



Long-term efficacy of allergen immunotherapy: what do we expect?

Evaluation of: Stelmach I, Sobocinska A, Majak P, Smejda C, Jerzynska J, Stelmach W. Comparison of the long-term efficacy of 3- and 5-year house dust mite allergen immunotherapy. *Ann. Allergy Asthma Immunol.* 109, 274–278 (2012). Allergen-specific immunotherapy (SIT) is the only treatment of allergic diseases able to maintain its efficacy after discontinuation of treatment. The available literature suggests that a 3-year duration of treatment maintains the efficacy on allergic symptoms for at least an equivalent period of time. The current paper compares the 3- and 5-year duration in children with dust mite-induced asthma, and confirms that 3 years of SIT maintains its effectiveness for a further 3 years after stopping, with no significant difference compared with 5 years. Thus, 3 years is likely to be an adequate duration of SIT; however, studies with more prolonged follow-up periods are needed to investigate the persistence of the clinical benefit over time.

KEYWORDS: allergen-specific immunotherapy • duration of treatment • long-term efficacy

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Allergen-specific immunotherapy (SIT) has proven efficacy in allergic rhinitis and asthma [1]. SIT modifies the immunological response to the administered allergen(s) [2] and this allows it to maintain its efficacy following treatment withdrawal [3]. However, the data on the long-term efficacy of SIT in respiratory allergy are not clear-cut. In 2007, Cox and Cohn reviewed the available literature on subcutaneous immunotherapy (SCIT) [4]. Eight studies were analyzed: four performed with grass pollen, one with birch pollen, one with ragweed pollen, one with cat and dog epithelia, and one with dust mites. In most studies, SCIT had a duration of 3 years and the time period of assessment ranged from 3 to 12 years. Cox and Cohn used the relapse rate of respiratory allergy to establish the persistence of SCIT efficacy and found contrasting outcomes ranging from 0% 3 years after stopping in one study with grass pollen to 45% 3 years after stopping in the study with dust mites [4]. The better outcome in subjects allergic to pollen with respect to those allergic to mites seems to suggest that the extent of exposure is critical in favoring resensitization once SIT is discontinued. This concept seems reinforced if one takes into account the different results obtained with venom immunotherapy (VIT) in subjects allergic to Hymenoptera stings. In fact, in such an allergy where the exposure to the responsible allergen is occasional, the long-term efficacy is very good, with an estimated incidence of systemic reaction to a sting of approximately

10%, even 10–15 years after stopping VIT [5]. In addition, the residual reactions reported thus far were rarely severe and never fatal.

Sublingual immunotherapy (SLIT) was also evaluated in terms of its long-term efficacy. In an open prospective study, 60 children with mite-induced asthma were assigned to a 4–5-year course of SLIT (35 subjects) or to symptomatic drug treatment (25 subjects), and followed up for another 5 years [6]. In the SLIT group, significant differences were found at the 10-year time point versus baseline concerning the presence of asthma and the use of asthma medications, whereas no difference was observed in the control group. In a randomized placebo-controlled trial performed with the grass pollen preparation in tablet form in patients with rhinoconjunctivitis caused by grass pollen, 2 years after the discontinuation of a 3-year treatment, the mean rhinoconjunctivitis daily symptom score was significantly reduced ($p < 0.004$) in the actively treated group compared with the placebo group [7]. In addition, the percentage of days with severe symptoms during the peak grass pollen exposure was (including the post-treatment period) lower in the active than in the placebo group in all seasons, with relative differences of 49–63% ($p < 0.0001$).

It is apparent that there is a general agreement on 3 years as an adequate duration of SIT, while there is considerable heterogeneity regarding the time interval to extend the follow-up after stopping, as well as on the criteria to assess the respiratory disease activity.

Summary of methods & results

In the current paper, Stelmach *et al.* studied the effect over time of a 3- or 5-year course of SIT with a house dust mite extract administered by the subcutaneous route in children with allergic asthma caused by exclusive sensitization to dust mites [8]. An observation period 3 years after stopping SIT was chosen. A total of 90 children entered the study and formed three groups of 30 subjects who either received a 3- or 5-year course of SIT or did not undergo SIT because their parents refused this treatment and so served as controls. The effectiveness of SIT was assessed by asthma remission, defined by the absence of any symptom requiring asthma medication for at least 12 months, by a negative result to bronchial provocation test, changes in lung function as measured by the forced expiratory volume in 1 s (FEV_1) and decrease in using inhaled corticosteroids, namely budesonide. The results showed that asthma remission occurred in 50 and 54% of children treated with SIT for 3 and 5 years, respectively, and in 3.3% of control subjects; a higher increase of FEV_1 was found in children treated for 5 years (from 91.8 to 98% of predicted value) compared with those treated for 3 years (from 90.9 to 92.5% of predicted value) and with control subjects (from 89.6 to 91% of predicted value); the median reduction of the budesonide dose was significantly higher in children treated for 5 years (75%) compared with 3 years (50%) at SIT stopping, but no differences were found at 3 years from stopping (100 and 94%, respectively), while the dose remained unchanged in control subjects. Some results seem to show a higher efficacy of the 5-year duration, however, from the clinical point of view, these are of limited importance. For example, this is true for the FEV_1 improvement, the magnitude of which was below the level of clinical perception. Consequently, the authors concluded that a SIT duration of 3 years is adequate to treat children with mite-induced allergic asthma, but that longer observation periods are likely to improve our knowledge on this issue.

Discussion & significance

The literature on the long-term efficacy of SIT for respiratory allergy is not abundant. Most studies are based on SIT duration of 3 years, which is the currently recommended length of treatment [9]. Instead, the period of observation after stopping SIT is quite variable, though most studies are based on time points within 3 years. Such time is surely sufficient to show the advantage of SIT over drug treatment concerning the cost-effectiveness.

In fact, the persistence of the clinical efficacy after treatment discontinuation is exclusive of SIT and achieves a progressive economic benefit for healthcare systems [10]. However, a longer time interval may be needed to show very long-lasting clinical efficacy, as observed in patients allergic to Hymenoptera stings treated with VIT, in whom a course of 5 years is currently recommended based on the observation that such duration provides the persistence of tolerance to stings 15 years after stopping the treatment [11]. The actual issue concerns what we expect from SIT: a complete cure of allergy or a momentary remission followed by a possible new treatment when the symptoms will reoccur? This is obviously related to the natural history of the disease. In a 23-year follow-up study on 738 college students with seasonal allergy, it was observed that at the end of follow-up, 55% of subjects had noted improvements (23% being symptom-free), while 33% were unchanged and 9% had worsened [12]. Therefore, the natural history has various trends in different individuals and this unavoidably influences the long-term outcome of SIT. It is likely that a trend towards improvement is associated with a longer duration of SIT efficacy, while the opposite may occur in subjects with a trend towards worsening; however, there is currently no possibility of predicting the course of allergy in single patients.

Future perspective

The data currently available indicate that a 3-year duration of SIT results in a sustained efficacy for at least an equivalent period of time following discontinuation of treatment. There is a need for studies evaluating the long-term efficacy of SCIT and SLIT for more extended periods of observation after stopping to properly assess the influence of immunotherapy on the natural history of respiratory allergy and, in particular, on the capacity to achieve complete control of the disease. Another important aspect is the identification of the different clinical phenotypes of allergic patients to be treated with SIT. For example, patients with more severe forms of disease are of particular interest. A recent post-hoc analysis of published studies using the grass-pollen tablet showed that the higher clinical efficacy of SLIT is observed in patients with more severe allergic rhinitis [13]. This phenotype is frequently resistant to drug treatment but is responsive to SIT [14] and deserves specific investigations on the appropriate length of treatment to attain durable clinical effects and consequently to give a significant benefit to the quality of life and the

economic burden of the disease, which are both of particular concern owing to the high number of missed work days and high consumption of drugs.

Financial & competing interests disclosure

F Frati and I Dell'Albani are employees of Stallergenes Italy. C Incorvaia is a scientific consultant for Stallergenes

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Executive summary

- The ability to maintain efficacy on allergic symptoms after discontinuation of treatment is characteristic of allergen-specific immunotherapy (SIT), while drugs are effective only during their administration. However, the optimal duration of SIT to provide long-term efficacy is not yet established.
- The paper evaluated here compared a duration of 3 or 5 years of SIT in children with dust mite induced asthma and found that 3 years is an adequate duration because the outcome with 5 years of treatment was not significantly better during a 3-year follow-up.
- This confirms that SIT keeps its effectiveness after discontinuation for a period of time at least equivalent to the duration of treatment.
- However, more prolonged follow-up is needed to improve our knowledge on the long-term efficacy of SIT.

References

- 1 Incorvaia C, Frati F. One century of allergen-specific immunotherapy for respiratory allergy. *Immunotherapy* 3, 629–635 (2011).
- 2 Larchè M, Akdis CA, Valenta R. Immunological mechanisms of allergen-specific immunotherapy. *Nat. Rev. Immunol.* 6, 761–771 (2006).
- 3 Passalacqua G. Specific immunotherapy: beyond the clinical scores. *Ann. Allergy Asthma Immunol.* 107, 401–406 (2011).
- 4 Cox L, Cohn JR. Duration of allergen immunotherapy in respiratory allergy: when is enough, enough? *Ann. Allergy Asthma Immunol.* 98, 416–426 (2007).
- 5 Golden DB. Discontinuing venom immunotherapy. *Curr. Opin Allergy Clin. Immunol.* 1, 353–356 (2001).
- 6 Di Rienzo V, Marcucci F, Puccinelli P *et al.* Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin. Exp. Allergy* 33, 206–210 (2003).
- 7 Durham SR, Emminger W, Kapp A *et al.* SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J. Allergy Clin. Immunol.* 129, 717–725 (2012).
- 8 Stelmach I, Sobocinska A, Majak P, Smejda C, Jerzynska J, Stelmach W. Comparison of the long-term efficacy of 3- and 5-year house dust mite allergen immunotherapy. *Ann. Allergy Asthma Immunol.* 109, 274–278 (2012).
- 9 Cox L, Nelson H, Lockey E *et al.* Allergen immunotherapy: a practice parameter third update. *J. Allergy Clin. Immunol.* 127, S1–S55 (2011).
- 10 Berto P, Frati F, Incorvaia C. Economic studies of immunotherapy: a review. *Curr. Opin Allergy Clin. Immunol.* 8, 585–589 (2008).
- 11 Golden DB, Moffitt J, Nicklas RA *et al.* Stinging insect hypersensitivity: a practice parameter update 2011. *J. Allergy Clin. Immunol.* 127, 852–854 (2011).
- 12 Greisner WA, Settipane RJ, Settipane GA. Natural history of hay fever: a 23-year follow-up of college students. *Allergy Asthma Proc.* 19, 271–275 (1998).
- 13 Howarth P, Malling HJ, Molimard M, Devillier P. Analysis of allergen immunotherapy studies shows increased clinical efficacy in highly symptomatic patients. *Allergy* 67, 321–327 (2012).
- 14 Frew AJ, Powell RJ, Corrigan CJ, Durham SR; UK Immunotherapy Study Group. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 117, 319–325 (2006).