

ALLERGEN-SPECIFIC IMMUNOTHERAPY

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ABSTRACT

Allergen-specific immunotherapy remains the only causal treatment of allergic disease to date. Its efficacy in symptom reduction was demonstrated in double blind, placebo-controlled studies of allergic rhinoconjunctivitis, allergic asthma, and Hymenoptera venom hypersensitivity, including long-term effects after discontinuation of treatment. In addition, immunotherapy decreases the risk of developing new sensitisations to aeroallergens in monosensitised patients and allergic asthma in patients with mere allergic rhinitis. The mechanism of immunotherapy entails redirection of the T lymphocyte response from a T helper cell Type 2 phenotype in favour of induction of regulatory T cells and/or immune deviation toward a T helper cell Type 1 phenotype, with resulting inhibition of downstream effector pathways and induction of immunoglobulin G-associated blocking antibodies. Two main application forms are used in clinical practice: subcutaneous immunotherapy and sublingual immunotherapy. The advantage of subcutaneous immunotherapy is its proven efficacy over a broad range of indications. Disadvantages are systemic allergic reactions and inconvenience for the patient due to frequent doctor visits. Sublingual immunotherapy has been shown to result in less systemic allergic reactions and may be more convenient due to home application; however, efficacy has only been proven for allergic rhinitis. For clinicians, the adherence to practice guidelines and thorough knowledge of allergen products, application routes, indications, immunomodulatory mechanisms, efficacy, safety, and cost-effectiveness is important for successful treatment and will be addressed in this review article.

Keywords: Allergen-specific immunotherapy (AIT), immunomodulatory mechanism, cost-effectiveness, efficacy, safety, sublingual immunotherapy (SLIT), subcutaneous immunotherapy (SCIT).

INTRODUCTION

In Europe, allergen-specific immunotherapy (AIT) for hayfever was first introduced in 1911 by Noon and Freeman.^{1,2} Treatment showed effectiveness and was frequently used in the 1920s and 30s for a range of seasonal and perennial allergens. Despite controlled clinical trials, which proved efficacy in respiratory disease³ and in hypersensitivity to Hymenoptera venom,⁴ a period of decreased use of AIT followed. This was firstly due to the introduction of safe and effective symptomatic treatments such as oral antihistamines and intranasal corticoid sprays in allergic rhinitis, and secondly to safety concerns.⁵ The recent revival of AIT is due to increased safety with standardisation and modification of allergens, recognition of risk factors for systemic reactions (SRs), and the understanding of underlying immunomodulatory mechanisms and

clinical benefits such as have been observed in the prevention of asthma development.^{6,7} For successful treatment, adherence to practice guidelines^{8,9} combined with the knowledge of allergen products, application routes, indications, immunomodulatory mechanisms, efficacy, and safety as well as management of allergic reactions is important.

ALLERGEN PRODUCTS

Allergens such as pollens, mites, and animal dander are preferable in a standardised form for regular administration and are subject to adequate quality control; their efficacy and safety should have been proven in controlled trials.¹⁰ Available commercial allergen extracts for subcutaneous immunotherapy (SCIT) are either aqueous, depot, or modified extracts. Aqueous extracts are used for rush and cluster SCIT but have the disadvantage of increased

side effects.¹⁰ In depot extracts the allergen is bound to a carrier to diminish degradation which reduces side effects and may increase efficacy. Modified extracts (recombinant allergens) contain a physical or chemical alteration. The intention is to increase safety through the reduction of allergenicity alongside the potential for immunomodulation. In Europe, mixing of unrelated allergens is not recommended, as efficacy has not been adequately investigated in clinical trials.¹¹ Cross-reacting allergens such as for grass species or different house dust mites may be administered as mixtures but have not been shown to have any advantage over single allergens due to substantial sequence of homology for shared major epitopes.¹⁰

APPLICATION ROUTES AND PRACTICAL MANAGEMENT

The decision on which route of immunotherapy to take depends, among other things, on assessment of relative contraindications and patient preference. Before starting treatment, the patient should receive written and verbal information about efficacy, adverse reactions, and application of treatment (duration and supervised observation times in clinic). Special emphasis should be made on the need for adherence to the treatment protocol, especially if treatment is self-administered at home.

The most common form of application is SCIT which involves repeated injections (preferably to the dorsal area of the upper arm). Depending on the extract, preseasonal courses (for seasonal aeroallergens) over a course of around 8 weeks with an ascending amount of allergen and for 3 years in a row, are available. Alternatively, an updosing phase with weekly injections over 2–3 months followed by a maintenance phase of 3 years can be applied. The ‘cluster dose’ regimen is an alternative in which the maintenance dose is achieved after shorter up dosing (generally 7–8 weeks) with a similar safety profile. Finally, ‘rush’ and ‘semirush’ protocols are used in situations where fast tolerance needs to be achieved, as for example in patients with an allergy to Hymenoptera. The application of these protocols needs to be evaluated against an increased risk of SRs.¹²

The duration of AIT is usually 3 years for treatment with aeroallergens. For Hymenoptera immunotherapy for 5 years is often recommended, as evidence exists that 5 rather than 3 years may result in longer-lasting benefits.¹³ Life-long

treatment may even be considered for patients with life-threatening reactions: those with SRs during SCIT and those with honey bee allergy.¹³

Concerns about the practical management of SCIT exist largely due to patient inconvenience caused by the necessity of frequent medically supervised administration. These concerns have been addressed with the development of other application forms such as sublingual immunotherapy (SLIT). SLIT (both drops and tablets) is available for aeroallergens such as grass pollen, birch pollen, and house dust mite. The first dose is administered under supervision in the clinical setting followed by usually daily self-administration over the course of 3 years. Side effects are common, encompassing local symptoms such as itching and swelling of the mouth and throat which usually subsides within 2–6 weeks.¹⁴ Grading is performed according to the severity of local symptoms and the need for symptomatic treatment or discontinuation of therapy. A small proportion of patients may have persistent symptoms but these are rarely so bothersome that treatment needs to be discontinued.¹⁵ International consensus guidelines on AIT application exist¹¹ and before starting AIT the package insert and manufacturer product information about the AIT extract should be consulted.

INDICATIONS AND CONTRAINDICATIONS FOR ALLERGEN-SPECIFIC IMMUNOTHERAPY

The approach to treatment of allergic disease in general consists of the combination of allergen avoidance, medications for symptom relief, and education of the patient. Taking into account various different considerations, AIT may be indicated in respiratory disease, allergic rhinoconjunctivitis, allergic asthma, and in sensitivity to Hymenoptera venom (Table 1). Patients are treated from the age of 5 years and onwards.

Allergic Rhinoconjunctivitis

In allergic rhinoconjunctivitis, AIT is indicated in patients with bothersome moderate-to-severe symptoms despite guideline-directed pharmacotherapy (daily adherence to oral antihistamine and a nasal corticosteroid spray). This concerns about 20% of allergic rhinitis patients.¹⁶ A clear history of the causative agent and supportive skin, as well as immunoglobulin (Ig)E tests are required before starting therapy.

Table 1: Considerations in different indications for allergen-specific immunotherapy.

Indication for allergen-specific immunotherapy	Considerations
Allergic rhinitis and allergic asthma	<ul style="list-style-type: none">• Evidence of specific IgE antibodies to clinically relevant allergens• Patient preference• Adherence• Response to avoidance• Response to symptomatic medications• Adverse reactions to symptomatic medications• Coexistence of allergic rhinitis and asthma• Possible prevention of asthma in patients with rhinitis
Reactions to Hymenoptera stings	<ul style="list-style-type: none">• History of a systemic reaction to a Hymenoptera sting (especially if associated with cardiovascular and respiratory symptoms and evidence of clinically relevant specific IgE antibodies)• Patients >16 years old with a history of cutaneous symptoms and clinically relevant specific IgE antibodies• Frequent and large disabling local reactions may potentially be an indication

IgE: immunoglobulin E.

Adapted from Cox et al. 2011⁹

In order to improve accuracy of diagnosis and precision of therapy, component-resolved diagnosis and the identification of minor and major allergens in a patient should be considered.¹⁷ For example, in a patient with a minor allergen as the major sensitiser, one may decide against AIT as the commercial extracts are standardised only for major allergens, which may lead to lack of effectiveness of AIT in this patient and more seriously, may result in adverse events.¹⁸ AIT should only be considered if markers of specific genuine sensitisation are positive and in accordance with clinical symptoms. Patients that profit most from treatment have been those who were unresponsive to available symptomatic treatment, had side effects to conventional treatment, and had complications of rhinitis (e.g. sinusitis). Treatment failure may occur in patients and this could be due to the poor quality of allergen extracts used in AIT.¹⁹ Sensitisation to minor allergens is also a factor as it may not be available in commercial extracts.¹⁸ Another reason for treatment failure is the lack of clinical relevance of those allergens applied. This is why previous detailed diagnostics are of eminent importance. Hymenoptera AIT is very effective, however a few fatalities have been reported in patients undergoing or following SCIT for Hymenoptera therapy after a field Hymenoptera sting. These usually include patients with other risk factors such as mastocytosis.¹⁰

Allergic Asthma

In allergic asthma, treatment is most effective in those patients who only recently started to perceive asthma symptoms. In patients with allergic asthma, AIT may reduce exacerbation rate²⁰ but care must be taken to ensure optimal asthma control before starting immunotherapy and during maintenance treatment. Patients with severe asthma, uncontrolled asthma, and frequent exacerbations are specifically excluded.

Venom Immunotherapy

Venom immunotherapy is indicated in patients with severe systemic allergic reactions and documented sensitisation. In cases where a milder reaction occurs other factors may have to be taken into account such as availability of healthcare, hobbies (e.g. bee keeping), and comorbidities (e.g. cardiovascular disease and mastocytosis). Large local reactions are not an indication for treatment. In guidelines for children with urticaria alone, immunotherapy is not recommended (risk of SR is 5%). Those patients who had SRs have a much higher risk of experiencing another SR (30–60%) in contrast to those with large local reactions only (5–10%).²¹

Contraindications for starting AIT are cardiovascular disease, severe uncontrolled asthma, treatment

with beta blockers (due to the risk of refractory anaphylaxis), compliance concerns, and pregnancy.^{9,11} Risks and benefits need to be evaluated in these individuals. Uncontrolled asthma remains the most important risk factor for severe adverse events and therefore, effective asthma therapy may need to be established first in order to achieve control before considering AIT. Official guidelines do not provide clear recommendations for this condition.²² In patients treated with beta-blockers the indication of this medication needs to be evaluated; if possible, together with the treating cardiologist or general practitioner. Therapy should be changed to another antihypertensive agent before starting AIT, although temporary discontinuation of a short-acting beta blocker prior to injection may be an option. If the contraindication risks outweigh the benefits for AIT it should be applied with caution and only by trained personnel in a clinical setting equipped for severe anaphylaxis.^{9,11} In cases of a beta blocker therapy, glucagon must be available for treatment of refractory anaphylaxis.^{23,24} On the other hand, the continuation of AIT during pregnancy seems to

be safe if treatment is started before pregnancy.²⁵ Finally risk-benefit needs to be evaluated in special cases; this includes individuals with venom allergy, cardiovascular disease, and beta blocker treatment which cannot be stopped. In these instances, AIT may still begin, but requires thorough monitoring.

MECHANISM

AIT reduces early and late phase responses to allergen challenge in target organs such as nose and lungs as well as to intradermal allergen challenge.²⁶ The immunomodulatory mechanism is complex²⁷ and several immunological effects have previously been described (Figure 1).²⁷

When AIT is administered, a decrease in the susceptibility of mast cells and basophils is observed very early on in the process (for example, in AIT to Hymenoptera venom, a decrease is observed in the first 6 hours during the build-up phase). An upregulation of histamine Type 2 receptors with a suppression of FcεRI-induced activation of basophils has been proposed as a mechanism.^{27,28}

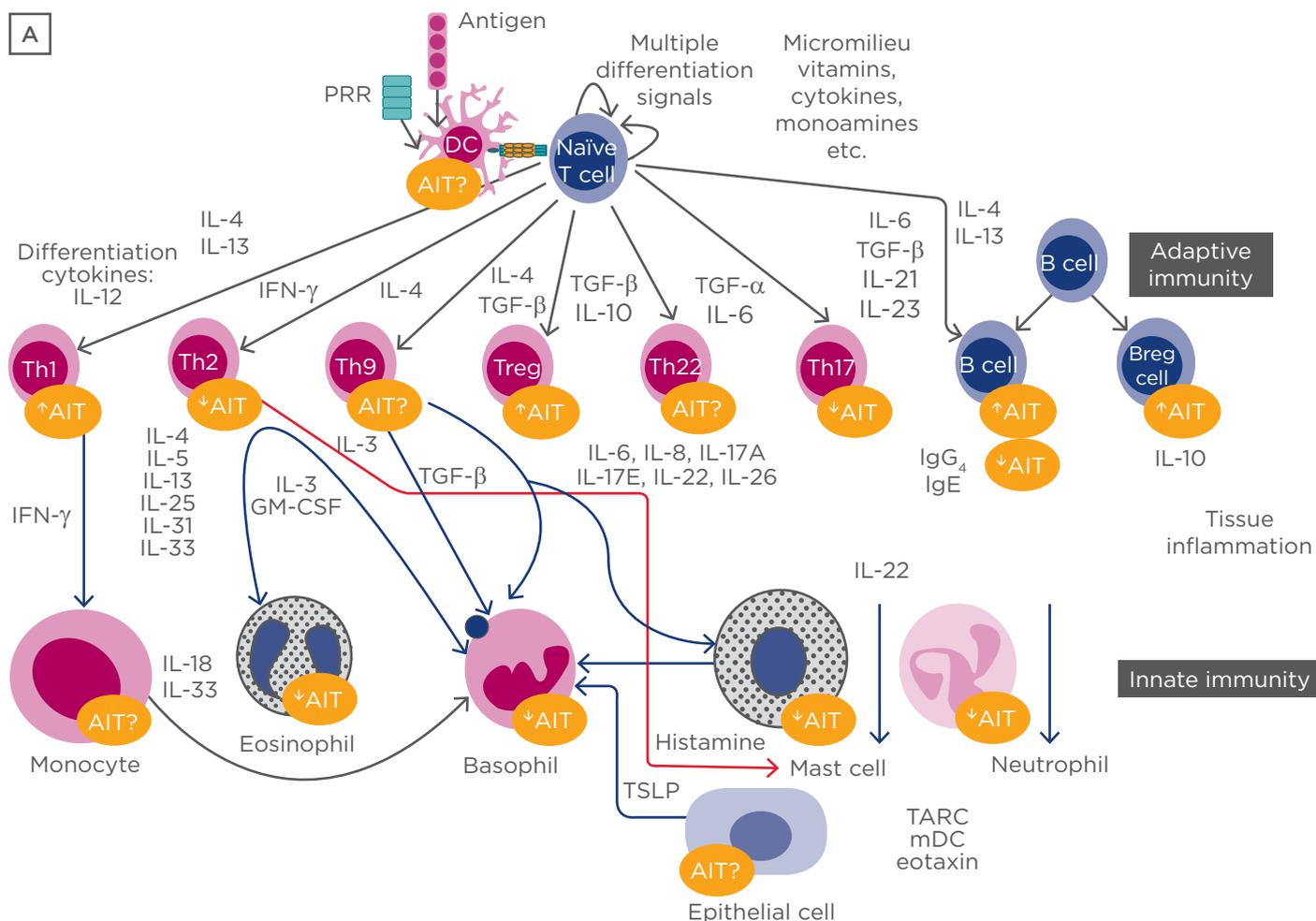


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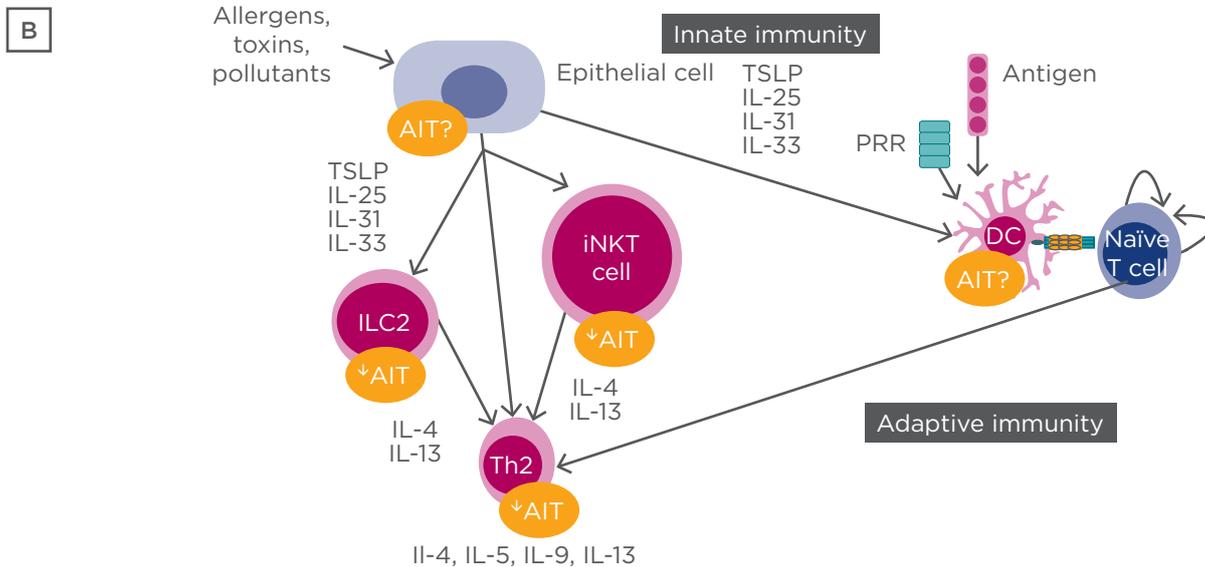


Figure 1: Cellular and molecular changes during AIT.²⁷

A) Differentiation of naïve T cells after allergen presentation in the presence of innate immune response substances that trigger PRR and vitamins, monoamines that control cellular differentiation, and coexposed substances with the antigen and status of the cells and cytokines in the microenvironment is shown. Naïve T cells can differentiate into Th1, Th2, Th9, Th17, and Th22 cells. Based on their respective cytokine profiles, responses to chemokines, and interactions with other cells, these T cell subsets can contribute to general inflammation. The increase in Th1 and Treg cell numbers plays a role in counterbalancing other effector cells. The balance between allergen-specific effector T cells (particularly Th2 cells) and IL-10-producing Treg cells is decisive for the development or suppression of allergic inflammation. Treg cells and their cytokines suppress Th2 immune responses and contribute to the control of allergic diseases in several major ways. Similarly, induction of IL-10-producing Breg cells plays an essential role in suppression of IgE and induction of IgG₄.

B) The suppression of peripheral ILCs, especially ILC2s, may contribute to Th2 suppression and immunologic tolerance induced by AIT.

AIT: allergen-specific immunotherapy; Th: T helper; Treg: allergen-specific regulatory T cells; Breg: regulatory B cells; IL: interleukin; ILC: innate lymphoid cells; iNKT: invariant natural killer; TSLP: thymic stromal lymphopoietin; PRR: pattern recognition receptors; IFN- γ : interferon gamma; TARC: thymus and activation-regulated chemokine; mDC: macrophage-derived chemokine; DC: dendritic cell; GM-CSF: granulocyte-macrophage colony-stimulating factor; Ig: immunoglobulin; TGF: transforming growth factor.

In the process of building up immune tolerance over time, T cell and B cell tolerances are induced. A particular target of AIT is the suppression of Type 2 immune cells (T helper 2 [Th2] cells, Type 2 innate lymphoid cells, and Type 2 cytotoxic cells) which normally produce interleukin (IL)-4, IL-5, and IL-13 with an induction of inflammation by mast cell, basophil, and eosinophil activation (Figure 1B).^{29,30} AIT generates, likely via involvement of dendritic cells and possibly other antigen-presenting cells, allergen-specific regulatory T (Treg) cells, while Th2 cells decrease²⁷ (Figure 1). Tregs, which are identified through high surface expression of CD4+CD25+, produce IL-10 which promotes IgG₄ switching and blocks IgE-facilitated antigen presentation by B cells^{26,31} (Figure 1A). Inhibition of Th2 cytokines such as IL-4 inhibits Th2 cell development and

B cell switching to IgE switching. Inhibition of IL-5 leads to downregulation of eosinophil activation and survival in tissues.³² Production of tumour growth factor beta from Tregs is promoted, which induces B cell switching to IgA at mucosal surfaces.¹⁰ A transient increase in specific IgE is observed early after start of therapy with blunting of seasonal increases.²⁶ As IgG₄ plays a key role in tolerance development further examinations of its affinity and specificity have taken place. It appears that during long-term administration the avidity and/or affinity of IgG₄ increases such that it becomes more efficient in competing with IgE for allergen binding, thereby blocking IgE-dependent functions such as basophil activation and IgE-facilitated antigen presentation.³³

Table 2: Factors associated with adverse reactions or more severe adverse reactions to allergen-specific immunotherapy.^{9,37,38,57}

- Uncontrolled asthma
- Dosage errors
- Induction phase of treatment
- Erroneous intravenous injection of dose
- Previous symptomatic reaction
- Extreme sensitivity to allergen
- Change to a vial of a new batch during maintenance therapy
- Pollen season
- Febrile illness
- Beta blocker
- Angiotensin-converting enzyme inhibitor (especially in venom allergy)

EFFICACY

AIT is effective in allergic rhinitis, allergic conjunctivitis, allergic asthma, and hypersensitivity to stinging insects.⁹ It is likely that children will respond better than adults due to their shorter disease duration.¹⁰ In contrast to symptomatic treatment, AIT has the potential to modify the pathophysiological mechanism of allergic disease leading to a sustained effect even after stopping treatment.³⁴

SCIT has proven to be effective in treating allergic asthma, leading to an improvement in asthma symptoms and reduced medication. It has been estimated that it is necessary to treat three patients (95% confidence interval [CI]: 3-5) in order to avoid one's deterioration in asthma symptoms.²⁰ In seasonal allergic rhinitis, SCIT led to a significant reduction in symptoms (standardised mean difference [SMD]: -0.73; 95% CI: -0.97 to -0.5, $p < 0.00001$) and medication score (SMD: 0.57; 95% CI: -0.82 to -0.33, $p < 0.00001$).¹⁶ In Hymenoptera allergy SCIT is the treatment of choice. Following SCIT, the rate of effective protection against a SR after a wasp sting is 95-98% and after a bee sting it is 80-85%.^{13,21}

In a recent meta-analysis for SLIT a significant reduction in symptoms (SMD: -0.49; 95% CI: -0.64 to -0.34, $p < 0.00001$) and medication requirements (SMD: -0.32; 95% CI: -0.43 to -0.21, $p < 0.00001$) were seen in allergic rhinitis patients.³⁵ It has been shown to be efficacious and safe including induction of long-term remission for allergic rhinitis.³⁶ In allergic conjunctivitis SLIT induced a significant reduction in ocular symptoms (SMD: -0.41;

95% CI: -0.53 to -0.28).³⁷ According to a recent review, data for asthma outcomes in studies with SLIT is lacking, thus more research is necessary before a conclusion can be drawn in regards to efficacy and safety.³⁸

Both SCIT and SLIT are effective therapies with evidence stronger in seasonal compared with perennial disease and stronger in adults compared with children.³⁹ Indirect comparison between the two treatments has been controversial.³⁹ Data on efficacy may favour SCIT whilst data on tolerability and safety favours SLIT. However, adequately powered, randomised, placebo-controlled, head-to-head trials are still needed.³⁹

OTHER POSSIBLE INDICATIONS

A possible indication for AIT is atopic dermatitis in a patient sensitised to aeroallergens. In a recent meta-analysis authors found limited evidence that AIT may be an effective treatment for atopic dermatitis although further research is required.⁴⁰ Immunotherapy for food allergy has been studied but is not established in general clinical practice. Current meta-analyses indicate that oral immunotherapy for peanuts cannot be recommended for routine practice. Even though it may result in desensitisation, long-term tolerance appears unlikely and the risk of SRs substantial, at least with the currently available methods.⁴¹ Similar results were found for oral immunotherapy in milk,⁴² egg,⁴³ and fruit allergies.⁴⁴ AIT for latex has also been under investigation; both SCIT and SLIT treatment was effective overall even though SCIT was accompanied by the frequent occurrence of side effects, while SLIT was better tolerated. Guidelines do not consider allergy to latex as an indication to desensitisation.⁴⁵

SAFETY

The application of allergens to an IgE-sensitised patient inevitably carries the risk of an anaphylactic reaction. Adverse reactions to SCIT and SLIT are graded according to World Allergy Organization (WAO) guidelines.^{14,46} According to safety recordings in the USA over the previous 50 years, one death per 2.5 million injections and one near-fatal reaction per 1 million injections occurs in SCIT.^{20,47} In a recent report gathering data from 2008-2013, a total of four fatalities were reported in 28.9 million injection visits.⁴⁸ Additionally, 1.9% of patients experienced SRs (0.08% and

0.02% experienced Grade 3 and 4, respectively). The frequency of SR (any severity) was one in nine patients in a meta-analysis examining trials in patients with asthma.²⁰ SRs occurred in 1.4% of patients receiving SLIT tablets including 0.03% Grade 3, but without Grade 4 reactions or fatalities.⁴⁸ In Europe, since the famous report about several fatalities after SCIT in 1986,⁵ fatalities have become rare and none have been reported in the last decade in Europe.²⁴ This is due to better knowledge and considerations of risk factors (Table 2) and improved adherence to practice parameter guidelines.⁹

Uncontrolled asthma remains a key risk factor for Grade 3 and higher SRs and lowering doses during the pollen season for highly positive skin tests reduced SRs in general ($p < 0.05$).⁴⁸ Fatalities occurred during the first hour after SCIT and in situations where adrenaline was not readily available. This emphasises the need for patient education and monitoring of asthma before injection, adequate post-injection time, supervision in a facility with trained staff, appropriate equipment for resuscitation, and readily available adrenaline for application.⁴⁸ Patients should be observed between 30 minutes (USA, most parts of Europe)⁹ and 60 minutes (UK).

MANAGEMENT OF ADVERSE REACTIONS

Personnel should be trained to treat anaphylaxis and have appropriate treatment available. Most importantly, this includes adrenaline (1 mg/mL for injection; 0.3 mL intramuscularly is indicated in anaphylaxis), antihistamine (e.g. 1 x clemastin 2 mg/mL intravenously), corticosteroids (e.g. 1 x 250 mg methylprednisolone intravenously), inhaled bronchodilator (e.g. 1 x 100–200 µg salbutamol), intravenous supplies (e.g. normal saline for infusion as needed), and oxygen and suction equipment. The most important immediate intervention is adrenaline.

NOVEL APPROACHES

Novel treatments are currently under investigation in order to increase efficacy and reduce SRs of immunotherapy. Anti-IgE (omalizumab) has been used as an add-on therapy to increase both efficacy⁴⁹ and tolerability⁵⁰ with a dramatic reduction of SRs. Costs have to be considered and therefore omalizumab remains a treatment option only in selected cases. Another strategy to increase efficacy and safety of AIT is the

use of an adjuvant. An example is bacterial immunostimulatory DNA sequences (such as immunostimulatory oligodeoxynucleotide sequences [ISS-ODN]) which are potent adjuvants to induce a strong Th1 response.⁵¹ Allergen ISS-ODN in particular has shown encouraging results in inducing immunomodulation with reduced SRs in patients with ragweed sensitisation.⁵² Furthermore, research has been performed in molecular vaccines including recombinant allergens, recombinant allergen derivatives, and synthetic peptides in order to increase safety and efficacy of AIT with the aim of developing a preventive allergy vaccination.⁵³ In cat allergy for example, the use of short synthetic peptides which represent major T cell epitopes of the allergen have shown efficacy and tolerability with reduced ability to cross-link IgE as well as activate mast cells and basophils, thus avoiding IgE-mediated reactions.⁵⁴

Finally, other routes of application apart from the well-established subcutaneous and sublingual route have received attention recently. One is the epicutaneous route, where an allergen is applied to the non-vascularised tissue. Clinical efficacy has been demonstrated in aeroallergy.⁵⁵ Furthermore, a reduction of food-induced anaphylaxis and an induction of Tregs has been demonstrated in mice.⁵⁶ Additionally, the intralymphatic application of AIT may offer an interesting alternative. Efficacy and immunomodulation have been demonstrated in a study of 165 participants with only three injections in 8 weeks without SRs.⁵⁷ Intralymphatic immunotherapy is already being practiced in certain centres and a European Academy of Allergy and Clinical Immunology (EAACI) interest group has been established.

PHARMACOECONOMICAL CONSIDERATIONS

Insufficiently treated allergies cause a substantial direct and indirect economic impact ranging from €55–€151 billion per annum due to absenteeism and presenteeism.⁵⁸ Available treatment options are associated with different levels of cost-effectiveness and recommendations such as the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines have called clearly for the demonstration of cost-effectiveness of treatment.⁸ A recent review comparing AIT with symptomatic treatment has shown evidence for cost savings from 6 years onwards for both SCIT and SLIT compared with standard symptomatic treatment

in respiratory disease.⁵⁹ Two main forms of economical evaluation have been performed in AIT. Cost-effectiveness studies addressed costs in monetary units and effects in physical units (e.g. symptom reduction), while cost-utility studies analysed the effect of treatment in health-related quality of life (e.g. quality-adjusted life years). Both cost-effectiveness and cost-utility studies⁶⁰⁻⁶⁹ have been performed in SCIT and SLIT and most studies have confirmed cost-effectiveness for AIT in comparison with standard pharmacological treatment. AIT has the potential not only to decrease healthcare costs (doctor's visits and drug use) but also indirect costs including decreased loss of work days, especially in the long-term.²⁷ Unfortunately there is a lack of generalisability due to heterogeneity between studies.

CONCLUSIONS

AIT remains the only treatment that modifies the underlying causes of allergic disease with resulting long-term remission. The use of standardised

allergens in which efficacy has been proven is recommended. Many products still lack adequate quality control and confirmation of efficacy, in particular allergen mixtures, which should be addressed in future research. The two main forms of application, SCIT and SLIT, have both been shown to have good efficacy and safety in allergic rhinitis. At present the choice between SCIT and SLIT depends largely on patient preference as adequate head-to-head trials are missing. Evidence in children for both application forms is weaker and should be further evaluated. SCIT is indicated in allergic asthma and Hymenoptera venom allergy. It may also be desirable to find alternative and possibly safer routes of applications for these indications. Further research needs to be performed in order to broaden the spectrum of indications to prevalent diseases such as atopic dermatitis and food and latex allergies. Finally, new treatment approaches are encouraging but need to be further evaluated in controlled clinical trials. More data on cost-effectiveness, especially in regards to long-term tolerance, remains an important goal.

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