Review Article

ALLERGY IMMUNOTHERAPY UPDATE

Tamara Jaye | MBBCh, DCH, Dip Allerg
Milpark Allergy, Netcare Milpark Hospital
Email | tamara.jaye@gmail.com

ABSTRACT

Allergy immunotherapy has recently been reviewed and the latest recommendations were published by the European Academy of Allergy and Clinical Immunology in 2018. This article summarises these recommendations. This therapy is an effective form of treatment for allergic conditions such as allergic rhinoconjunctivitis, allergic asthma, and bee and wasp hypersensitivity. A formal diagnosis of an allergy (ie the presence of both a convincing clinical picture and confirmation through skin-prick testing or allergen-specific IgE), is necessary for allergy immunotherapy to be initiated. Patients should be considered on a case-by-case basis, with various factors being examined prior to this therapy: their current allergy treatment, compliance, long-term treatment goals and co-morbid health problems. Standardised allergy immunotherapy products administered at regulated doses is the current recommendation and long-term allergy protection is possible with extended treatment. Allergy immunotherapy for food allergies is subject to extensive research, the latest guidelines suggesting that this should be administered only within research settings at this stage. In cases of atopic dermatitis, this therapy has its place in the treatment of aeroallergens. South Africa has a number of standardised allergy immunotherapy products available which are used countrywide. The most common allergens treated in South Africa are grass, house-dust mite and hymenoptera bee stings

INTRODUCTION

In 1911, Englishman Leonard Noon published a paper in *The Lancet* that described the use of prophylactic inoculations for Timothy Grass pollen in patients with hay fever. His results were the first which showed that allergic symptoms could be treated successfully with this regimen.[1] After 108 years, this form of treatment is essentially still being used by allergists throughout the world.

Allergy immunotherapy (AIT) is currently the only form of disease-modifying treatment available for allergic conditions.[2,3] It is largely effective for treating asthma, allergic rhinitis (AR), allergic conjunctivitis and bee and wasp venom allergy.[4] It is available internationally as subcutaneous injections (SCIT) and sublingual immunotherapy (SLIT) in tablet form, perlingual spray and sublingual drops.[5]

The pathophysiologic changes that occur as a result of immunotherapy involve the lymphocyte profile shifting from a Th-2-predominant pathway into an allergen-protective Th-1 pathway. The result of this change is that Th-2 inhibits the production of various cytokines such as interleukins 4, 5 and 13. Interferon gamma and IL-12 also increase. The regulatory T lymphocytes (Treg) are activated with increased production of IL-10 and transforming growth factor beta. Immunoglobulin E (IgE) increases initially following therapy; thereafter, a decrease is observed, with an associated shift of IgG1 into IgG4 and IgA. There is a consequent inhibition of eosinophils, mast cells and basophils. Whether the immunotherapy is administered through a subcutaneous or a sublingual route, a similar immunological picture emerges.[3]

However, many treatment challenges still exist in the allergy world. The variety of products available, definition inconsistencies and conflicting outcomes of research can make the approach to using AIT potentially confusing for the practising allergist.[6] Uncertainty surrounds the long-term benefits of AIT, its safety in young children, the challenge of the polysensitised patient and using AIT as prophylaxis.[6,7] In order to respond to these issues, several guidelines have recently been published which use evidence-based clinical research to provide the current gold standard in AIT.[5,8,9,10]

PATIENT CONSIDERATIONS

Before initiating immunotherapy, these matters should be discussed with the patient and their family: the various available options such as SCIT vs SLIT, the disadvantages, the side-effects of the medication, adherence to treatment and the cost.[5]

Immunotherapy should be considered only in allergic patients who have a clinically significant allergy.[5] This means that the allergy symptoms should present soon after an exposure to the allergen, and the presence of IgE to the allergen must be proved, either through a positive skin-prick test (SPT) or an IgE-specific allergen test.[5] Importantly, the guidelines suggest that only clinically efficacious standardised AIT products at standardised doses should be prescribed.[6]

Immunotherapy is usually instituted only after appropriate measures to reduce allergen exposure and the correct use of pharmacotherapy have been tried.[5] Pharmacotherapy usually works much more quickly than immunotherapy in relieving allergy symptoms and is often very effective at reducing allergic symptoms. The efficacy of immunotherapy, in comparison, is often evident only after several months of treatment, although studies show that both SCIT and SLIT are able to reduce allergy symptoms within the first year of initiating therapy.[5] When counselling the patient and their family, it is important to emphasise that immunotherapy is a commitment, in terms of both time – as it needs to be taken regularly for several years – and cost.[6]

A number of indications for the use of AIT on an allergy patient are possible. After inadequate control with pharmacological means, SCIT or SLIT can be initiated to treat moderate to severe AR in cases of inadequate control using pharmacotherapy. In these cases, a three-year course is suggested.[5] This has been shown to be advantageous for up to two years and, in some cases, even longer after treatment, as illustrated by the Preventive Allergy Treatment (PAT) study.[5] In this study, children were followed up ten years after they had received a three-year course of subcutaneous immunotherapy with a standardised allergen extract for birch pollen or grass extracts.[18] The results confirmed immunotherapy to be a first-line treatment for the cure of allergies.[18] The clinical symptoms of seasonal rhinoconjunctivitis were no longer evident following cessation of immunotherapy after three years, and these benefits persisted long term.[18] Importantly, this study also showed that AIT had a protective effect against the development of asthma in this population of children. Therefore it offers the added benefit as a secondary preventive treatment for respiratory allergic disease.[18]

Other reasons to consider the use of AIT include:
- the cost of the patient's chronic allergy medications, especially if multiple drugs have been required for symptomatic relief;
- the side-effect profiles of these medications;
- non-compliance and the suboptimal use of symptomatic medications or medication-delivering devices such as asthma pumps or nasal sprays.[5]

Immunotherapy might also be considered as an option in cases of moderate to severe AR when other measures are optimally in place but the patients' daily functioning and sleep are still affected.[5]

The current recommendations suggest that SCIT and the initial SLIT dose should be administered by trained medical staff, and that patients should be monitored for 30 minutes post-administration of the AIT drug before being discharged.[5]

SAFETY OF IMMUNOTHERAPY

AIT is generally well tolerated and safe when given to carefully selected patients. however, both local and systemic reactions may occur with this therapy.[10] Following subcutaneous administration of AIT, the area may become swollen and red. Severe reactions include anaphylaxis, the reported incidence being between 1% and 4%.[10] The signs and symptoms of anaphylaxis vary and may involve the skin, the gastrointestinal or respiratory systems, and/or the cardiovascular or neurological systems.[10] The symptoms generally present within 30 minutes of exposure to the immunotherapy.[10] Adrenaline is the medication of choice, and anti-histamines, bronchodilators and corticosteroids may be used as adjunctive therapies.[10] SLIT has had no reported cases of anaphylaxis in an estimated one billion doses that have been administered.[19] Reactions to SLIT that have been reported are often localised, with oromucosal pruritis being the most common.[19] This generally occurs at the initiation of immunotherapy and settles down within a few days of treatment without any further medical management being required.[19]

CONTRAINDICATION FOR IMMUNOTHERAPY

Certain medical conditions such as severe asthma, autoimmune disease, HIV and pregnancy are relative contraindications for immunotherapy.[8,10]

In high-risk venom patients who have cancer or a history of cancer, for example, the guidelines suggest that immunotherapy may be initiated if the cancer is well controlled or in remission.[8] Autoimmune disease may be an absolute or a relative contraindication for hymenoptera immunotherapy.[8] It is a relative contraindication if the autoimmune disease is in remission; however, it is an absolute contraindication if the disease is active.[8] In addition, although data are lacking, a hypothetical risk does exist that immunosuppressive medication may interfere with the AIT.[8] Immunotherapy can be safely used in stable organ-specific autoimmune disease such as Crohn's or Hashimotos thyroiditis.[8] In mastocytosis, venom immunotherapy is recommended; however, these patients will often require a prolonged course.[8] Although immunotherapy is generally well tolerated in people with mastocytosis, these patients may have a greater chance of developing a reaction to immunotherapy.[8]

Severe cardiovascular disease is considered to be a relative contraindication for AIT; however, the guidelines recommend that even in an elderly patient with cardiovascular disease, venom immunotherapy may be advised.[8] The reason for this is that the symptoms following a sting may well be more harmful to the patient than the potential adverse effects of immunotherapy.[5,8]

Beta blockers have been associated with serious and treatment-associated anaphylaxis and so their presence as part of the patient's current treatment regimen would be considered to be an absolute contraindication for aeroallergen immunotherapy.[10] However, in life-threatening stinging-insect hypersensitivity, beta blockers would be considered only a relative contraindication for hymenoptera immunotherapy because the greater risk of a fatal outcome following a sting outweighs the possible side-effects of the immunotherapy.[8,10]

Regarding the age cut-offs for AIT, the age of the patient needs to be assessed in the context of the immunotherapy.[10] The paediatric population requires further well-designed research and so the age at which to initiate immunotherapy has been arbitrarily recommended to commence from six years of age

and onwards.[10] In the paediatric population, severe systemic reactions to stinging insects are not common in very young children. Therefore, there is not a great need for AIT in this age group. However, if necessary, venom immunotherapy can be used, and the recommendations in these cases would then be the same as those for adults.[8] Another reasonable indication for AIT in young children might be in milder cases of allergy, the aim there being the prevention of long-term effects of AR as well as possible prophylaxis to prevent the development of asthma.[5,10]

The use of AIT in elderly patients needs to be considered individually, taking into account various factors, such as age, co-morbid illness and the extent of the allergy.[10]

In pregnancy, immunotherapy appears to be safe; however, empirical data are scarce. The current recommendation, therefore, is not to initiate therapy in pregnancy.[6] However, if a patient is already receiving treatment, the maintenance dose can be continued.[6]

TABLE I: CONTRAINDICATIONS FOR AND SPECIAL CONSIDERATIONS OF AIT USE

Contraindications for AIT use	Uncontrolled/severe asthma Beta blockers for aeroallergen immunotherapy Severe cardiovascular risk for aeroallergen treatment Active autoimmune disease Active malignancies
Special considerations for AIT use	Elderly Children under six years old Pregnancy Beta blockers for venom immunotherapy Cardiovascular disease in venom immunotherapy

ALLERGIC RHINITIS

It would be reasonable to consider the use of immunotherapy in adults, as well as in younger children, for the treatment of symptoms affecting daily functioning and sleep, the prevention of long-term effects of AR, and as a form of prophylaxis to prevent disease-allergic progression.[5] Most patients with AR are polysensitised, and the current guidelines suggest that if a patient is polysensitised to homologous allergens – for example, two different grasses – a single preparation of the two allergens can be given.[11] Current data have suggested that poly-allergic patients with allergens that are unrelated may be given two separate immunotherapy preparations 30 to 60 minutes apart in different locations on the body.[5]

VENOM IMMUNOTHERAPY

Venom immunotherapy is indicated for moderate-to-severe systemic reactions.[8] It can, however, also be used effectively in adults with skin involvement only if this has an impact on their quality of life (QoL).[8] H1 antihistamines as pre-treatment have been found to improve tolerability of the immunotherapy by reducing both large local and severe systemic reactions.[8] The effectiveness of the immunotherapy is unchanged with these medications.[8]

Various protocols exist for venom immunotherapy scheduling.[8] These include up-dosing followed by maintenance schedules (which take several weeks to months to reach maintenance dose) and rush and ultra-rush regimens.[8] Rush immunotherapy is a protocol by which the patient receives daily doses of immunotherapy instead of a dose every few days until maintenance is achieved; ultra-rush protocols take several hours until the maintenance dose is achieved.[8] Considered against side-effect profiles up-dosing and maintenance have been found to be the safest protocols.[8] Immunotherapy given for a minimum of five years has been shown to be superior to shorter courses of immunotherapy; and lifelong therapy should be considered in patients with severe initial systemic reactions, systemic adverse events during venom immunotherapy, and honeybee venom-allergic patients with a high risk of future honeybee stings.[10]

IgE-MEDIATED FOOD ALLERGIES

The current recommendation for food-allergy immunotherapy is that it should be performed only by experienced personnel in research centres or in clinical centres with extensive experience in food-allergy immunotherapy.[6,9] Clinical trials have found immunotherapy to be effective in children from four to five years of age who have experienced clinical allergies to hen's eggs, cow's milk and peanut.[9] Well-designed longitudinal prospective studies are still needed to fill the many knowledge gaps in the use of AIT for IgE-mediated food allergies before Food Allergen Immunotherapy protocols for clinical practice can be finalised and AIT can become standard medical therapy for these conditions.[9]

ALLERGIC CONJUNCTIVITIS

AIT should be considered a treatment option in cases of AR and AR with conjunctivitis, which have proven IgE sensitisation to a single allergen or multiple allergens, and also in the case of moderate-to-severe symptoms despite avoidance measures.[5] Long-term efficacy is commonly achieved after three years of treatment with both SLIT and SCIT.[5]

ECZEMA

The role of immunotherapy in eczema treatment was found to be inconclusive in a number of studies.[12] However, it is effective in the management of house-dust mite (HDM) allergy.[13] A systematic review and meta-analysis of eight studies from Canada showed that immunotherapy decreases symptoms in specific environmental allergies such as birch pollen.[10] From this it appears that immunotherapy is beneficial for AD, specifically those associated with aeroallergens. In addition, despite previous studies, new research seems to suggest that immunotherapy is not associated with eczema flare-ups.[14]

IMMUNOTHERAPY IN SOUTH AFRICA

The kits needed to perform immunotherapy are available in South Africa and enable a variety of allergens to be tested (Immunospec, personal communication). Practitioners using immunotherapy in South Africa include general practitioners, paediatricians and ear, nose and throat (ENT) specialists. Johannesburg has the highest number of patients on immunotherapy, followed by the

TABLE II: PRODUCTS AVAILABLE IN SOUTH AFRICA			
PRODUCT	FORM OF IMMUNOTHERAPY	SCHEDULE	INDICATION
Oraltek	SLIT	No initiation phase	Aeroallergens
Alxoid	SCIT	Initiation and maintenance	Aeroallergens
Venox	SCIT	Initiation and maintenance	Bee sting
Alutek	SCIT	Initiation and maintenance	Alternaria Horse allergy

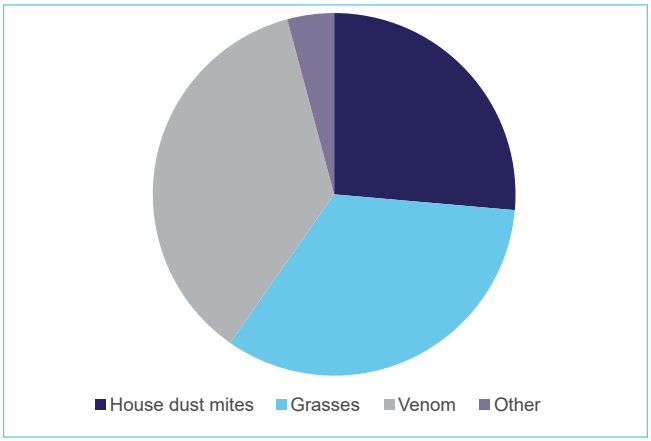

Figure 1: Common allergies treated in South Africa

Western Cape and then KwaZulu-Natal (Immunospec, personal communication).

The most common indications for immunotherapy in South Africa are for grasses, HDM and bee sting. These are followed by cat, dog and mould allergens (Immunospec, personal communication).

THE FUTURE OF ALLERGY IMMUNOTHERAPY

Although we are still using Noon's basic concept of allergen administration to cure allergic disease, some very exciting and promising developments are occurring with allergy immunotherapy.[15] A novel form of immunotherapy – intralymphatic immunotherapy (ILIT) – is currently undergoing investigation. This new method of immunotherapy entails the administration of three ultrasound-guided allergen injections into the inguinal lymph nodes at four-week intervals. The entire course for ILIT is predicted to take only two months. This is in stark contrast to current regimens which estimate that the length of effective treatment is close to three years.[15] Currently, there is limited evidence for its routine use, and no products in this form are available.[15] Epicutaneous immunotherapy (EPIT), another form of AIT which allows allergens to be administered via intact skin, has been used for both milk and peanut allergies. This form of immunotherapy has a favourable side-effect profile and studies are ongoing.[16,17]

These potentially exciting new developments are an indicator that interest and research are alive and well in the field of immunotherapy, and we look forward to what lies ahead. We are hopeful that straightforward and easy-to-administer treatment protocols which will yield effective and long-lasting therapy for the sufferers of these often debilitating conditions are just around the corner. The benefits will be immense.

DECLARATION OF CONFLICT OF INTEREST
The author declares no conflict of interest.

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