

Rostrum

Sublingual immunotherapy in children – ready for prime time?

After a decade of controversies, high-dose sublingual immunotherapy (SLIT) has been demonstrated to be a safe and effective therapy option for adults and children with pollen. Studies have clearly shown that there is a dose-response relationship with regard to reduction of symptoms and symptomatic medication intake. Moreover, comparison of different trials indicate the fact that clinical efficacy of SLIT may depend on the duration of therapy. Therefore for both, children and adults, SLIT should only be performed with high-dose preparations providing documented efficacy for a sufficient period of time to ensure that the best benefit is achieved.

Do we have sufficient evidence?

Although there is still an ongoing discussion on discrepancies and inconsistencies in published meta-analyses (47), SLIT seems to be increasingly accepted as an alternative to subcutaneous application of allergen extracts in adults with pollen induced allergic rhinitis, especially patients with time-consuming jobs or fear of injections (1, 2). SLIT has its origin in the development of an oral route of allergen delivery as proposed 40 yr ago in some European countries (3). Several investigators have demonstrated that gut adsorption of proteins is sufficient to provoke an immune response (4). Despite the theoretical advantage of oral immunotherapy (OIT), many of the early studies failed to demonstrate clinical efficacy (5, 6). Preparations for OIT as a precursor to SLIT can be regarded as 1st generation preparations (see Table 1). Although we have to assume that immunological mechanisms of SLIT and oral SIT are fundamentally different, first SLIT studies were mainly performed with oral preparations and can therefore be designated as 2nd generation preparations. Trials using these preparations were less convincing since efficacy determined on the basis of symptom and/or medication scores was not

consistently or only rarely demonstrated (7–9). The meta-analysis by the Cochrane Collaboration evaluated efficacy of SLIT in allergic rhinitis in adults suffering from allergy to seasonal allergens for a number of studies performed between 1993 and 2001 (1). The studies included belong mainly to the 2nd generation preparations (see Table 1) and demonstrated large between-trial heterogeneity and inconsistent results. Overall, there was a low but significant reduction in both symptom scores (SMD -0.42; 95% CI -0.69 to -0.15) and medication requirements (SMD -0.43; 95% CI -0.63 to -0.23). Nevertheless, none of the studies included showed significant superiority to placebo for both, symptom and medication scores.

In 2001, the ARIA Workshop Report stated that SLIT required at least 50 to 100 times the cumulative dose of SCIT in order to achieve efficacy: “Efficacy has (only) been documented for high allergen dose sublingual-swallow specific immunotherapy in double-blind, placebo-controlled studies carried out in allergic rhinitis. Lower doses are not effective” (10). This statement is of limited value from a practical point of

Table 1. Orally and sublingually applied allergen preparations for immunotherapy

Generations	Characteristics
1st (since 1970)	Oral preparations (inadequately powered, controlled studies)
2nd (since 1990)	Oral preparations, not especially developed for SLIT Mainly low major allergen content (poor documentation) No to moderate documentation of clinical effects
3rd (2003 – now)	Preparations with high major allergen content; developed for sublingual application Clinical documentation in randomized, double-blind, placebo-controlled (DBPC) clinical trials following ICH, ‘good clinical practice’ (GCP) and EMEA guidelines Sufficiently powered studies Standardization in terms of major allergen content

view when considering the major allergen contents necessary in SLIT preparations, because SLIT products from different suppliers have not been promoted bases on non-identical dose definitions (11) and are not immediately comparable with regard to peak dose. The apparent multiple 'high-dose' of a SLIT preparation might therefore only be based on a relatively low allergen dose of the SCIT preparation of the same supplier (12). Consequently it is essential to be aware of the absolute major allergen contents of preparations in order to make direct comparisons. Nevertheless, most SLIT studies included in the Cochrane meta-analysis (1) did not fulfil the ARIA criteria, since the cumulative dose for SLIT was rarely higher than 50-times that of SCIT and most studies used low-dose preparations.

In 2008, the ARIA Workshop Report was updated and stated that "SLIT is effective for rhinitis and asthma induced by birch, cypress, grass, olive, *Parietaria pollens* and house dust mites" (13). The doses of allergens in different studies ranged from 3- to 375-times the cumulative dose of subcutaneous immunotherapy and no definite conclusion could be drawn. However, large studies showed that a low dose is ineffective and that a daily dose of 25 µg of Phl p 5 is required to achieve efficacy, while higher doses are not more effective" (13). This defined dose based on results of only one trial (14) is of limited help, since each allergen manufacturer in Europe has established its own In House Reference Standard extract (IHRS) and the commercial batches are tested *in vitro* in comparison to an IHRS using different techniques which are neither validated in terms of their general analytical performance nor standardised between laboratories (15). Therefore, comparisons between sublingual preparations of different manufacturers are not meaningful on the basis of the major allergen content declared by the manufacturers themselves. In order to overcome this situation, the European Union CREATE project was initiated with the aim to develop international reference preparations with verifiable allergen content (16). The CREATE reference preparation and one of the candidate ELISAs with a well matched antibody pair from the project were used by a German research institute to investigate ten grass pollen SLIT preparations from various suppliers on the market (17). The content of the grass pollen group 5 allergen in the maintenance dose of the different preparations differed by a factor of 123. Three high-dose sublingual grass pollen preparations (AllerSlit.[®] forte, Grazax[®], Oralair[®]) are now available in

Europe as 3rd generation preparations. These preparations are also standardized in terms of the grasses group 5 or Phl p 5 major allergen content.

Dose-response and administration time relationship

A number of clinical trials have shown clinical efficacy and immunological and a clear dose-response relationship for SLIT preparations of several allergens (e.g. ragweed, grass pollen) (18–23, 48). Although reaching a threshold cumulative dose is important for clinical efficacy, it can be presumed that sufficient amounts of allergen are only captured by oral mucosal dendritic cells when high peak allergen doses are applied. Exposure to high doses of allergen during immunotherapy may promote the skewing of allergen-specific T cell response from a Th2 to a Th1 pattern in atopic patients (24). The clinical studies conducted so far have shown a correlation between duration of therapy and clinical efficacy, since a second (19, 25) and a third (26, 27) year of SLIT further improve symptom and medication scores. An update of the Cochrane meta-analysis has suggested that the treatment effect increases if therapy is continued for longer than 12 months (28). A new systematic review including a meta-regression analysis of 31 randomized, double-blind, placebo-controlled (DBPC) SLIT studies showed that (higher) allergen doses in combination with (longer) administration time were associated with lower clinical scores ($p = 0.048$) (29). Our own comparison of DBPC studies that used grass pollen preparations with different major allergen content in the peak dose confirm these results. High-dose preparations administered over a long time period resulted in highest efficacy, while low-dose preparations did not achieve significant efficacy independent of administration-time (Table 2).

SLIT in children

Until 2007, consensus statements and systematic reviews with meta-analyses stated that there was still a lack of strong evidence for efficacy in children. Last year two large placebo controlled randomized studies utilizing high-dose grass pollen preparations demonstrated the significant effect of sublingual grass pollen immunotherapy in children between the ages of 6 and 12 yr (30, 31). The beneficial influence of SLIT and drugs over drugs alone was clinically relevant and SLIT effect sizes were rather similar to those previously demonstrated with the same preparations in

Table 2. Major allergen content and efficacy for different grass pollen SLIT preparations (Reductions were calculated by $[(\text{Active} - \text{Placebo})/\text{Placebo}] \times 100$)

Study	Patients group	Major allergen content in the peak dose acc. to the cited publications	Duration of SLIT [months]	Efficacy active vs. placebo (mean reduction) on		
				Combined SMS*	Symptom score	Medication score
Moreno-Ancillo et al. 2007 (<i>SLITone</i> [®]) (44)	Adults	0.2 µg Phl p 5	10	no difference	no difference	no difference
Bufe et al. 2004 (<i>Sublivac</i> [®]) (45)	Children	3.6 µg Phl p 5	36	no difference	no difference	no difference
Emminger et al. 2008 (<i>Grazax</i> [®]) (46)	Adults	15 µg Phl p 5	34 (3 yr)	not available	29%	40%
Didier et al. 2009 (300IR) (<i>Oralair</i> [®]) (38)	Adults	20 µg grasses group 5 allergen	4–5	30%	27%	35%
Pfaar/Klimek 2008 (<i>AllerSlit[®] forte</i>) (19) and Worm 2008 (18)	Adults	40 µg grasses group 5 allergen	18	46%	not available	not available
Wahn et al. 2009 (<i>Oralair</i> [®]) (31)	Children	20 µg grasses group 5 allergen	5	34%	28%	48%
Bufe et al. 2009 (<i>Grazax</i> [®]) (30)	Children	15 µg Phl p 5	6–7	23%*	27%*	20%*

*on peak grass pollen season.

adults. Moreover there was no indication for additional safety concerns in children.

Therefore it seems likely, that the induction of tolerance via the sublingual route in even younger children, for example, to prevent the outset of allergic asthma, will soon be addressed in clinical trials.

Immunology of SLIT

There is a growing evidence to support the (prominent) role of regulatory T cells (T regs) in controlling development of asthma and allergic diseases (32), in other words in achieving the intended long-term effect of allergen-specific immunotherapy. The induction of a T reg response has been confirmed for SCIT (33), but by contrast there is still no firm evidence that SLIT can induce T regs (34), although preliminary *in vitro* data suggest that SLIT may increase interleukin (IL)-10 which has a distinct role in supporting a subsequent tolerogenic immune response (32). During SLIT, allergen-specific IgG4 levels demonstrated a clear dose response to increasing peak doses since only a high-dose SLIT regimen resulted in appreciable specific IgG4 increase (35). Low doses – such as those reached using 1st or 2nd generation preparations – failed to show any effect (36). A time-dependent effect on specific IgG1 and IgG4 was seen with different preparations (19, 25, 37, 38).

The future

Given the new evidence of clinical trials it now seems appropriate to speculate about the possible impact on the choice of therapeutic options for specific immunotherapy as practised in Europe.

3rd generation SLIT preparations are potent allergen extracts which can be prescribed for children with grass pollen allergy. These prepa-

rations represent a novel alternative for allergen immunotherapy which may have impact on allergy care and allergy service provided by specialists as well as on health economy and reimbursement issues in different countries. Up to now there are no reports about randomized head to head studies comparing high dose SLIT with SLIT protocols. Other novel therapeutic options including SCIT with recombinant or mutated hypoallergenic allergen or the application of anti-IgE either as only intervention or in combination with other specific immunotherapeutic measures (43) are likely to become reality in allergy care in the future (39–43).

Faced with these new options, it seems that the pediatric allergist will be one of the specialists to adequately diagnose allergy identifying individual triggers underlying allergic diseases and to decide which of the therapeutic options will be appropriate for which patient in order to achieve optimal therapeutic success. Therefore, for the foreseeable future the decision for allergen specific immunotherapy, be it high-dose SCIT with hypoallergenic preparations, SLIT with 3rd generation preparations or treatment with one of a new generation of products, should primarily remain in the hands of the allergy specialists.

U. Wahn¹, H.-J. Malling², J. Kleine-Tebbe³

¹Klinik für Pädiatrie m. S. Pneumologie und Immunologie, Charité, Berlin,

²Allergy Clinic, University Hospital of Copenhagen (Rigshospitalet), Copenhagen, Denmark,

³Allergy & Asthma Center Westend, Berlin, Germany

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