

## EDITORIAL

# Clinical & Experimental Allergy

## Immune mechanisms of SCIT and SLIT: facing possible differences?

This editorial discusses the findings of the article in this issue by K. Aasbjerg et al. [11] pp. 417–428.

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Allergen immunotherapy (AIT) is still the only curative approach to reduce the clinical symptoms associated with allergic rhinitis, asthma and venom-induced anaphylaxis. Subcutaneous (SCIT) and sublingual immunotherapy (SLIT) with allergen extracts are the most widely prescribed AIT regimens, SCIT representing the more frequently used conventional treatment. More recently, SLIT has emerged as an effective and safe alternative to SCIT, and its efficacy in seasonal allergy has been documented [1–5]. The immune mechanisms induced by AIT are still being elucidated, and it is still not entirely clear which alterations of the allergen-specific cellular and humoral responses translate into the long-lasting relief of allergic symptoms. Up to now, most studies have investigated the mechanisms underlying SCIT and only a few studies have focussed on SLIT [6–10]. Based on these studies, one may gain the impression that the basic systemic mechanisms induced by either route of allergen administration are similar, namely downregulation of the disease-eliciting allergen-specific Th2 response by allergen-specific Th1 cells and regulatory T cells and the induction of allergen-specific IgG4 antibodies with IgE-blocking activity.

In this issue of *Clinical & Experimental Allergy*, Aasbjerg and colleagues have directly compared SLIT and SCIT in terms of clinical efficacy, humoral changes, that is, allergen-specific IgE and IgG4 levels, IgE-blocking factor and IgE-blocking activity of sera as determined by facilitated antibody binding (FAB) and basophil activation testing (BAT) [11]. Thirteen grass-

pollen-allergic patients who had received grass-pollen SLIT and 10 patients who had received grass-pollen SCIT for 15 months were compared with nine non-treated grass-pollen-allergic control patients. Nasal challenge symptom scores were collected based on self-reported symptoms using a visual analogue score (VAS) after a non-blinded challenge. Compared with the control group, VASs were reduced in both AIT-treated groups although at different time points. SCIT-treated patients showed significant improvement already after 3 months, SLIT-treated individuals after 15 months of treatment. In both active groups, allergen-specific IgE and IgG4 levels, IgE-blocking factor and basophil activation differed significantly from the non-treated controls.

Although performed in a very limited number of patients and focussing on only a few parameters, data reported by Aasbjerg et al. indicate that SCIT induces earlier and stronger immune responses than SLIT. Several reasons may account for this observation. One relevant factor that needs to be taken into consideration is the route of administration which determines the amount of allergen reaching the immune system of the patients. It needs to be noted that upon subcutaneous injection, the full dose of allergens enters the human body. In contrast, sublingual administration is a non-invasive way of allergen delivery on a continuously moisturized surface. Aasbjerg et al. roughly calculated the total amount of administered allergen related to the major allergen Phl p 5 and report that SCIT-treated patients received 6 times less allergen than SLIT-treated individuals (around 280 µg Phl p 5 vs. 1800 µg Phl p 5 in total). However, keeping in mind that sublingually administered allergens are diluted and flushed away by saliva, the actual amounts of allergens that finally penetrated the mucosa and encountered antigen-presenting cells have to be estimated much lower than the initially administered amounts. It may even be possible that the total amount of allergen that finally reached the immune

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system was much lower in the SLIT-treated group than the SCIT-treated group.

Another relevant difference between both forms of AIT is the use of an adjuvant. The SCIT vaccine contained aluminium hydroxide (alum), whereas the SLIT vaccine did not. *In vivo*, alum enhances priming of naïve T cells and boosts the production of specific antibodies. This may be referred to the fact that alum triggers responses of antigen-presenting cells by altering membrane lipid structures [12]. In addition, alum has very recently been demonstrated to allow host DNA access to the cytoplasm of dendritic cells, which results in upregulation of MHC class II molecules and prolonged interaction with CD4<sup>+</sup> T cells [13]. Hence, the stronger immune responses induced by SCIT may be referred to the presence of an adjuvant. In this regard, higher levels of allergen-specific IgG4 antibodies have been observed when monophosphoryl lipid (MPL)-A, a ligand for toll-like receptor 4, was added to a SLIT vaccine [14].

We are left with the question whether the stronger immune responses induced by SCIT translate into higher clinical efficacy? In this respect, some caution is needed with the study of Aashbjerg et al. Based on the limited number of patients, the purely subjective evaluations of symptoms and the lack of the respective placebocontrol groups, it is impossible to draw conclusions on the clinical efficacy of SCIT and SLIT from the presented study. Another currently discussed issue is briefly touched by Aashbjerg et al., namely, which form

of AIT is better accepted by the patients? However, the patient numbers and treatment period are too limited to evaluate the compliance in each group. Recent work by Kiel et al. including almost 6500 patients has shown that the persistence and compliance for SCIT is better than for SLIT [15]. Besides, for both forms of AIT, the persistence and compliance of the patients have been shockingly low.

In summary, the work by Aashbjerg et al. demonstrates that SLIT and SCIT induce similar systemic changes, namely an increase in allergen-specific IgG4 with blocking activity and a reduction in basophil responsiveness. Still, both AIT regimens differ with regard to the magnitude and first appearance of these alterations. Possibly these differences may simply be explained by the amount of immunologically active allergen and the use of adjuvant. A very interesting observation in the presented study is the significantly stronger increase in allergen-specific IgE induced by SLIT as compared to SCIT. This finding indicates that other mechanisms may be involved in SLIT. One may also speculate that the low doses of applied allergen induced an IgE-boost similar to allergen exposure during the pollen season. Further investigations on immunological as well as clinical aspects are definitely needed.

**Conflict of interest:** The authors declare no conflict of interest.

## References

- 1 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* 2006; 117:319–25.
- 2 Dahl R, Kapp A, Colombo G *et al.* Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; 118:434–40.
- 3 Dahl R, Kapp A, Colombo G *et al.* Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. *J Allergy Clin Immunol* 2008; 121:512–8.e2.
- 4 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* 2012; 129: 717–25.e5.
- 5 Durham SR. Sublingual immunotherapy: what have we learnt from the 'big trials'? *Curr Opin Allergy Clin Immunol* 2008; 8:577–84.
- 6 Fanta C, Bohle B, Hirt W *et al.* Systemic immunological changes induced by administration of grass pollen allergens via the oral mucosa during sublingual immunotherapy. *Int Arch Allergy Immunol* 1999; 120:218–24.
- 7 Bohle B, Kinaciyan T, Gerstmayr M, Radakovics A, Jahn-Schmid B, Ebner C. Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation. *J Allergy Clin Immunol* 2007; 120:707–13.
- 8 Scadding GW, Shamji MH, Jacobson MR *et al.* Sublingual grass pollen immunotherapy is associated with increases in sublingual Foxp3-expressing cells and elevated allergen-specific immunoglobulin G4, immunoglobulin A and serum inhibitory activity for immunoglobulin E-facilitated allergen binding to B cells. *Clin Exp Allergy* 2010; 40:598–606.
- 9 Piconi S, Trabattoni D, Rainone V *et al.* Immunological effects of sublingual immunotherapy: clinical efficacy is associated with modulation of programmed cell death ligand 1, IL-10, and IgG4. *J Immunol* 2010; 185: 7723–30.
- 10 Scadding G, Durham SR. Mechanisms of sublingual immunotherapy. *Immunol Allergy Clin North Am* 2011; 31:191–209, viii.
- 11 Aashbjerg K, Backer V, Lund G *et al.* Immunological comparison of allergen immunotherapy tablet treatment and subcutaneous immunotherapy against grass allergy. *Clin Exp Allergy* 2014; 44:417–428.
- 12 Flach TL, Ng G, Hari A *et al.* Alum interaction with dendritic cell membrane lipids is essential for its adjuvant activity. *Nat Med* 2011; 17: 479–87.

- 13 McKee AS, Burchill MA, Munks MW *et al.* Host DNA released in response to aluminum adjuvant enhances MHC class II-mediated antigen presentation and prolongs CD4 T-cell interactions with dendritic cells. *Proc Natl Acad Sci USA* 2013; **110**:E1122–31.
- 14 Pfaar O, Barth C, Jaschke C, Hormann K, Klimek L. Sublingual allergen-specific immunotherapy adjuvanted with monophosphoryl lipid A: a phase I/IIa study. *Int Arch Allergy Immunol* 2011; **154**:336–44.
- 15 Kiel MA, Roder E, Gerth van Wijk R, Al MJ, Hop WC, Rutten-van Molken MP. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. *J Allergy Clin Immunol* 2013; **132**:353–60.e2.