

Sublingual immunotherapy: where do we stand? Present and future

Giovanni Passalacqua^a, Ruby Pawankar^b, Carlos E. Baena-Cagnani^{a,c} and Giorgio Walter Canonica^a

^aAllergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa, Genova, Italy, ^bNippon Medical School, Tokyo, Japan and ^cFaculty of Medicine, Catholic University of Cordoba, Cordoba, Argentina

Correspondence to Professor Ruby Pawankar, MD, PhD, Department of Otolaryngology, Nippon Medical School, 5, Sendagi, Bunkyo-Ku, Tokyo 113-8603, Japan

Tel/fax: +81 3 5802-8177; e-mail: susan@nms.ac.jp

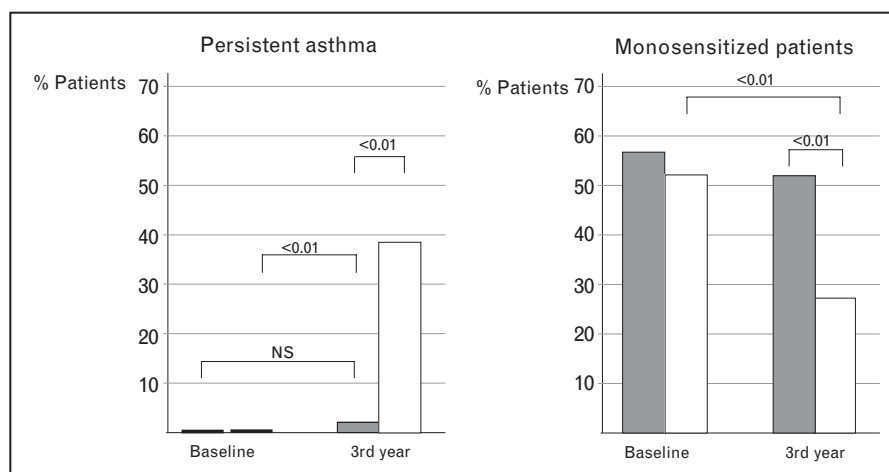
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The prevalence of allergic rhinitis is high and markedly increasing worldwide [1]. Although not life threatening, it has a significant impact in terms of impaired quality-of-life (QOL), socially, at school and in the workplace and its huge economic burden is not negligible [2]. More importantly, allergic rhinitis is often associated with relevant comorbidities, including asthma, conjunctivitis, sleep disturbances and rhinosinuses. Of note, allergic rhinitis is considered a clinical manifestation of a systemic immunological disorder that involves the respiratory tract (United Airways Disease) [3]. In light of this fact, it is not surprising that allergic rhinitis is often associated with asthma, is an independent risk factor for the development of asthma itself [4] and the presence of allergic rhinitis often worsens the QOL of patients with asthma [5]. We have currently several effective pharmacological treatments available, namely topical corticosteroids, topical and systemic antihistamines and leukotriene modifiers [6]. Nevertheless, none of the drugs are able to alter the immunological changes underlying the abnormal response to allergens and, consequently, the natural history of respiratory allergy and of atopy in general. By contrast, allergen specific immunotherapy (SIT) is the only treatment that, in addition to its clinical efficacy, can modify the response to allergens at an early stage and, thereby modify the natural history of respiratory allergic disease. This has been consistently demonstrated with subcutaneous immunotherapy, which maintains its efficacy even after its discontinuation, prevents the onset of new sensitizations and reduces the risk of developing asthma [7,8].

After more than 20 years of clinical trials, postmarketing surveys and mechanistic studies, sublingual immunotherapy (SLIT) is nowadays regarded as a real step forward in the management of allergic rhinitis, as it currently represents the only realistic alternative to the traditional injection route [9]. The clinical efficacy (in terms of symptom improvement) has been shown for the most

common allergens in numerous clinical trials and confirmed in meta-analyses in adult and pediatric populations [10,11]. Although meta-analyses have serious limitations, essentially due to the great heterogeneity of the clinical trials, so far they are the only instruments available for attempting to achieve an overall evaluation of the results of numerous trials according to evidence-based principles. It is true that there are still uncertainties due to the large variability of the doses of allergen employed in many clinical trials [12], and to the various schedules of administration, that make SLIT less rigidly formalized than injection SIT. On the contrary, it is difficult to seriously question the immunological effects of the treatment, as mechanistic studies have repeatedly demonstrated that SLIT is able to affect the T response by modulating some of the activities of T regulatory cells [13,14], independently of the extract used. In addition, the recent large clinical trials conducted with grass tablets [15,16] have consistently shown the dose-dependency of the clinical effects of SLIT. This fact strongly increases the robustness of the proof of efficacy, according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) recommendations [17]. Of note, in both those clinical trials, the magnitude of the effect over placebo largely exceeded the 20% suggested threshold, required for defining an immunotherapy as clinically effective [18]. Finally, taking into account the economic aspects, which are of relevance in the case of allergic rhinitis, SLIT has been formally shown capable of reducing both the direct and indirect costs of the disease [19–21].

It is also important to consider the effects of SLIT in a broader sense, which is not only limited to reduction in symptoms and medication use during exposure to allergens. In this respect, there are now clinical data demonstrating the preventive effects of SLIT, in particular in reducing the risk of inception of asthma in children with allergic rhinitis [22,23]. The most recent open-controlled study [23] on this aspect, conducted on more than 200 children, receiving either SLIT or drugs only for 3 years, showed a 40% reduction in the onset of persistent asthma in the SLIT-treated patients, associated with a significant decrease in the onset of new sensitizations (Fig. 1) [23]. The good safety profile of SLIT in children, even below the age of 5 [24], expands in principle the possible use of

Figure 1 Rate of onset of persistent asthma in the sublingual immunotherapy-treated patients and controls

NS, not significant; SLIT, sublingual immunotherapy. □, controls; ■, SLIT.

this treatment in taking advantage of the preventive effects since the earliest steps of the development of allergic diseases [25]. Of note, SLIT has been suggested to be of benefit also in children with mild-to-moderate atopic dermatitis and who are sensitized to house dust mite [26].

Despite the optimistic results of studies so far conducted, some important points still need to be addressed, including the optimal dose for each allergen and the optimal duration of a SLIT course needed to achieve the maximum benefits and the longest duration of the effects. In this context, recent large trials have started to provide some valuable information, at least for grass allergens, suggesting that an 8-week preseasonal treatment achieves the best benefits [27]. The preliminary results of a 15-year-follow-up study demonstrated that the optimal duration of a SLIT course should be 4 years [28]. Also, there is a general trend toward a uniformity of the administration schedules, with no up-dosing regimens and daily administrations, which are easier to manage and patient-friendly. Finally, a dichotomy exists between allergists from Europe and USA, as the latter use mixtures of different allergens for the same patient. In this regard, some case reports have suggested that mixing different allergens in SLIT may lead to severe adverse events [29,30]. This is not true when only few standardized allergens are given as done in Europe [31,32].

In conclusion, SLIT should be regarded as an additional effective therapeutic option for the treatment of allergic rhinitis, provided that a specialist prescribes it, after a detailed and appropriate diagnosis has been made and the risk to benefit and cost/benefit issues have been extensively evaluated.

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