**Title: An update on allergen immunotherapy**

***Author:*** *Professor S. Hasan Arshad DM, FRCP*

**From:**

Clinical and Experimental Sciences,

Faculty of Medicine

University of Southampton, UK

**Address for Correspondence**

MP 810, South Block, Southampton General Hospital,

Tremona Road, Southampton, United Kingdom

Email: [sha@soton.ac.uk](mailto:sha@soton.ac.uk)

**Conflict of interest statement:** The author has recently attended an advisory board meeting for Allergy Therapeutics, a manufacturer of allergen immunotherapy products

**Manuscript (An update on Allergen Immunotherapy)**

The use of allergen specific immunotherapy to modify the natural course of established disease is unique to allergy medicine among non-communicable diseases. The aim is to induce tolerance to the causative allergen and as a result induce long-term disease remission. This strategy has been successfully used in allergic rhinitis, asthma, venom and drug allergy and, most recently, food allergy and atopic dermatitis have been the focus of research.

Allergen immunotherapy (AIT) was first used to treat hay fever in 1911 at St. Mary’s Hospital, London. It became popular in the developed world in the post-world war era. Significant progress has been made in the quality and standardization of allergen extracts, and evidence has accumulated regarding its efficacy and safety. With these attributes it is startling to see how underused this treatment remains. In the UK, it is largely confined to specialist centres and offered to a small fraction of patients who could potentially benefit. There is a lack of awareness of AIT not only in the general population but also among physicians. The Royal College of Physicians has produced several reports describing allergy as an unmet need.1 Subsequently, allergy was approved as a distinct discipline with specialist training, which has resulted in increasing use of AIT.

**Methods of administration:** AIT is usually administered as subcutaneous injections (subcutaneous immunotherapy or SCIT) or sublingual immunotherapy (SLIT).

Although a number of variations in the protocol exist, traditionally SCIT is given at weekly intervals until a maintenance dose is reached (usually 4-6 months) and then at 4-8 weekly intervals for 3-5 years (Table 1). The treatment is given by trained personnel in outpatient clinics or day centres, where facilities are available to manage rare occurrence of systemic reactions or anaphylaxis.2 SCIT should not be given to those with poorly controlled asthma or significant cardiovascular disease as the risk of adverse reaction is higher.3

SCIT is associated with the use of significant healthcare resources and inconvenience for the patient given the need for multiple hospital visits and the long duration of therapy. Rush or cluster protocols have been developed with the aim of reducing the up-dosing duration from months to weeks or even days and have generally been shown to be safe and effective; however, their use remains limited.4

SLIT has become popular since the 1990s.5 Sublingual drops, spray or dissolvable tablets of allergen extract are administered once a day (at home) for 3-5 years. A major advantage being the very low risk of systemic reactions and, as a result, the convenience of SLIT being administered at home and the ability to use this even in young children (Table 2).

Both SCIT and SLIT can cause local or systemic reactions. Swelling and redness at the injection site in SCIT and oral itching and tingling in SLIT are common local adverse effects. Systemic reactions are uncommon.3,6 In SCIT, mild to moderate systemic reactions occur in approximately 0.1%, while severe reactions are rare (1 in 1 m injections). Systemic reactions in SLIT are extremely rare.7

**Efficacy:** Most systematic reviews reached the conclusion that both SCIT and SLIT are effective in improving symptoms and quality of life and need for medication.8 A major advantage is that the effect persists for years after completion of treatment. This has been well documented for SCIT to pollen, for allergic rhinitis,9 and house dust mite extract, for both allergic asthma and rhinitis.10 Similar evidence is accumulating for SLIT.11. A recent study using house dust mite sublingual extract in allergic rhinitis demonstrated remission for 7-8 years.11 Topical steroid is an inexpensive, effective and relatively safe treatment for most allergic conditions; hence, the cost-effectiveness of AIT is often questioned. However, despite its higher cost in the short term, most studies indicate significant cost-savings and improvement in quality of life in the long term.12

Allergic patients are often sensitised to several allergens. That does not preclude AIT to a single relevant allergen. For example, a patient could be effectively given AIT using grass pollen extract for severe hay fever, ignoring other allergen sensitisation.13 AIT using mixed allergens is also possible but evidence regarding their efficacy is less clear.13 A number of factors influence efficacy and safety e.g. if all allergens are clinically relevant, that they can be mixed in a single solution and that their potencies are cumulatively safe to administer and yet individually high enough to be effective.

**Mechanisms of action:** Although the exact mechanisms remain uncertain, following AIT, inflammatory cells such as mast cells, basophils and eosinophils become unresponsive to allergens. This is mediated through the induction of “T regulatory cells”, inhibiting allergy promoting “T helper-2” cells.14 Further, B cells produce IgG4 antibodies, which bind to the allergens without initiating a reaction, thus acting as ’blocking antibodies’.14

**Indications:** The management of allergic conditions includes avoidance of allergen (if possible), pharmacotherapy and immunotherapy (Figure 1). AIT is commonly used for pollen, insect venom, house dust mite and animal dander allergy. Its use for mould and cockroach allergen is less well documented. Patients are selected based on an allergy focussed history and evidence of sensitisation on skin prick test or blood test (measurement of specific IgE to the suspected allergen). For example, a patient with severe seasonal hay fever symptoms and positive skin test to grass pollen would be a suitable candidate.

**Allergic conditions with potential use of AIT:**

**Allergic Rhinitis:** AIT should be considered in patients with moderately severe allergic rhinitis who do not respond adequately to standard pharmacotherapy such as antihistamines, steroid nasal spray and eye drops.3 These patients suffer from severe symptoms and their quality of life and work is so adversely affected that they may have to resort to systemic steroids. Standardised allergen extracts are available for grass and tree pollens, house dust mites and animal dander. Mixes of grass and tree pollens can be used, which are generally effective against common types of pollens in the local environment.

For seasonal allergic rhinitis, SCIT to grass and/or tree pollen can now be administered as four pre-seasonal (January to April) injections at 1-2 weeks intervals, and hence there is no need to maintain treatment all year round.15-17 Thus, it significantly reduces health care cost in terms of repeated administration of injections and it is convenient to the patients.

**Asthma:** Recent systemic reviews confirm efficacy of AIT, including a steroid-sparing effect, in allergic asthma.18 Although both SCIT and SLIT are effective in reducing symptoms and medication requirement, SCIT is more effective than SLIT. In the UK, AIT is rarely used for asthma, partly because of the risk of adverse reaction with SCIT in uncontrolled asthma and partly because of the lack of evidence for its cost-effectiveness, given currently available effective treatments for asthma.

**Atopic dermatitis:** There is some evidence of efficacy of both SCIT and SLIT using house dust mite extracts in mild-to-moderate atopic dermatitis, achieving better control of disease and reducing objectively defined scores for severity and extent of eczema.19 However, current use in the UK and throughout the world remains limited because of the lack of evidence from large randomised controlled trials.

**Venom Allergy:** Bee and wasp allergy can cause anaphylaxis (and occasionally death). AIT is recommended to prevent further allergic reactions in those who have had a severe reaction, are sensitised and there is risk for further stings e.g. in bee keepers or gardeners. A recent meta-analysis confirmed its effectiveness in preventing further allergic reactions with improvement in quality of life.20 The treatment is usually given using SCIT to the relevant allergen (bee or wasp) for 3-5 years.

**Drug Allergy**: Drug allergy is an adverse reaction to the drug mediated by an immunological mechanism. The most pragmatic approach is to avoid the drug in question and use an alternative. When this is not possible (e.g. with insulin), desensitisation is possible to allow safe use.

**Food Allergy**: AIT for food allergy such as to cow’s milk, egg and peanut has been investigated using raw or heat modified proteins. Children often tolerate the food when given in gradually increasing amounts so far as they continue to consume the food on a daily basis.21 However, adverse reactions are relatively common and the tendency to react to the food reappears if daily consumption is not maintained. AIT to food remains in the research arena.

**Prevention of development of allergy:** AIT may prevent development of new sensitisations. Taking this forward, a recent small study administered house dust mite SLIT extract to infants who were at risk of development of allergy (due to parental history), but have not yet acquired allergic sensitisation. The treatment prevented development of allergic sensitisation.22 This may lead to a new indication of AIT with the potential of reducing increasing prevalence of allergic disease. However, large randomised controlled trials are required.

**Future use of AIT:** Research is being conducted to individualise AIT, using recombinant antigen technology, to produce allergen extract against specific proteins to which the patient is allergic, rather than the whole allergen. Another approach is to produce extracts using modified proteins or peptides that may increase safety and efficacy. Use of adjuvants to stimulate the immune system to enhance protective immune response is being developed; one example of this is Pollinex Quattro, mentioned above. These approaches have the potential of reducing length of treatment, while improving safety and efficacy.

**Key messages:**

* Seasonal allergic rhinitis and venom allergy are the two most common clinical indications for the use of allergen immunotherapy in the UK
* It is less commonly used for perennial allergic rhinitis due to house dust mite allergy and only in selected cases of asthma
* Systemic allergic reactions to allergen immunotherapy are extremely uncommon in the hands of an expert
* Increasing confidence in the safety and efficacy of sub-lingual immunotherapy has made allergen immunotherapy more feasible
* The use of allergen immunotherapy in atopic dermatitis and food allergy is a research focus but as yet not in common clinical use

**Key words:** Allergen, Immunotherapy, Asthma, Rhinitis, anaphylaxis, pollen, house dust mite, Immunoglobulin E

**CME Questions:**

**Q1: Which of the following management strategy for allergic disease has been shown to influence the natural course of the disease?**

1. Patient education
2. Allergen avoidance
3. topical Steroids
4. Allergen specific Immunotherapy
5. Antihistamines

**ANSWER: d)** Allergen specific immunotherapy is the only treatment that has been shown to influence the natural course of allergic diseases, such as allergic rhinitis and asthma with long term remission. Other treatment modalities are effective in reducing symptoms and/or controlling inflammation while the treatment continues but the disease recurs as soon as the treatment is stopped.

**Q 2: In the UK, allergen Immunotherapy is used in the treatment of which of the following condition?**

a) Latex allergy

b) Atopic dermatitis

c) Allergic rhinitis

d) Idiopathic anaphylaxis

e) Food allergy

**ANSWER: c)** Allergen specific immunotherapy is used for seasonal allergic rhinitis due to pollen allergy and less commonly for perineal allergic rhinitis due to house dust mite or pet allergies. It is not used clinically for atopic dermatitis or food allergy except within the confines of a clinical trial. Latex allergy is managed with avoidance and use of alternative material and not with allergen immunotherapy. In idiopathic anaphylaxis (as the name indicate) the cause factors is unknown and hence allergen immunotherapy is not indicated.

**References**

1. Lee TH. Allergy: the unmet need. Clinical medicine (London, England) 2003;3:303-5.

2. Walker SM, Durham SR, Till SJ, et al. Immunotherapy for allergic rhinitis. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 2011;41:1177-200.

3. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: A practice parameter third update. Journal of Allergy and Clinical Immunology 2011;127:S1-S55.

4. Tabar AI, Echechipía S, García BE, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with Dermatophagoides pteronyssinus. Journal of Allergy and Clinical Immunology 2005;116:109-18.

5. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organization Journal 2014;7:1-52.

6. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008-2012: an update on fatal and nonfatal systemic allergic reactions. The Journal of Allergy and Clinical Immunology: In Practice 2014;2:161-7. e3.

7. Cox LS, Linnemann DL, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: A comprehensive review. Journal of Allergy and Clinical Immunology 2006;117:1021-35.

8. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. Journal of Allergy and Clinical Immunology 2015;136:556-68.

9. Durham SR, Walker SM, Varga E-M, et al. Long-Term Clinical Efficacy of Grass-Pollen Immunotherapy. New England Journal of Medicine 1999;341:468-75.

10. Des Roches A, Paradis L, Knani J, et al. Immunotherapy with a standardized dermatophagoides pteronyssinus extract. V. Duration of the efficacy of immunotherapy after its cessation. Allergy: European Journal of Allergy and Clinical Immunology 1996;51:430-3.

11. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy according to its duration: A 15-year prospective study. Journal of Allergy and Clinical Immunology 2010;126:969-75.

12. Berto P, Frati F, Incorvaia C. Economic studies of immunotherapy: A review. Current Opinion in Allergy and Clinical Immunology 2008;8:585-9.

13. Nelson HS. Multiallergen immunotherapy for allergic rhinitis and asthma. Journal of Allergy and Clinical Immunology 2009;123:763-9.

14. Shamji MH, Durham SR. Mechanisms of immunotherapy to aeroallergens. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 2011;41:1235-46.

15. Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. Allergy 2001;56:498-505.

16. Gawchik SM, Saccar CL. Pollinex Quattro Tree: allergy vaccine. Expert Opinion on Biological Therapy 2009;9:377-82.

17. Rosewich M, Lee D, Zielen S. Pollinex Quattro: an innovative four injections immunotherapy in allergic rhinitis. Human vaccines & immunotherapeutics 2013;9:1523-31.

18. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane database of systematic reviews (Online) 2010;8.

19. Bae JM, Choi YY, Park CO, Chung KY, Lee KH. Efficacy of allergen-specific immunotherapy for atopic dermatitis: A systematic review and meta-analysis of randomized controlled trials. Journal of Allergy and Clinical Immunology 2013;132:110-7.

20. Boyle RJ, Elremeli M, Hockenhull J, et al. Venom immunotherapy for preventing allergic reactions to insect stings. Cochrane Database Syst Rev 2012;10:Cd008838.

21. Wood RA. Food allergen immunotherapy: Current status and prospects for the future. The Journal of allergy and clinical immunology 2016;137:973-82.

22. Zolkipli Z, Roberts G, Cornelius V, et al. Randomized controlled trial of primary prevention of atopy using house dust mite allergen oral immunotherapy in early childhood. The Journal of allergy and clinical immunology 2015;136:1541-7.e1-11.

**Table 1: A sample schedule for subcutaneous immunotherapy**

|  |  |  |  |
| --- | --- | --- | --- |
| Dilution | Concentration | Volume (ml) | Dosage (SQU\*) |
| 1:1000 | 100 SQU\*/ml | 0.2 | 20 |
|  |  | 0.4 | 40 |
|  |  | 0.8 | 80 |
| 1:100 | 1000 SQU/ml | 0.2 | 200 |
|  |  | 0.4 | 400 |
|  |  | 0.8 | 800 |
| 1:10 | 10 000 SQU/ml | 0.2 | 2000 |
|  |  | 0.4 | 4000 |
|  |  | 0.8 | 8000 |
| 1:1 | 100 000 SQU/ml | 0.1 | 10 000 |
|  |  | 0.2 | 20 000 |
|  |  | 0.4 | 40 000 |
|  |  | 0.6 | 60 000 |
|  |  | 0.8 | 80 000 |
|  |  | 1.0 | 100 000 |
| Maintenance phase | 3-5 years | 1.0 | 100,000 |

**Note:** SQU (Standard Quality Units) is used here as a generic term to indicate standardization of allergen content, but the specific units and the amount of allergen varies depending on the type of allergen and the manufacturer. The conventional schedule for SCIT with unmodified allergen extracts consists of a dose build up by means of one-weekly injections, followed by maintenance dose injections at 4-8 weeks intervals. Rapid up-dosing is possible with a rush protocol.

|  |  |  |
| --- | --- | --- |
|  | **Subcutaneous Immunotherapy** | **Sublingual Immunotherapy** |
| **Convenience** | Inconvenient for patients | Convenient for patients |
| **Staff time** | Significant demand on staff time | Minimum use of healthcare resources |
| **Safety** | Local adverse effects are common and rarely systemic reactions occur | Local adverse effects are common but systemic reactions do not occur |
| **Feasibility** | Require expertise and facilities that may not be readily available | Does not require specific expertise or facilities |
| **Efficacy** | Effective in allergic rhinitis, asthma and insect allergy. | Effective in allergic rhinitis and asthma. |
| **Long term effects** | Long term remission in disease may occur | Long term effects are uncertain |
| **Cost** | Cost of treatment extract is lower, but overall cost, given an increased use of healthcare resources, may be higher | High cost of treatment extract, but minimal use of healthcare resources |

**Table 2: Attributes of subcutaneous and sublingual allergen immunotherapy**

**Figure 1:** **Management of allergic conditions**

**Allergen Avoidance**

**Allergy Management**

**Allergen Immunotherapy**

**Sub-Cutaneous Immunotherapy**

**Pharmacotherapy**

**Sub-Lingual Immunotherapy**