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Allergen-specific immunotherapy for allergic rhinitis in the elderly: is it never too late?

Evaluation of: Bozek A, Ignasiak B, Filipowska B, Jarzab J. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. *Clin. Exp. Allergy* 43(2), 242–248 (2013). There is a well-accepted tenet in allergen-specific immunotherapy (SIT), especially for respiratory allergies such as rhinitis and asthma: this approach should be, in general, reserved for the pediatric population and young adults. This belief is based on the fact that SIT is considered the only therapy able to modify the course of allergic diseases. In the case of allergic rhinitis, for example, SIT could reduce the risk of asthma developing. Therefore, SIT is evaluated with 'the sooner the better' conviction. In elderly people with respiratory allergies, the 'course' of the disease is considered too advanced and therefore the room and therapeutic value of SIT is considered very limited. Bozek *et al.* evaluated the clinical efficacy of sublingual SIT (SLIT) with house dust mite (HDM) extracts in elderly (age >60 years) patients with a long history of allergic rhinitis due to HDM allergen exposure. In a 3-year double-blind placebo-controlled study, SLIT was able to significantly reduce the nose-related symptoms and the medication score. The conclusions of the authors were that SLIT with HDM allergens resulted in a significant clinical improvement in the active group compared with the placebo group, particularly during the period of the year in which the heating would be on. This therapy was well tolerated. These observations may lead to the more frequent use of SLIT immunotherapy in the elderly.

KEYWORDS: allergic rhinitis ■ HDM ■ house dust mite ■ immunotherapy ■ randomized clinical trial

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Specific immunotherapy (SIT) is a therapeutic approach in which administration of purified allergen extracts by sublingual or subcutaneous routes is performed with the aim to obtain immunological and clinical tolerance to those allergens [1], which are responsible for eliciting an abnormal IgE response, resulting in the clinical manifestation of allergy [2]. SIT has been shown to be efficacious in patients with mild-to-moderate disease, but also in patients considered to be not responding to symptomatic treatment such as antihistamine drugs or topical corticosteroids [3]. The most relevant potential characteristic of SIT is that it could modify the course of clinical allergy disease (the so-called 'disease-modifying' treatment) [4], therefore differentiating SIT from symptomatic treatment. SIT is able to reduce the risk of new allergic sensitizations [5]. In allergic children with rhinitis, SIT has been shown to reduce the development of asthma [6]. The clinical efficacy of SIT is not immediate but once established, SIT could offer clinically relevant and long-lasting relief of allergic symptoms [7]. A 3-year subcutaneous SIT in children with seasonal allergic rhino-conjunctivitis has demonstrated an ability to reduce the risk of developing asthma during treatment and 2 years after discontinuation of SIT. This

supports the concept of a long-term preventive effect of SIT. Immunotherapy is effective in the treatment of allergic respiratory diseases such as asthma [8] and rhinitis [9], latex allergy [10] and atopic dermatitis [11] in children and young adults. Sublingual SIT (SLIT) is clinically effective in the treatment of respiratory allergy due to pollen [12] and other allergens such as *Alternaria alternata* [13]. SIT is a useful treatment for allergic rhinitis, especially when the range of allergens responsible is narrow. Treatment with SIT might limit the tendency to acquire new sensitizations [14]. A well-accepted tenet in SIT is the fact that this therapeutic approach is worthwhile when it is initiated as soon as possible [15]. Even if, in general, SIT is not indicated in children before the age of 5 years [16], clinical studies have shown that SIT is safe and well-tolerated in subjects of 3–5 years of age [17]. Therefore, SIT for respiratory allergies is generally not considered a therapeutic strategy for elderly people and the real effect of this therapeutic approach in this class of patients is controversial [18].

Summary of methods & results

In this paper, Bozek *et al.* evaluated 111 60–75-year-old patients with allergic rhinitis and

confirmed *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* allergies [19]. The patients were individually randomized to active or placebo groups using a double-blind method. The subjects with allergic rhinitis, who fulfilled the Allergic Rhinitis and its Impact on Asthma criterion and had a positive skin prick test, were positive for specific IgE, and had positive nasal provocation tests with *D. pteronyssinus* and *D. farinae*, were included in the study. The patients were randomly selected to receive SLIT (Staloral 300 SR *D. pteronyssinus* and *D. farinae* 50/50% extract; Stallergenes) or the corresponding placebo. The recruitment period was limited to 3 months (November to January). There was a 2-week run-in period. The mean treatment duration was 28.2 months (range: 3–36 months). Forty seven patients completed 3 years of SLIT, while 48 subjects finished the placebo treatment within that time frame. Four patients in the active group and nine patients in the placebo group prematurely terminated study participation. The patients' allergic rhinitis symptoms were monitored using a seven-point visual graphic scale (published by the Joint Task Force and modified by Allergic Rhinitis and its Impact on Asthma [20]) for grading the severity of nasal (sneezing, runny nose, congestion, itchy nose and postnasal drip) and non-nasal (eye symptoms, throat symptoms, chronic cough, ear symptoms and headache) symptoms in addition to mental function and quality of life changes. The total nasal symptom score decreased by 44% in the active group and 6% in the placebo group after 3 years of SLIT. This difference was only significant in the active group ($p < 0.05$). At the end of therapy, the total medication score of the active group decreased significantly by a maximum of 51% ($p < 0.05$), whereas the total medication score of the placebo control group showed an insignificant decrease ($p = 0.56$). There was no statistical difference at the end of the study period regarding the mean non-nasal (eye symptoms, throat symptoms, chronic cough, ear symptoms and headache) score between the two groups. Active treatment was not able to reduce in comparison with specific IgE levels to *D. farinae*. There were no systemic adverse reactions during the study. The authors concluded that sublingual allergen SIT in elderly patients with a house dust mite (HDM) allergy to *D. pteronyssinus* and *D. farinae* given for 3 years induced a significant clinical improvement compared with the placebo. The clinical benefit was particularly strong during the period of the year in which the heating would be on.

Discussion & significance

It is well established that SIT for the treatment of seasonal rhinitis is quite effective, especially in children and young adults [21]. In subjects affected by respiratory allergies due to perennial allergens, in particular HDM, the clinical efficacy of SIT is not so relevant in terms of reducing symptom score and rescue medication (i.e., symptomatic drug use) [22]. In fact, in the case of perennial allergies, it could be extremely difficult to determine whether the patient's symptoms are due to a specific allergen or whether they have nonallergic rhinitis and have been simply sensitized to an allergen that is not clinically relevant. The results of the Bozek *et al.* study are therefore certainly interesting and promising [19]; interesting because they have dealt with an allergy respiratory disease (HDM) not so easily treatable with SLIT and because they carried out their study in a population (subjects >60 years of age) generally not involved in SIT trials. With the positive results of their study, Bozek *et al.* have now opened a new clinical opportunity for the immunotherapy approach of allergy diseases for elderly people [19]. In evaluating the results of this trial, however, we have to take into account some limitations. First, from a clinical point of view, it is difficult to understand whether the differences observed between the two groups regarding the primary end point could be translated into a real positive impact for the patient (i.e., the absolute difference of the symptoms score of 1.3 in a scale from 0 to 7 and an absolute difference in medication score of 0.1 point). However, the symptom score in comparison with baseline was reduced by 44%, which could be a clinically relevant effect. By contrast, the medication score of SIT in comparison with placebo, even if statistically significant, appears marginal from a clinical and practical point of view. Probably the weakest point of this study is related to the relatively small sample size of the present trial. Looking at recorded protocol [101], the author stated that the primary outcome measure of the study should have been the number of participants with adverse events. The change from baseline of nasal symptoms after immunotherapy was actually only a secondary end point of the trial. Therefore, the statements in the final publication are not completely in line with the statement in the clinical trials database protocol definition. As a consequence, it could be questioned if the enrolled sample size ($n = 108$) is correctly powered in order to assess the clinical efficacy of SLIT in HDM allergic rhinitis in elderly patients. In conclusion, the trial conducted by Bozek *et al.* in

elderly patients is undoubtedly promising [19], but further controlled trials are needed. Regarding the question of the title: “SIT: is it never too late?”, we have to say that at the moment we do not have a well-established, evidence-based answer. As also stated by the authors of the study in their conclusion, in order to consider SIT as a valuable therapeutic option, further confirmatory controlled studies are required.

Future perspective

Respiratory allergies (allergic rhinitis and allergic asthma), from an epidemiological point of view, are conditions on a continuous increase. They affect not only the pediatric population and young adults, but also people 50 years of age and older. SIT has been shown to be efficacious in patients with mild-to-moderate allergic respiratory diseases, but it is also effective in patients considered not responding to symptomatic treatment. Furthermore, SIT is so far the only therapy able to modify the course of allergic diseases. Considering that the allergologist has to face

and fight this ‘epidemic’ more frequently, also in elderly patients, it is of great relevance to understand whether this therapeutic strategy could be worthwhile, also in this population group. The study of Bozek *et al.*, carried out in allergic subjects aged >60 years, gives an encouraging message in this respect, suggesting that SIT could have a therapeutic role, also in elderly allergic patients [19]. However, in order to consider SIT in elderly patients with allergy as a valuable therapeutic option, further confirmatory controlled studies are required.

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The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Executive summary

- Specific immunotherapy (SIT) is potentially considered the only therapy able to modify the course of allergic diseases such as allergic rhinitis and asthma, but it is, in general, used mainly in pediatric patients and young adults.
- In elderly people with respiratory allergies, the ‘course’ of the disease is considered too advanced and therefore the therapeutic value of SIT is considered very limited.
- Bozek *et al.* have recently evaluated the clinical efficacy of sublingual SIT with house dust mite extracts in elderly (age >60 years) patients with a long history of allergic rhinitis.
- In a 3-year double-blind placebo-controlled study, sublingual SIT was able to significantly reduce the nose-related symptoms and medication score.
- The results of Bozek *et al.* may lead to the more frequent use of SIT in elderly allergic patients; however, further confirmatory controlled studies are required.

References

Papers of special note have been highlighted as:

■ of considerable interest

- 1 Walker SM, Durham SR, Till SJ *et al.* BSACI guidelines. Immunotherapy for allergic rhinitis. *Clin. Exp. Allergy* 41, 1177–1200 (2011).
- 2 Jutel M, Akdis M, Blaser K, Akdis CA. Mechanisms of allergen specific immunotherapy—T-cell tolerance and more. *Allergy* 61, 796–807 (2006).
- 3 Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst. Rev.* 1, CD001936 (2007).
- **Important meta-analysis demonstrating the efficacy of sublingual immunotherapy in seasonal allergies.**
- 4 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).

- **First prospective study demonstrating that specific immunotherapy (SIT) is able to modify the allergic march in rhinitis patients.**
- 5 Des Roches A, Paradis L, Menardo JL, Bouges S, Daurès JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J. Allergy Clin. Immunol.* 99(4), 450–453 (1997).
- 6 Jacobsen L, Niggemann B, Dreborg S; The PAT investigator group. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 62(8), 943–948 (2007).
- **Pivotal study demonstrating that SIT is able to modify the allergic march in rhinitis**

patients, reducing the risk of developing asthma.

- 7 Bousquet J, Lockey RF, Malling HJ. WHO position paper. Allergen immunotherapy: therapeutic vaccines for allergic disease. *Allergy* 53(Suppl. 44), 1–42 (1998).
- 8 Abramson M, Puy R, Weiner J. Immunotherapy in asthma: an updated systematic review. *Allergy* 54, 1022–1041 (1999).
- 9 Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 117, 319–325 (2006).
- 10 Bernardini R, Pecora S, Milani M, Burastero SE. Natural rubber latex allergy in children: clinical and immunological effects of 3-years sublingual immunotherapy. *Eur. Ann. Allergy Clin. Immunol.* 40(4), 142–147 (2008).

- 11 Cadario G, Galluccio AG, Pezza M *et al.* Sublingual immunotherapy efficacy in patients with atopic dermatitis and house dust mites sensitivity: a prospective pilot study. *Curr. Med. Res. Opin.* 23(10), 2503–2506 (2007).
- 12 Durham SR, Walker SM, Varga EM *et al.* Long-term clinical efficacy of grass pollen immunotherapy. *N. Engl. J. Med.* 341, 468–475 (1999).
- **Very important article demonstrating the long-lasting effect of SIT in the treatment of allergic rhinitis.**
- 13 Pozzan M, Milani M. Efficacy of sublingual specific immunotherapy in patients with respiratory allergy to *Alternaria alternata*: a randomised, assessor-blinded, patient-reported outcome, controlled 3-year trial. *Curr. Med. Res. Opin.* 26(12), 2801–2806 (2010).
- 14 Milani M, Pecora S, Burastero S; EFESO Investigators Study Group. Observational study of sublingual specific immunotherapy in persistent and intermittent allergic rhinitis: the EFESO trial. *Curr. Med. Res. Opin.* 24(9), 2719–2724 (2008).
- 15 Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 60, 4–12 (2005).
- **Very important article: the first Cochrane meta-analysis of SIT.**
- 16 Bufe A, Ziegler-Kirbach E, Stoeckmann E *et al.* Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 59, 498–504 (2004).
- 17 Fiocchi A, Pajno G, La Grutta S. Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. *Ann. Allergy Asthma Immunol.* 95(3), 254–258 (2005).
- 18 Ortolani C, Agostinis F, Amoroso S. Practice parameters for sublingual immunotherapy. *Monaldi Arch. Chest Dis.* 65(1), 44–46 (2006).
- 19 Bozek A, Ignasiak B, Filipowska B, Jarzab J. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. *Clin. Exp. Allergy* 43(2), 242–248 (2013).
- 20 Spector SL, Nicklas RA, Chapman JA *et al.*; Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; Joint Council of Allergy, Asthma, and Immunology. Symptom severity assessment of allergic rhinitis: part 1. *Ann. Allergy Asthma Immunol.* 91(2), 105–914 (2003).
- 21 Fiocchi A, Fox AT. Preventing progression of allergic rhinitis: the role of specific immunotherapy. *Arch. Dis. Child. Educ. Pract. Ed.* 96, 91–100 (2011).
- 22 Cox L, Nelson H, Lockey R *et al.* Allergen immunotherapy: a practice parameter third update. *J. Allergy Clin. Immunol.* 127(Suppl. 1), S1–S55 (2011).

■ Website

- 101 House dust mite SLIT in elderly patients. www.clinicaltrials.gov/show/NCT01605760