New Applications for Sublingual Immunotherapy in Allergy

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Abstract: Specific immunotherapy is the only treatment targeting the causes, and not only the symptoms, of allergic diseases. Sublingual immunotherapy (SLIT) was introduced and developed to solve the problem of the adverse reactions, uncommon but possibly severe and rarely fatal, to the traditional subcutaneous immunotherapy (SCIT). The evidence of SLIT efficacy concerns rhinitis and asthma caused by sensitization to pollens and to house dust mites, but there are increasing data suggesting that SLIT could be applied in forms of allergy hardly feasible for SCIT because of its poor safety (this is true for food allergy and latex allergy) or could be considered for new applications, such as atopic dermatitis or baker's asthma. In particular, there are placebo-controlled trials indicating good efficacy and safety of SLIT in patients allergic to latex and to foods and in children with atopic dermatitis, that indicate SLIT as a real treatment option in such clinical entities. This article also discusses some patent related to the field.

Keywords: Sublingual immunotherapy, efficacy, safety, atopic dermatitis, food allergy, latex allergy, baker's asthma, Hymenoptera venom allergy.

INTRODUCTION

Specific immunotherapy is the only treatment targeting the causes of allergic diseases and not only the symptoms as drugs do. Sublingual immunotherapy (SLIT) was introduced and developed to solve the problem of the adverse reactions, uncommon but possibly severe and rarely fatal, to the traditional subcutaneous immunotherapy (SCIT) [1, 2]. Different alternative routes of administration of allergen extracts for immunotherapy were proposed, but eventually SLIT emerged as a true option to SCIT. This was demonstrated by a number of studies showing that this route of immunotherapy is comparably clinically effective, provided allergen doses as high as 50-100 times those used with SCIT are administered, and has a much better profile of safety and tolerability than SCIT [3-5]. In fact, adverse reactions to SLIT are usually local, involving the mouth or the gastrointestinal tract, and severe systemic reactions are extremely rare.

The evidence of SLIT efficacy concerns rhinitis and asthma caused by sensitization to pollens and to house dust mites [4, 6, 7], but there are increasing data suggesting that SLIT could be applied in forms of allergy hardly feasible for SCIT because of its poor safety (this is true for food allergy and latex allergy) or could be considered for new applications, such as atopic dermatitis or baker's asthma.

SLIT IN FOOD ALLERGY

Food allergy affects about 10% of children and 2-3% of adults and is expressed with a number of clinical manifestations, the most severe being anaphylaxis [8]. The management of food allergy is commonly based on elimination from the diet of the foods identified by diagnostic work-up, but inadvertent assumption of small amounts of the culprit food is always possible and this may expose the patients to severe and also potentially fatal reactions [8]. The attempt to prevent anaphylaxis to peanut by SCIT with an aqueous peanut extract revealed not feasible because of a poor tolerance in treated patients, which led the authors to claim for less allergenic preparation [9]. Indeed, food allergens modified by chemical reduction and alkyla-tion were introduced [10], but derived materials for immunotherapy are not yet commercially available.

The option to desensitize food allergic subjects by noninjection route was tested by two techniques: the oral and the sublingual administration. The first method, recently named specific oral tolerance induction (SOTI) is based on oral assumption of increasing amounts of the causative food [11], and was demonstrated as effective in allergic to peanut [12-14], to cow's milk [15-17] and to egg [18]. However, SOTI has to be considered a desensitization method (similar to that performed with drugs) more than immunotherapy, since to maintain the tolerance the patient must assume a daily fixed amount of the food. Instead, a placebo-controlled trial demonstrated that SLIT offers promising outcome: 23 adult patients with hazelnut allergy underwent SLIT with a standardized hazelnut extract for 12 weeks, and the actively treated showed a significant increase in tolerance to hazelnut and a good safety, with only 0.2% of the total doses administered provoking systemic effects [19]. The authors three years later reported follow-up data showing that patients maintained the tolerance [20]. Thus, SLIT seems to

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be a way forward in treating food allergy and other studies testing the most common responsible foods are warranted.

SLIT IN LATEX ALLERGY

Latex allergy especially affects health care workers with a spectrum of clinical reactions from contact urticaria to anaphylaxis. This allergy is mainly managed by avoidance, but immunotherapy may be indicated when reactions occur even to minimal exposures. Similarly to food allergy, the attempt to treat latex allergic patients by SCIT resulted less than ideal. The first controlled study used a rush schedule and reported an high number of adverse reactions [21], subsequent trials with less aggressive protocols had a safety profile more acceptable but the clinical efficacy was disputable [22, 23]. The introduction of SLIT was associated to better results: in a randomized controlled study, 26 latex-allergic children received a latex extract (12 subjects) or placebo (14 subjects), being possible to observe that actively treated had after three months of treatment a significant ($p = 0.01$) clinical improvement, with further advance ($p = 0.0005$) after one year [24]. The clinical efficacy was accompanied by an optimal safety profile, with no significant reaction to SLIT. The follow-up of the study for further three years consolidated the evidence of efficacy and safety of latex SLIT in pediatric patients [25]. A report of an anaphylactic reaction to the same latex SLIT extract in an adult patient partially affected this confidence [26], but a recent study on rush latex SLIT showed a good safety profile also in adults [27]. However, future studies with less allergenic preparations, such as those with recombinant allergens with multiple mutations and reduced IgE-binding affinity [28] are needed to further improve the safety of SLIT in latex-allergic patients [29].

SLIT IN ATOPIC DERMATITIS

Atopic dermatitis (AD) is a model of systemic allergy, since the causative allergens may enter through the skin, but may also be ingested or inhaled, the skin remaining the site of clinical manifestations [30]. Management of AD is based on identification and elimination of exacerbating factors including irritants and allergens, adequate hydration of the skin, control of itching, prevention of infections, and appropriate use of topical or systemic medications [31]. New approaches include the controlled delivering of antigens, in order to substantially reduce contact between the antigen and the IgE receptor in the skin [32], and, very recently, non irritant fabric and clothes to further reduce skin irritation [33].

Allergen immunotherapy has long been considered contra-indicated in AD, because of expert opinions suggesting that this treatment could worsen the status of the disease. Actually, a large number of studies of immunotherapy with house dust mites extracts is available. Dust mites, namely *Dermatophagoides pteronyssinus* and *farinae* are the best fitting allergen for application in AD, because of the high prevalence of sensitization and the high levels of specific IgE to the major allergen Der p 1 in patients with AD, and because the proteolitic activity of Der p 1 can destroy epithelial tight junctions and facilitate the penetration of allergens through the skin, reducing interleukin (IL)-2 production and activating the release of inflammatory cytokines such as IL-6 e IL-8, which enhance local inflammation [34, 35]. Moreover, the atopy patch test with dust mites extract induces an inflammatory reaction of the skin typical of AD and correlates well with the status of the disease [36].

However, the high number of immunotherapy studies with mite extracts for patients with AD needs to be accurately examined. A recent review by Bussmann *et al*. selected 23 papers published between 1974 and 2006, but only five could be evaluated because of the high heterogeneity of the remaining studies [37]. Of note, four of the five studies reported a significant improvement of AD following immunotherapy. In addition, three more studies were recently published, one using SCIT and the others using SLIT with *Dermatophagoides* extracts. The SCIT study was conducted on 86 patients treated for one year: the results showed a reduction of AD severity, as assessed by a 46% decrease of the commonly used SCORAD, and a statistically significant clinical improvement in 59% of patients, along with a very good tolerability of immunotherapy [38]. Concerning the SLIT studies, the first was a placebo controlled trial including 56 children, 28 actively and 28 placebo treated: the difference in SCORAD between actively and placebo treated was significant ($p = 0.025$) starting from 9 months after SLIT initiation, along with a significant reduction in drug use. Only two patients had AD exacerbation during SLIT [39]. The other was a prospective open study on 86 patients (adults and children): there was a 46% reduction in SCORAD in comparison with baseline value, and a significant improvement, defined as a SCORAD reduction of > 30%, was observed in 59% of patients; no severe adverse events were observed during the trial [40].

Therefore, SLIT seems to be a promising approach to treat AD, but more studies are needed to validate this therapeutic tool in such application.

SLIT IN BAKER'S ASTHMA

Cereals (wheat, barley, rye and oats) are the major source of human feeding and a quite common cause of allergic reactions in children and adults, including atopic dermatitis, urticaria/angioedema, gastrointestinal disorders, and anaphylaxis, also associated to physical exercise [41]. A particular form of cereal allergy is Baker's asthma, which is an occupational allergy defined by the occurrence of asthma following exposure to flours [42]. The cereals components able to induce IgE-mediated hypersensitivity are contained in the Osborne's three protein fractions, which comprise albumin/globulins, gliadins, and glutenins [43]. The most relevant allergens are alpha-amylase inhibitors, omega(5)-gliadins and lipid transfer proteins, all being involved in anaphylactic reactions as well as in Baker's asthma [44].

Management of cereal allergy is based on their elimination from the diet, on drug treatment of acute reactions, and, for Baker's asthma, on changing work. Allergen immunotherapy is used, though rarely, in common practice when the allergic subject cannot avoid the contact with flours, but there are no published studies on its efficacy and tolerability. We reported the case of a patient with both asthma from flour inhalation and gastrointestinal symptoms

from ingestion of cereal-based foods who was successfully treated with SLIT by a four cereal (wheat, rye, barley and oats) extract [45].

Starting from 6 months after SLIT initiation, the patient showed an increasing tolerance to ingestion of cereals and to respiratory exposure to flour. After 1 year, he had no more flour-induced asthma and was able to eat small amount of bread and pasta with no gastrointestinal symptoms. After 2 years he could eat normal servings of any bakery product. Of note, at that time a remarkable decrease of cereal specific IgE was detected: the level changed from 38.7 to 9.2 kU/L for wheat, from 40.1 to 8.2 kU/L for barley, from 29.2 to 6.6 kU/L for rye, and from >100 to 43.4 kU/L for oats. No adverse event to SLIT occurred. These findings suggest that SLIT with cereal extracts can be clinically and immunologically effective in baker's asthma as well as in food allergy caused by cereals, and make worthy to investigate this issue in randomized controlled studies.

SLIT IN HYMENOPTERA VENOM ALLERGY

Subjects with allergic reactions to Hymenoptera (including honeybees, wasps, yellow jackets and hornets) stings are successfully treated by venom immunotherapy [46]. This treatment was introduced in 1978 by a placebo controlled trial [47] and is performed by the subcutaneous route with excellent efficacy and good safety. It is important to note that thus far no fatal reaction was reported neither as a treatment failure nor as an adverse reaction to SCIT. Venom immunotherapy is indicated in patients with systemic reactions and positive diagnostic tests [46], while large local reactions (LLR) to stings, i.e. local reactions with a diameter larger than 10 cm up to loco-regional oedema, are not an inclusion criterion. However, such reactions are often very disturbing making difficult, especially when the arms are involved, to attend to daily common activities. One study found that SCIT reduced the LLR diameter by more than 50% in almost 60% of treated patients [48]. A recent double-blind, placebo-controlled trial investigated the effectiveness of SLIT with honeybee venom: 30 patients with LLRs were randomized to active or placebo treatment, being possible to observe a reduction of the mean diameter of LLRs from 20.5 to 8.5 cm ($p = 0.014$) with active but insignificant changes with placebo SLIT [49]. The authors defined the study a proof-of-concept, suggesting further investigations for SLIT in Hymenoptera venom allergy, however it is our opinion that its use in subjects with anaphylactic reactions to stings, optimally protected by SCIT with good treatment safety, seems hardly feasible.

MAIN ISSUES IN NEW SLIT APPLICATIONS

After the first studies conducted with low allergen doses it became apparent that cumulative dosages 50-100 times higher than those administered with SCIT were needed to ensure clinical efficacy in allergic rhinitis and asthma [50]. For some of the new applications, such as latex allergy or Baker's asthma, this SLIT/SCIT dose ratio is maintained, while for dust mite extracts in atopic dermatitis a lower ratio was used, as reported in Table **1**. However, the good results observed make possible that in such application also lower doses may be clinically effective. In large local reactions to Hymenoptera stings, a monthly dose about 5 times higher than SCIT was equivalent in terms of size reduction of the reactions. Concerning food allergy, no dose comparison is

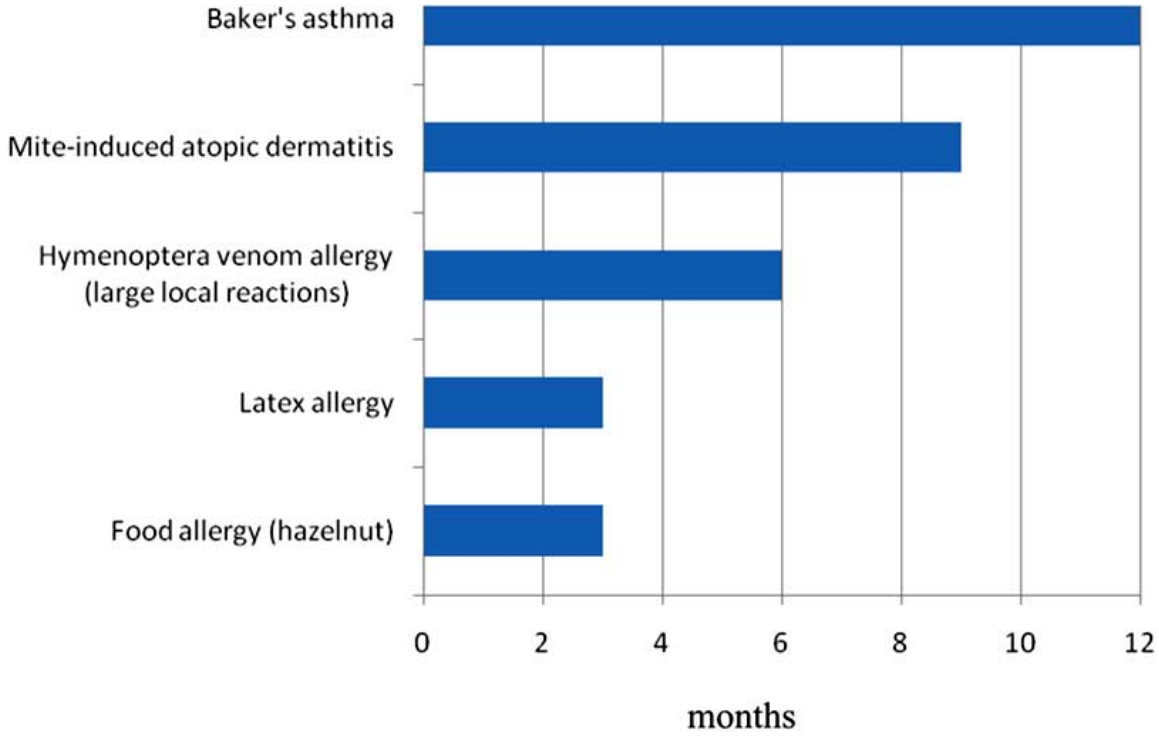

Fig. (1). Duration of SLIT required to achieve clinical efficacy in the different applications.

feasible because the only study of SCIT was conducted by a peanut extract, not yet tested with SLIT.

Table 1. Comparison of Cumulative Doses Administered by SLIT and SCIT in the New Applications

Application	SLIT/SCIT Ratio
Latex allergy	More than 50
Baker's asthma	About 100
Atopic dermatitis	About 10
Hymenoptera venom allergy (large local reactions)	About 5

Another important aspect is the time interval needed to achieve clinical efficacy. In respiratory allergy this time commonly corresponds to 3-6 months, while for some of the new indications longer time intervals seem necessary, as showed in Fig. (**1**).

CURRENT & FUTURE DEVELOPMENTS

Allergen immunotherapy has unique characteristics in the treatment of allergic diseases. The limit of SCIT have always been the adverse reactions, quite rare but sometimes severe and potentially life-threatening. Advances in material to perform SCIT included more purified products such as depigmented allergen extracts, allergoids, with reduced capacity to elicit severe adverse reactions, peptides or small aminoacid sequences, recombinant allergens, hypoallergenic vaccines where the IgE binding sites have been modified, or allergen-CpG fusion molecules [51]. Following various attempts to introduce noninjection routes of administration, SLIT eventually demonstrated to join to clinical efficacy a very good safety [52, 53]. Such safety profile is likely to be related to the particular characteristics of the oral mucosa as a tolerogenic site [54], and offers opportunities of applying immunotherapy also in situations where the injective route is too risky. This is true for food allergy [55] and latex allergy, in which experiences with SCIT were burdened by unacceptable safety, while initial studies indicate SLIT as a feasible approach.

SLIT seems promising also in fields where SCIT gave inconclusive results: in AD more than 20 studies with SCIT did not allow firm conclusions due to great heterogeneity and conflicting findings, and in Baker's asthma SCIT is sometimes practiced but no trials are available. Especially in the first case, SLIT seems to offer concrete possibilities of early intervention in children, who are the most frequently affected by AD, often with a severe impairment of quality of life.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

SLIT = Sublingual immunotherapy

SCIT = Subcutaneous immunotherapy

SOTI = Specific oral tolerance induction

AD = Atopic dermatitis

IL = Interleukin

SCORAD = Scoring atopic dermatitis

Ku/L = Kilo unit/liter

LLR = Large local reactions

CpG = Cytosine - phosphate - guanine

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