Rostrums

Sublingual immunotherapy: The optimism and the issues

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The acceptability of sublingual immunotherapy (SLIT) in guidelines or statements has recently increased. SLIT is currently used in Europe, Asia, and Australia for the treatment of allergic respiratory diseases. Four meta-analyses have shown that SLIT is an effective tool for the treatment of patients with asthma and/or rhinitis, and only conflicting results were reported for children with allergic rhinitis. Moreover, it offers logistic advantages and is safe. However, some unmet needs are to be faced, such as the difficulty of manufacturers to achieve the homogeneity of standardized vaccines, the magnitude of their clinical efficacy, and the pivotal question of an early intervention with SLIT in young children with IgE-mediated disorders. Altogether, SLIT has already given convincing results in respiratory diseases both in adults and children. In the future, this route of administration of allergic vaccines may improve even the treatment of patients with IgE-mediated food allergy. These patients indeed deserve better than allergen avoidance. The immunomodulatory treatment of allergic diseases probably has found a new tool; however, a more balanced understanding of this form of allergen immunotherapy is needed. This aim could be achieved through: (1) the improvement of products standardization quality; (2) an attempt to modify in children the natural course of allergic diseases; and (3) new research on mechanisms of action.
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Allergen immunotherapy is a subject widely debated by allergists. For many decades, the discussion on allergen immunotherapy had focused on subcutaneous route of administration of the vaccines (subcutaneous immunotherapy [SCIT]); currently, ''pro'' and ''con'' sessions are focused on the sublingual route (sublingual immunotherapy [SLIT]).

SLIT has been used thus far in Europe, Asia, and Australia for the treatment of allergic respiratory diseases[1] and is now considered an efficacious and safe alternative to SCIT, whereas the use of local nasal immunotherapy (LNIT) is progressively declining.[2,3] Moreover, recent published data have highlighted the effectiveness of SLIT in patients with sensitization to foods[4] and also in children with a mild form of atopic dermatitis (AD).[5]

The historical studies with SCIT were performed in children aged 3 to 14 years,[6,7] and neither serious side effects nor life-threatening events were reported. Nonetheless, a subsequent well-conducted trial reported severe asthma, generalized urticaria, angioedema, and anaphylaxis in treated children less than 5 years of age.[8]

Since then, the preschool age is regarded as a prudent limit for immunotherapy in view of the possible risk of severe side effects. Indeed, this age is considered a relative contraindication for SCIT,[9] because severe side effects are more difficult to treat in very young children, and injection immunotherapy carries the risk of important untoward reactions.[10] Recent data, however, have demonstrated that SLIT is safe in young children and offers new possibilities for the treatment of pediatric patients.[11,12]

Although the precise mechanisms underlying the induction of immune tolerance by SLIT remain unclear, the contact of the allergen with antigen-presenting cells (APCs) in oral mucosa is likely to be critical. Therefore, one explanation for the specific mechanisms of action of SLIT may be the profound difference between both oral APCs and oral Langerhans cells (LCs) and their skin counterparts.[13,14]

The sublingual route has attracted the greatest interest in recent years, as shown by the number of double-blind, placebo-controlled trials and the fact that SLIT has spread widely in Europe[15]; however, some issues with SLIT still need to be addressed, such as the actual difficulties in determining the optimal doses of the vaccines, the magnitude of their clinical efficacy, the pivotal challenge of early intervention in young allergic children, and the choice of future developments. Another unresolved question concerns the multiallergen mixes by SLIT. So far in the United States, vaccines are often used as multiple allergens; however, in Europe, they are used as single allergens or antigen(s) with multiple component activities.

ALLERGEN STANDARDIZATION(S)

The quality of the allergen vaccines is critical for both diagnosis and treatment. Where possible, standardized vaccines of known potency and shelf life should be used. The most common vaccines used in clinical allergy

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practice are now available as standardized products, but this standardization is currently nonhomogeneous.

The vaccines administered by the sublingual route are based on the aqueous biological extracts from the natural allergen sources as both drops (in glycerosaline solution) or fast-dissolving tablets. Sublingual vaccines prepared from raw allergic materials, such as grass or tree pollens,[16,17] are previously exposed to both macroscopic and microscopic examination in order to determine electrophoretic profiling and evaluate of bacteriological load and biological activity.

Allergens are commonly extracted at 4°C with an ammonium bicarbonate solution, and their protein extract is ultrafiltrated to remove small (<1 kd) molecules. The resulting extract contains all the water-soluble allergens and proteins from the raw material; these include active ingredients (major or minor allergens) as well as nonbioactive components, such as other proteins, glycoproteins, and carbohydrates.[18]

In some instances, allergens are previously modified in order to produce allergoids; chemical modification involves formaldehyde or glutaraldehyde treatment to cross link the proteins. To produce monomeric allergoids appropriate for SLIT, carbamilation of the aminogroups in lysine residues is often used, which maintains native allergen molecular size and confers resistance to gastroenteric enzymes.[19]

Each manufacturer has its in-house reference preparation (IHPR) to determine the immunologic activity of an allergen preparation. The IHPR is subsequently used as a reference to adjust allergenic activity of each commercial batch *in vitro* (Table I).

The production of whole standardized vaccines is now a realistic goal that should be reached. However, current barriers to achieve whole and common standardization include the use of global IgE binding by radiollergosorbent test (RAST) or enzyme-linked immunosorbent assay (ELISA) using pooled sera from allergic individuals as a measure of total potency.[20]

IgE-binding assays (RASTs) are often unable to detect the differences in individual major quantities or ratios between major allergens for products with multiple components activities, such as grass pollens and at lesser extent house dust mites.[21]

To overcome these drawbacks, the European Commission has been funding a large, multidisciplinary project to improve allergen standardization in Europe. The project aims to develop candidate reference materials consisting of purified natural or recombinant major allergens.[22] Because each supplier uses its own standardization procedure, it is not possible to compare the amounts of allergens present in the extracts of the different manufacturers. Therefore, it is suitable that actual situation will change in the near future; however, the drawback regarding this issue is the fact that the production of the allergen extract is often part of the allergy companies' intellectual property.

The Allergic Rhinitis and its Impact on Asthma document (ARIA) identified that SLIT doses higher than those in SCIT are required to obtain clinical efficacy.[23] In clinical trials, antigen doses from 5 up to 375 SLIT/SCIT ratio were used.[2] Other studies, on the contrary, have shown that cumulative doses close to those used for SCIT can be successfully used.[24,25]

TABLE I. Main standardization references used among the several sublingual vaccines with different allergen units currently produced by manufacturers

- IU: International unit
- AU: Allergy unit
- BAU: Biological allergy unit
- BU: Biologic unit
- IR: Index of reactivity
- TU: Therapeutic units

Maintenance doses from 0.5 μg up to 210 μg per week can be achieved with SLIT according to the different allergens used.

In SCIT, the antigen in combination with adjuvants such as calcium phosphate or alum is directly injected into the subcutis underlying the epithelium, where professional APCs as LCs reside.

In SLIT, antigen first has to be exposed to the oral mucosa before it can be taken by LCs or other APCs; of note, the oral mucosa shows limited absorption of allergens. One explanation for the claimed dose dependence might be that an insufficient amount of the antigen is available for the presentation by APCs using the sublingual route at low allergen doses.

Therefore, high-dose regimens likely facilitate capture of sufficient amounts of allergens by sentinel dendritic cells within the oral mucosa, which represents a critical step to induce an adequate and long-lasting T-cell response.[26,27]

Thus, an implement of the standardization(s) of allergen products for the therapy is required by manufacturers in order to avoid large differences among different suppliers.

THE EFFICACY AND THE SAFETY

In 1993, the European Academy of Allergy and Clinical Immunology position paper on specific immunotherapy proposed that SLIT might be used as a therapy to be investigated in order to prove its efficacy and safety.[28] In 1998, the World Health Organization position paper[9] found 4 double-blind, placebo-controlled trials on SLIT and proposed that SLIT may be used in adults with allergic rhinitis, whereas there was insufficient evidence to use it in children.

In 2001, the ARIA document examined 10 double-blind, placebo-controlled studies and indicated that SLIT has been evaluated in studies carried out on allergic rhinitis induced by certain pollens and mites.[23]

The American Academy of Allergy, Asthma & Immunology (AAAAI)- American College of Allergy, Asthma and Immunology (ACAAI) clinical guidelines published in 2003[29] concluded that SLIT requires further evaluation before it can be recommended in routine clinical practice. The American Societies of Allergy underlined that

currently no vaccines for sublingual use were available in United States. However, both the AAAAI and ACAAI formed a joint task force with the purpose of providing a comprehensive and updated report on SLIT for the North American allergy community.[30]

Meanwhile, 4 meta-analyses on the efficacy and safety of SLIT in the treatment of rhinitis in adults and children[31] and both asthma and rhinitis[32-34] were produced. The conclusions of these studies recommended the use of SLIT in patients with allergic respiratory diseases, except for children with allergic rhinitis in whom the results are more controversial. The balance sheet for SLIT is improving, and the efficacy of this treatment is recognized in patients with both asthma and rhinitis.

However the degree of efficacy of SLIT has not been frequently compared with that of SCIT; only a double-blind, double-dummy controlled trial provided evidence that no significant difference exists between SCIT and SLIT in term of symptom improvement and rescue medication use.[35] In this field, other comparative trials would be suitable, particularly in patients who are allergic to ''strong pollens'' such as *Parietaria judaica* or grass pollens.

There is a robust evidence to support the excellent safety profile of SLIT; in more than 20 years of clinical trials, no life-threatening events or fatality have ever been reported[36]; its safety profile has been confirmed in clinical trials with children less than 5 years old in whom the most frequently reported side effects were related to local itching and oral discomfort.[12] Abdominal pain and/or diarrhea occurred in some cases, which could be reduced by temporary dose decrease.

The worsening of allergic symptoms such as rhinoconjuctivitis, wheezing, and urticaria is uncommon, but the appearance of mild to moderate systemic adverse events should be taken into consideration as a possible side effect.[37] Recently, for the first time, 2 cases of anaphylaxis were reported in adult patients during administration of rush SLIT to latex[38] or during SLIT with mixed extracts of inhalant allergens.[39]

TREATMENT OF CHILDREN: THE PIVOTAL CHALLENGE

The concept of specific desensitization lies at the heart of our speciality because allergen immunotherapy is the only antigen-specific immunomodulatory treatment routinely available. At the core of this concept, there is the likely hypothesis of a critical window in early life during which immunologic and respiratory response phenotypes are commonly programmed. If this hypothesis is correct, damping the cycles of early viral- and/or allergy-mediated damage in at-risk subjects or in children at the beginning of disease progression would facilitate transit through this life phase without development of persistent diseases.

With respect to the allergy pathway, the intervention on allergy T_H2 memory development may be a successful strategy for asthma prophylaxis or early therapy.

Immunotherapy confers long-term benefit up to 12 years after its discontinuation,[40,41] and in children, immunotherapy has been shown to prevent the onset of new sensitizations[42] and to reduce the evolution from rhinitis to asthma.[43] Also, SLIT shows long-lasting effects[24] and interferes with the progression of rhinitis towards asthma.[25]

All these are pivotal approaches because immunotherapy might be even more effective in younger children in whom allergen-specific T_H2 memory is less well established and hence more susceptible to downregulation.[44] Therefore, by translating our basic science into clinical practice, the secondary prevention of asthma and allergy with allergen immunotherapy may offer more possibilities of success for the treatment of IgE-mediated disorders in the future (Fig 1).

The single notion of atopic march—that is, that a child progresses from atopic dermatitis to asthma and hay fever with increasing age—is currently considered elusive.[45]

The Multi-Centre Allergy Study, a German birth cohort study that followed 1314 children from birth to 7 years of age,[46] showed that early wheeze and specific sensitization patterns are able to predict wheezing and asthma at school age irrespective of early eczema or rhinitis. Therefore, the best method for early treatment of IgE-mediated disorders is treating more allergen sensitizations and symptoms than diseases themselves.

Precocious allergen immunotherapy should be adopted particularly in young children allergic to perennial allergens: allergy to house dust mites and/or animal dander should be the main target of this strategy.[47] Food-allergic disorders affect 6% to 8% of children in their first 3 years of life[48] and then decrease in prevalence over the first decade. However, it is estimated that about 4% of the population is affected by food allergies.[49]

The issue of the natural course of food allergy is currently more controversial than considered in past years. It is generally thought that milk allergy is short lived; however, in a recent study of 118 children with cow's milk allergy followed to 8.5 years,[50] the authors found that for those with IgE-mediated cow's milk allergy, only 75% were tolerant by the age of 5 years and 15% were still allergic by the age of 8.5 years. This study indicated that after the age of 5 years, the rate of allergy loss is quite slow.

Although resolution is also reported, persistence of childhood food allergies is common with certain foods, especially peanuts, tree nuts, and seafood.[51] The only current treatment options in food allergy are allergen avoidance and adequate pharmacotherapy in the case of accidental ingestion. Moreover, treatment with humanized anti-IgE antibodies seems to be able to protect at least a subset of patients by increasing their threshold dose for allergic responses.[52] However, it is to be underlined that the strict allergen avoidance is often an ''uncomfortable therapy'' and a great burden for the majority of children and their families.

A recent study investigated the effects of a SLIT with hazelnut extract in hazelnut food allergy. It was shown that the threshold dose eliciting objective symptoms could be increased after 2 to 4 months of SLIT using the spit-out method.[4] In recent years, increasing amounts of the

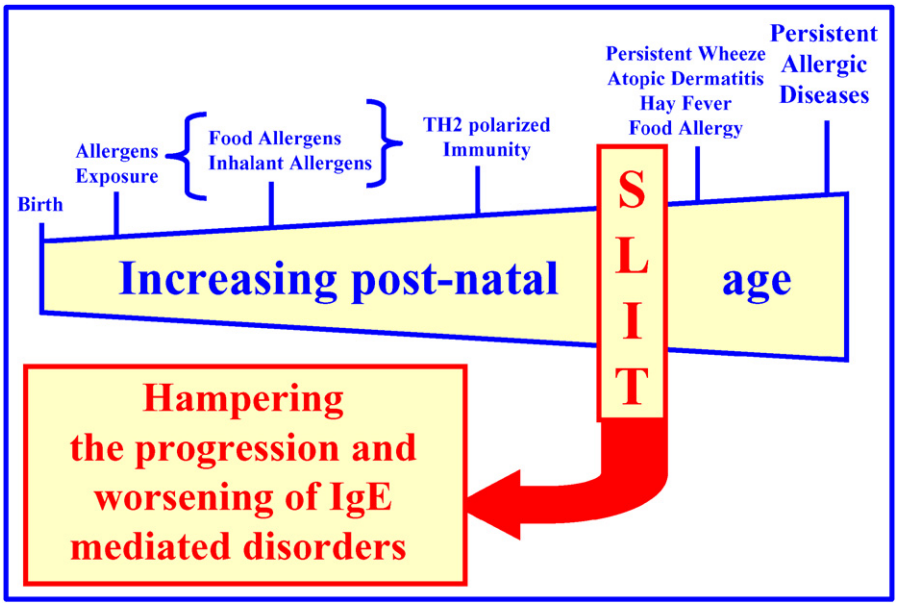

FIG 1. Role and timing of SLIT in hampering the progression of allergic diseases. In children with IgE-mediated allergic disorders, a preventive effect is expected.

corresponding food allergens have been administered orally, with the aim of achieving tolerance.[53-55]

Further studies are awaited in order to establish whether oral hyposensitization or specific oral tolerance induction will be an effective and safe alternative to the elimination diet in children with persisting IgE-mediated food allergy.

THE CHOICE OF FUTURE DEVELOPMENTS

Before further advances in understanding the efficacy and mechanism of action of SLIT can be made, there are still a few needs to be met:

- Allergen dosage and formulation. A noticeable difference among published controlled trials concerns the amount of allergen administered. It is likely that, compared with SCIT, vaccination by the sublingual route requires at least 50 to 100 times more allergens to reach similar levels of efficacy.[23] According to other reports, however, cumulative doses employed for SLIT may not greatly differ from the ones used for SCIT.[56,57] In the majority of cases, SLIT is administered in the form of drops with limited use of tablet formulation. The change from drops to tablet formulation could provide, at least in adult patients, an advance in SLIT dosing and vaccine development. On the other hand, this aim is far from being achieved at the moment because each manufacturer uses its own standardization, formulation, and administration schedules.
- Early intervention. Inhaled glucocorticoid therapy improves asthma control, but it is not clear whether this treatment can prevent the progression of asthma. The early use of inhaled glucocorticoid therapy for wheezing in preschool chidren has not been demonstrated to change the natural history of asthma or wheeze in childhood and to prevent lung function decline or to reduce airway reactivity.[58-60] Selective eradication of the ubiquitous allergen exposure might be not achievable. In fact, drastic reduction of house dust mites has been found to increase rather than to decrease the risk of atopy,[61] possibly through the concomitant eradication of other protective environmental exposures. The excellent safety profile of SLIT and the fact that injections are not required with this method raise the possibility that SLIT could be given to children less than 5 years of age in an attempt to modify the natural course of the allergic diseases. Children with repeated wheeze in the first 5 years of life who develop sensitization to perennial allergens and become prone to a chronic asthma evolution[47] may be suitable for SLIT treatment; likely, the time is ripe for new challenges on this field, such as secondary prevention of IgE-mediated disorders with allergen immunotherapy.
- Multiple sensitizations. The major criticism of allergen immunotherapy regards the patients with multiple sensitizations,[9] especially in Europe where single-allergen vaccines are used. This issue is of particular relevance in adults in whom multiple sensitizations to inhalant allergens are frequently found. To some extent, it is possible in patients with multiple sensitizations to extrapolate the allergens that are responsible for allergic symptoms; however, some failures of allergen immunotherapy are due to the wrong treatment of patients with very extensive positive skin prick tests to pollens, house dust mites, molds, and cat or dog dander.

- Food allergy. The next generation is likely to be a more atopic population according to the increasing evidence from recent birth cohorts and epidemiologic studies.[62] Food allergy is increasing worldwide,[63] and the attention towards an immunomodulatory treatment against food IgE-mediated disorders is recent. Some attempts with oral hyposensitization have been carried out, resulting in quite positive effects; in the future, this approach may become an efficacious treatment for children with persistent food allergy who would deserve better than strict allergen avoidance.

In the last few years, 95 years after the first attempts, allergen immunotherapy has been defined as ''a new strategy to counter allergy,''[64] and current evidence on SLIT suggests new possibilities for its routine clinical practice, especially in childhood.

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