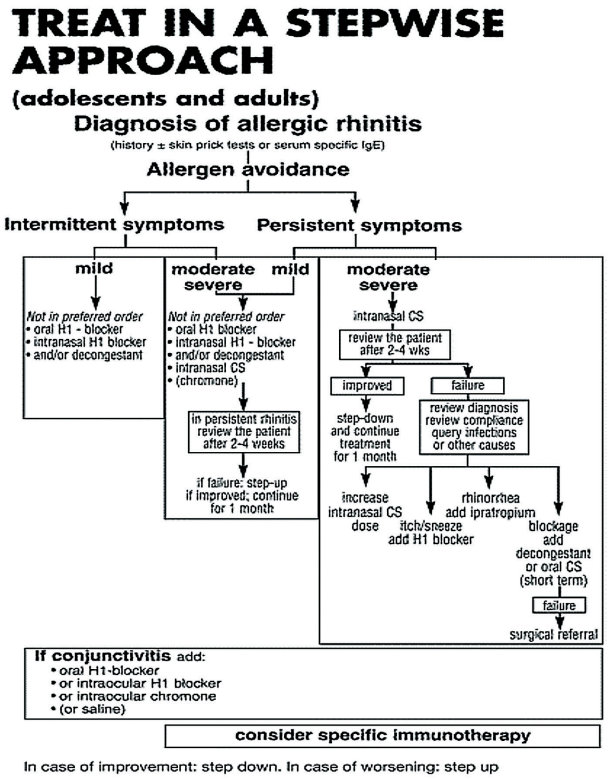

FIG. 5

Basic treatment plan for rhinitis according to ARIA guidelines.[4]

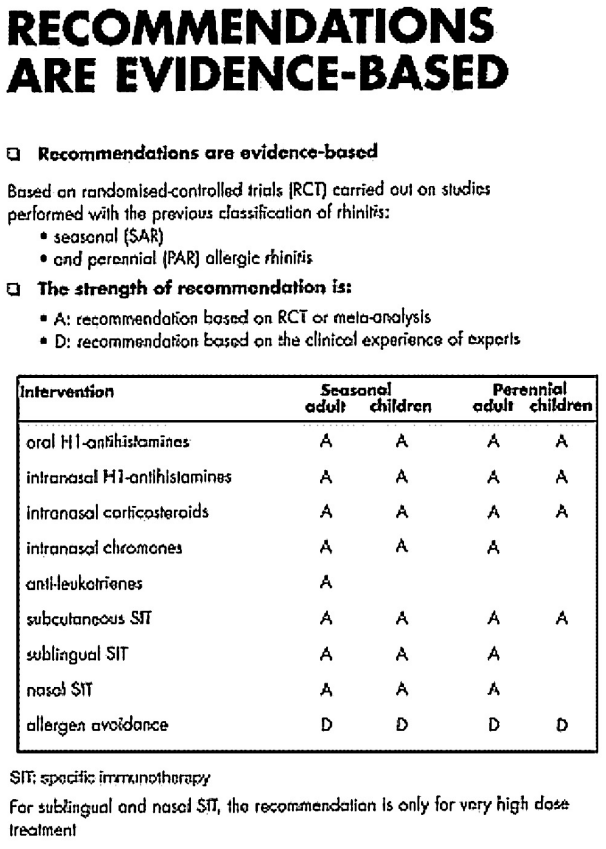

FIG. 6

Level of evidence for different rhinitis treatments.[5]

The following year this view was supported by Blackley, in a subsequent report based on self-experimentation. In 1900, Curtis reported that immunization with water-based extracts of some pollens appeared to benefit patients with seasonal rhinitis and asthma. In the meantime, attempts to protect humans and animals from the effects of bacteria-derived toxins led eventually to the description of anaphylaxis/hypersensitivity reactions by Portier and Richet in 1902. This concept of hypersensitivity was subsequently applied to the pathogenesis of hay fever, and later to asthma.

Studies of active immunization with allergen extracts as a treatment modality for hay fever began at St Mary's Hospital in London. Two papers by Noon[6] and Freeman[7,8] from St Mary's Hospital, published in 1911 in the *Lancet*, described conjunctival challenge of patients with allergic rhinoconjunctivitis. Conjunctival challenge testing is done by placing an allergenic extract into the conjunctival sac of the eye, followed by observation for redness, itchiness, tearing and similar symptoms. Such challenges lead to initial mast cell activation, with the release of mediators such as histamine. This reaction may be followed by an inflammatory reaction analogous to the late-phase reactions in the nose and lower airways.[9] Noon[6] and Freeman[7,8] also reported successful treatment of rhinoconjunctivitis using subcutaneous inoculation of grass pollen extract, which paved the way for the development of immunotherapy.

'Immunotherapy or desensitization is a technique where initially a very small dose of a specific allergen is introduced into the patient, increasing this in a regular fashion until the patient achieves tolerance or is desensitized to the allergen being injected.'

In the United States and Europe the technique of allergen immunotherapy is commonly practised, whereas in the UK it is only offered in specialist centres. In Europe and the USA immunotherapy is considered standard treatment for a wide range of allergies. It is indicated in patients with the diagnosis of a clinically specific antigen sensitivity, determined by appropriate skin or *in vitro* testing.[10,11] The usefulness of allergen immunotherapy is highlighted in the WHO report,[12] which advocates its use in selected patients with specific IgE antibodies to clinically relevant allergens. Allergen-specific immunotherapy has been shown to be effective in the treatment of pollen-induced rhinitis compared to placebo.[13,14]

The study by Durham *et al.*[15] provides good evidence that allergen immunotherapy has long-term, perhaps permanent, benefits. These results provide evidence of decreased immunologic reactivity for at least three years after the discontinuation of immunotherapy for the treatment of hay fever.[15]

The indications and contraindications for immunotherapy in the UK are as follows.

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Indications[16]

(1) Wasp or bee sting anaphylaxis
(2) Severe seasonal rhinitis or hay fever caused by grass pollen.

Absolute contraindications[17–19]

(1) Previous anaphylactic reaction to immunotherapy
(2) Inadequate clinical experience in administering immunotherapy
(3) Lack of adequate resuscitation facilities and equipment
(4) Concomitant administration of β-blockers.

Relative contraindications[17–19]

(1) FEV_1 <70 per cent of predicted, unless it is established that the potential benefits outweigh the risks
(2) Unstable asthma which is defined as nocturnal asthma
(3) Patients with autoimmune disease or malignancy
(4) Pregnancy
(5) Bronchospasm during treatment
(6) Patients with eczema
(7) Children with asthma as the sole condition
(8) Patients on β-blocker eye drops.

Immunotherapy may be administered as subcutaneous injections, sublingually, or via the nasal route.[16]

Subcutaneous injection immunotherapy

A detailed clinical and allergy history, RAST test and skin prick tests are essential before commencing treatment. A typical course of therapy consists of subcutaneous injections of the highest or a maintenance dose of an allergen extract injected every two to six weeks for a period of three or more years. Induction of clinical tolerance to the maximal dose is initially achieved by means of a series of weekly injections at escalating doses, usually given over a period of four to six months.[20] Acute reactions include severe asthma, angio-oedema and life-threatening anaphylaxis.[21] The patient should therefore be monitored closely for at least 20 min after each injection.[17,22]

Local reactions such as a raised itchy red wheal and tenderness subside within a short time. Rarely, troublesome reactions consisting of large brawny swellings may occur 12–36 h later, but resolve over a number of days. Mild systemic reactions occur occasionally, and include hay fever-like symptoms and worsening of asthma. There are no long-term side effects published in the literature.

Local nasal immunotherapy

Specific nasal immunotherapy applies the same principles as conventional immunotherapy and permits localized treatment in individuals with only minimal allergic reactions. In this form of treatment the specific allergen is administered directly into the nose. Various studies have documented the clinical efficacy of this route using extract in both aqueous[23–25] and powder form.[26–29] A recent multicentre double-blind trial[30] using the powder form of allergen extracts for mites and pollen concluded that local nasal immunotherapy (LNIT) is safe and effective for AR. Moreover, with good patient compliance it can be carried out at home.[31]

- **This paper reports the results of a survey of British otorhinolaryngologists into the management of allergic rhinitis**
- **Routine management included allergen avoidance, intranasal corticosteroids, antihistamines, chromones, decongestants and surgical procedures**
- **Immunotherapy was not widely available in Britain, with only 6 per cent of respondents offering this treatment to their patients. Reasons given were cost, access to therapy, inconvenience, and safety concerns**

Sublingual immunotherapy (SLIT)

The sublingual route represents a viable, safe alternative to subcutaneous immunotherapy.[32] Sublingual immunotherapy has been investigated in a number of randomized controlled trials[33–35] which have deemed it safe in both children and adults. Mild gastrointestinal symptoms were the most frequently reported side effects; these could be treated by adjusting the dose appropriately. Its safety is also supported by pharmacokinetic and immunological data.[31] A recent Cochrane Review by Wilson *et al.*[36] concluded that SLIT is a safe treatment that significantly reduces symptoms and medication requirements in AR.

Mechanisms of action

A number of theories have been put forward in the literature, including blunting of seasonal elevations in IgE,[37] a decrease in serum neutrophil and eosinophil chemotactic activity,[38,39] and a reduction in the number of mast cells[40,41] and mast cell mediators.[42] A more recent theory suggests that there is a suppression of allergen-induced T-lymphocyte proliferative responses with an increase in the circulating numbers of allergen-specific $CD8^+$ T lymphocytes.[43] Today there is convincing evidence of a so-called 'Th1–Th2' concept:[45–47] $CD4^+$ regulatory T cells secrete one of two different sets of cytokines, namely Th1 (e.g. INF-γ and IL-12) and Th2 (e.g. IL-4, IL-5 and IL-13), cytokines that determine the direction of the inflammatory response. Th1 are viewed as the 'good' cytokines which inhibit atopy immunopathology, whereas Th2 are seen as the 'bad' cytokines.[44] The mechanism is likely to involve modification of the T-lymphocyte response to subsequent allergen exposure with a shift in the Th2/Th1 T-lymphocyte balance, either by a shift in the upregulation of Th1 responses (increased Il-12 and IgG response) or by decreasing/downregulation of Th2 responses (decrease in IL4/5, IgE and proinflammatory cytokines).[44–46]

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Conclusion

A review of the literature and recent guidelines on the treatment of AR suggest that allergen-specific immunotherapy has a major role in the treatment of severely symptomatic patients who have failed to respond to conventional treatment. Currently only a small proportion of otolaryngologists advise immunotherapy. Cost, access to therapy, inconvenience of the treatment to the patients, and most importantly safety concerns have made this treatment a less favourable option. We believe that the onus is on the otolaryngologist to provide this service in conjunction with the immunologist. This is likely to result in an improved quality of life for patients with severe allergic rhinitis and its effects.

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Mr G Dhanasekar takes responsibility for the integrity of the content of the paper.
Competing interests: None declared

Appendix 1

Immunotherapy for allergic rhinitis - a questionnaire survey from all UK ENT consultants

1. Do you deal with allergic rhinitis patients?
   ☐ Yes ☐ No (If no, please exit questionnaire)
2. What percentages of your patients are diagnosed with allergic rhinitis?
   ☐ <5% ☐ 5–9% ☐ 10–14% ☐ 15–19% ☐ >20%
3. What therapy do you usually advocate?
   ☐ Avoidance +/- surgery ☐ Medical therapy +/- surgery
   ☐ Immunotherapy ☐ None of the above
4. Do you advise/advocate immunotherapy (IT]?
   ☐ Yes ☐ No If no, why? ☐ Ineffective
   ☐ Cost
   ☐ Complications
   ☐ Access
   ☐ Others (please exit questionnaire)
5. When do you advise IT?
   ☐ After failed medical therapy ☐ Failure to comply with medical therapy ☐ Other
6. What percentage of your patients with allergic rhinitis do you think will benefit from IT?
   ☐ <5% ☐ 5–9% ☐ 10–14% ☐ 15–19% ☐ >20%
7. Do you administer IT to your patients?
   ☐ Yes ☐ No
8. Do you refer your patients to other centers for IT?
   ☐ Yes ☐ No
9. Do you think IT is cost effective compared to other treatment modalities?
   ☐ Yes ☐ No
10. Is your previous answer based on
    ☐ Proper scientific/economic evaluation of IT treatment cost by your department
    ☐ Studies done by other NHS departments
    ☐ Studies done by non-UK departments
    ☐ None of the above
11. Do you think IT should be readily available to you to prescribe at your place of work?
    ☐ Yes ☐ No
12. Do you think IT should be available only in major hospitals (teaching/tertiary referral centers)?
    ☐ Yes ☐ No

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