



Allergen-specific immunotherapy

We recommend against allergen-specific immunotherapy as a routine treatment option for AE.	↓↓↓	<p style="text-align: center;">>50%</p>  <p style="text-align: center;">(8/13) Expert Consensus</p>
We suggest that AIT is considered for selected patients with aeroallergen sensitization and a history of clinical exacerbation after exposure to the causative allergen	↑	<p style="text-align: center;">100%</p>  <p style="text-align: center;">(11/11) Expert Consensus</p>

Introduction

The cause of symptoms in allergic patients is that the sensitized individual reacts with an allergic immune response to an otherwise harmless allergen. The aim of allergen-specific immunotherapy (AIT) is to theoretically cure allergic diseases. The idea behind it is that an immune tolerance is achieved in the sensitized patient by modifying the immune response and re-gaining regulatory capacities of humoral and cellular immune components.¹ Such changes may lead to the clinical improvement of allergic symptoms, reduced use of symptomatic rescue medications and improve QoL. The first promising and successful results were established and published in 1911.²

According to recent recommendations, ASIT is advised for a minimum period of 3 years, however according to long-term efficacy data, the longer the treatment the better. For AIT purified, non-allergenic, highly-immunogenic modified allergen extracts have been recommended. The routes of AIT may be of sublingual, oral, subcutaneous, or even transdermal and intralymphatic forms have recently been introduced.¹ Among these the sublingual (SLIT) and subcutaneous (SCIT) ways of application are the most commonly used forms, both being equally efficacious and safe, however SLIT formulation ensures greater liberty for the patient, while the SCIT secures better compliance and treatment adherence. Both SCIT and SLIT have seen low overall therapy compliance as well as varying levels of treatment literacy. In one meta-analysis, SCIT discontinuation ranged from 6 to 84% whereas SLIT discontinuation ranged from 21 to 93%.³

The role of allergen sensitization in AE pathogenesis has been investigated, but remains to be fully elucidated.

Inflammatory processes seem to be mediated by both an immediate-type reaction, initiated by the internalization of the complex IgE specific/allergens from epidermal dendritic cells, and a delayed T cell reactivity, characterized by a Th2 inflammatory pattern.⁴

One of the most important allergen sources in AE are house dust mites due to the perennial exposure. Recent studies focused the attention also on the role of pollen allergens as trigger for AE flare-ups.

AIT consists of administering increasing doses of allergen in order to modulate the response and promote peripheral immune tolerance mechanisms. AIT induces a shift from a Th2 to a Th1 immune

response pattern, a decrease of mediator release from mast cells and the production of blocking antibodies IgG4 .

Favourable effects of AIT on disease symptoms of AE appear to be higher if accompanying relevant type I sensitizations are present, but only house dust mite-sensitized patients have been studied in larger studies in AE patients.

Here, the data for subcutaneous immunotherapy are stronger when compared to sublingual therapy and patients with severe AE (SCORAD > 50) showed better results.⁵

Systematic Reviews

In recent years, different attempts to perform systematic review and meta-analysis on ASIT in AE were made. The first systematic review of the literature analyzed 10 studies in 2007 [distinguishing among placebo-controlled and observational studies].⁶ The authors concluded that the overall effect was in favor of AIT, but no conclusion and recommendation could be formulated at that moment. In 2013 Bae et al.⁷ performed a meta-analysis including 8 studies. The authors concluded that their meta-analysis provided moderate-level evidence for the efficacy of SIT against atopic dermatitis. They stated however that there is only a moderate quality of the evidence supporting the use of AIT.

Gendelman and Lang⁸ analysed the double-blinded controlled trials published about SCIT and SLIT until 2013, including 8 studies, using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. Based on finding serious methodological problems, the authors concluded that only a weak recommendation could be given for use of AIT in patients with AE.

There has been recent data published on the efficacy of adjuvant SLIT treatment in AE patients in a small pilot study. The results indicated good efficacy and clinical response in mild-to-moderate AE. Furthermore AIT improved skin permeability barrier functions as well.⁹

Finally, a Cochrane systematic review was published in 2016.¹⁰ The authors included 12 studies and stated that this small number of studies was insufficient to give conclusive results .

The most recent guidelines of dermatological societies suggest to evaluate AIT in patients with AE and sensitization to aeroallergens, and not fully responding to symptomatic treatment, leaving the final decision to the clinician

AIT prescription should be considered individually for each patient, evaluating the risk/benefit ratio, and discussed with the patient.¹¹

Based on this evidence, we **suggest** that AIT may be considered for selected patients with house dust mite, birch or grass pollen sensitization, and a history of clinical exacerbation after exposure to the causative allergen or a positive corresponding atopy patch test. Moreover, AIT shall be applied in patients with respiratory atopic diseases and an approved indication of that therapeutical procedure with AE as a comorbidity.

References

- [1] Kucuksezer UC, Ozdemir C, Cevhertas L, Ogulur I, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy and allergen tolerance. *Allergol Int.* 2020;69; 549-560.
- [2] Noon L. PROPHYLACTIC INOCULATION AGAINST HAY FEVER. *The Lancet.* 1911;177; 1572-1573.
- [3] Cox LS, Hankin C, Lockey R. Allergy immunotherapy adherence and delivery route: location does not matter. *J Allergy Clin Immunol Pract.* 2014;2; 156-160.
- [4] Wollenberg A, Christen-Zäch S, Taieb A, Paul C, Thyssen JP, de Bruin-Weller M, et al. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. *J Eur Acad Dermatol Venereol.* 2020;34; 2717-2744.
- [5] Novak N, Bieber T, Hoffmann M, Fölster-Holst R, Homey B, Werfel T, et al. Efficacy and safety of subcutaneous allergen-specific immunotherapy with depigmented polymerized mite extract in atopic dermatitis. *J Allergy Clin Immunol.* 2012;130; 925-931.e924.
- [6] Novak N. Allergen specific immunotherapy for atopic dermatitis. *Curr Opin Allergy Clin Immunol.* 2007;7; 542-546.
- [7] 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. *J Allergy Clin Immunol.* 2013;132; 110-117.
- [8] Gendelman SR, Lang DM. Specific immunotherapy in the treatment of atopic dermatitis: a systematic review using the GRADE system. *Ann Allergy Asthma Immunol.* 2013;111; 555-561.
- [9] Hajdu K, Kapitány A, Dajnoki Z, Soltész L, Baráth S, Hendrik Z, et al. Improvement of clinical and immunological parameters after allergen-specific immunotherapy in atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2021;35; 1357-1361.
- [10] Tam H, Calderon MA, Manikam L, Nankervis H, García Núñez I, Williams HC, et al. Specific allergen immunotherapy for the treatment of atopic eczema. *Cochrane Database Syst Rev.* 2016;2; Cd008774.
- [11] Ridolo E, Martignago I, Riario-Sforza GG, Incorvaia C. Allergen immunotherapy in atopic dermatitis. *Expert review of clinical immunology.* 2018;14; 61-68.