

Editorial

Allergen-specific sublingual immunotherapy: less mystic, more scientific

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The paradigm of modern medicine and future therapeutic strategies is dictated by the wish to understand patho-physiologic mechanisms and to develop compounds supposed to target relevant structures. Ironically, the first report on specific immunotherapy is more than 95 years old (1), but our understanding on how allergic reactions are provoked has only really progressed during the last 30 years when the discovery of IgE and the progress in T- and B-cell biology have directed our approaches to the pathomechanisms of allergic reactions. The scientist's goal is to unravel a causal and tailored treatment for a given condition. In this context, specific immunotherapy is a paradigmatic approach in which we are able to improve allergic diseases based on our knowledge concerning the causative agents and mechanisms. For years, the gold standard of specific immunotherapy was represented by the subcutaneous application [subcutaneous immunotherapy (SCIT)] of increasing doses of allergens (2). Since the mid-1980s, an alternative route of administration has been proposed by applying drops with allergens in the sublingual region: the sublingual immunotherapy (SLIT; 3). Although increasing numbers of reports from clinical studies have clearly shown that the SLIT approach can be considered as a meaningful alternative to SCIT (4, 5), it is still not widely used and many allergists were concerned about issues like the patients' compliance, the clinical efficacy when compared with that of SCIT and the lack of understanding of the immunological mechanisms underlying SLIT. The increasing number of clinical trials performed according to modern standards in pharmacological research as well as the meta-analyses based on the Cochrane database by Wilson et al. (6) have largely contributed to convince more and more allergists that

SLIT is an efficient and safe approach to treat at least allergic rhinoconjunctivitis and asthma in adults as well as in children. Two reports aimed to compare SCIT vs SLIT and performed according to state-of-the-art designs (double-dummy, placebo-controlled) further contributed to convince the scientific community on the clinical efficacy (7–8). While safety is no more an issue because of the complete lack of reported severe reactions, the problem of patient adherence has also been addressed by Marogna et al. (9), showing a high compliance in patients treated with SLIT. Moreover and most importantly, a long-lasting effect has been shown in several studies which documented an effect over a period of 3 years, the prevention of asthma and even a preventive effect on the appearance of further sensitizations (10, 11).

A further and more recent progress in SLIT has been the development of allergen tablets as an alternative to drops. In the present issue of *Allergy*, two reports on the use of grass allergen tablets are presented. Kleine-Tebbe et al. (12) showed that even if at high concentrations of 1 000 000 SQ-T, the overall incidence of adverse events may be high, however, they are always mild to moderate in their intensity. These events were dose-dependent and none of the patients display otherwise clinically relevant reactions. Similarly, in another study using grass tablets with 75 000 SQ-T, Dahl et al. (13) confirmed the safety of this treatment in that no serious adverse events were reported. Moreover, they also confirmed the significant reduction in the symptom score as well as in the medication score as expected from previous studies performed with drops. Thus, the clinical development of grass allergen tablets can be considered as a welcome new and safe alternative to SCIT.

While safety and efficacy have now been largely documented, the immunological mechanisms underlying SLIT have only started to be investigated. Recently, the putative role of FcεRI-expressing Langerhans cells from the oral mucosa has been proposed by Allam et al. (14). This observation revealed that the oral mucosa may represent a privileged site for tolerance induction. In the present issue of *Allergy*, Moingeon et al. (15) have provided a comprehensive review of the possible mechanisms underlying SLIT. This paper provides the current understanding in this field and highlights the role of dendritic cells and regulatory T cells in the context of allergy vaccines. Interestingly, another research report from Allam et al. (16) in the present issue underlines the differences between dendritic cells of the oral mucosa and those of the nasal mucosa. These differences may be of relevance when considering different routes of application for future immunotherapeutic strategies.

Besides the significant progress made in the last year in understanding the immunological mechanisms underlying SLIT and the proof of its efficacy and safety in the treatment of allergies, we are still confronted with several new questions which should be addressed in the near future, i.e. where does the tolerance induction take place? What makes the oral mucosa prone to induce immunological tolerance? Can we increase the penetration of allergens through the mucosal epithelial barrier? Can the use of adjuvants be effective in SLIT? Is the use of recombinant allergens or modified allergens which have lost their IgE-binding ability meaningful for SLIT? Which is the optimal concentration and regimen to induce tolerance in allergic patients by SLIT? Can the use of SLIT be extended to food allergies? (A recent paper suggests that this seems to be the case at least for hazelnut; 17). Can the SLIT strategy be of interest to treat atopic dermatitis in its initial stage and thereby be helpful in controlling the postulated atopic march?

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