

# Sublingual Immunotherapy in Allergic Rhinitis and Asthma: A Review of Recent Clinical Evidence

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## ABSTRACT

A growing body of evidence is accumulating in support of sublingual immunotherapy (SLIT) for the treatment of allergic rhinitis and asthma. Several European countries use SLIT in preference to the more established subcutaneous immunotherapy (SCIT) because of improved safety and ease of administration, particularly among children and those with asthma. However uncertainty persists, particularly in the United States where SCIT is widely accepted and utilized, and SLIT is still subject to review. Contributing to this uncertainty is the apparent between-trial heterogeneity regarding efficacy; a lack of understanding regarding the mechanism of action; failure to define optimal allergen doses; and, until recently, the

lack of evidence demonstrating satisfactory patient compliance with this home-based treatment.

In the following review we look at conclusions drawn from trials conducted before 2003 and examine newer evidence obtained from recent trials recruiting larger cohorts. Our aim was to summarize the evidence presented in the medical literature, to address questions arising from these studies, and to determine whether the most recent evidence supports the contention that SLIT can be considered as a valid alternative to SCIT in allergic rhinitis and allergic asthma.

In response to suggestions that between-trial heterogeneity might stem from differences between allergens prepared by different companies or arise as a consequence of limited cohort size, we present the evidence with clear distinction between trials according to source of allergen preparation and where possible examine studies based upon relatively large cohorts.

## INTRODUCTION

Allergen-specific immunotherapy involves the administration of specific allergens to achieve a hyposensitization such that the symptoms occurring during the natural exposure to the allergen are reduced. In particular, it is used for allergic disorders such as seasonal and perennial allergic rhinitis and allergic asthma.

First practiced in the early 1900s, subcutaneous injection (subcutaneous immunotherapy [SCIT]) of allergens became the first well-accepted route for administration based on clinical and immunological efficacy. However in 1986 the British Committee on Safety of Medicines spuriously reported several deaths caused by SCIT,<sup>1</sup> which were subsequently shown to be the result of human error. In response to this, alternative routes of administration were investigated. Of these, sublingual immunotherapy (SLIT), in which liquid drops or allergen tablets are placed under the tongue for 1-2 minutes before being swallowed, and local nasal immunotherapy (LNIT), which involves spraying a solution or dry powder into the nostril, were found to be viable alternatives.

In 1998 a World Health Organization (WHO) led committee of experts, representing 9 individual and international allergy organizations, presented a position paper advocating the use of immunotherapy for the treatment of allergic rhinitis and asthma.<sup>2</sup> These recommendations were based on studies demonstrating efficacy with allergens administered via subcutaneous injection. However, it was also noted that treatment with SCIT is, in some cases, associated with the occurrence of systemic reactions, including, in rare instances, anaphylaxis, with severe asthma appearing to be a significant risk factor for these adverse events. On the basis of this latter point some<sup>3</sup> but not all<sup>4</sup> guidelines

list asthma as a contraindication for immunotherapy despite its demonstrated efficacy. At the time, SLIT and nasal immunotherapy were considered to be promising alternatives, but in need of further studies to better define the appropriate patients and allergen dosage. Subsequent to this a meta-analysis of 16 SCIT trials concluded that SCIT is effective in the treatment of allergic rhinitis, treatment being associated with an odds ratio of 1.8 (95% confidence interval [CI] 1.48 to 2.23) for improvement in symptoms.<sup>5</sup> Similarly a Cochrane meta-analysis of 54 trials<sup>6</sup> (later updated and extended to 75 trials<sup>7</sup>) found that SCIT significantly reduces asthma symptoms and medication scores. Thus, confidence in the efficacy of immunotherapy with SCIT was established. However because of the requirement for injections and frequent visits to the physician, as well as the potential for anaphylaxis with SCIT, interest in SLIT was maintained.

SLIT is now widely used throughout Europe and it has received approval from the WHO working group and the international ARIA (Allergic Rhinitis and its Impact on Asthma) consensus group,<sup>8</sup> for use in patients with allergic rhinitis and asthma. Further support for the use of SLIT was provided by a recent Cochrane review of 22 randomized controlled trials comparing SLIT to placebo in allergic rhinitis.<sup>9</sup> In this extensive review it was concluded that SLIT treatment significantly improves rhinitis symptom scores and anti-allergic medication requirements compared to placebo. However, considerable unexplained heterogeneity was also noted between studies, despite adjustment for type of allergen (seasonal versus perennial), age (adults versus children), and study length.

Despite demonstration of the efficacy of SLIT in controlled trials and its inclusion in official European guidelines,

there remains some uncertainty as to whether SLIT is a reliable and efficacious option to the more established SCIT.

In the following report we present a brief overview and update regarding evidence for the efficacy and safety of SLIT relative to placebo and relative to SCIT in allergic rhinitis and asthma. Emphasis was placed on recently completed trials reported in the literature between 2003 and 2006 and not included in the previously published meta-analyses. Although numerous excellent reviews of immunotherapy have been previously published,<sup>10,11</sup> this review differs in that we have focused on recently published trials recruiting relatively large cohorts (many of the trials included in the Cochrane Review of Wilson et al<sup>9</sup> included less than 50 patients) and we have clearly distinguished between preparations produced by different suppliers of allergens. This approach was adopted in response to reports that product-specific differences might be a major source of between study heterogeneity in trials of SLIT and therefore might bias outcomes.<sup>12</sup> This issue is discussed in the following review as are some previously unanswered questions relating to patient compliance and the duration of effectiveness for which data has only very recently become available. The aim of this review was to assess whether the evidence from recent trials, conducted under rigorous controlled conditions, support the contention that SLIT is a valid alternative to SCIT in allergic rhinitis and allergic asthma.

## **METHODOLOGY**

In February 2006, the Medline PubMed database was searched for relevant articles using the following key words and phrases: sublingual immunotherapy; SLIT; SCIT; subcutaneous immunotherapy; immunotherapy comparisons; immunotherapy rhinitis; immunotherapy

asthma. Of the identified hits, abstracts of those articles published between 2003 and 2006 were reviewed for suitability and full-text versions obtained where appropriate. In addition, articles referred to in review articles and meta-analyses were obtained in full-text form where appropriate.

## **SUBLINGUAL IMMUNOTHERAPY VERSUS PLACEBO**

### **Allergic Rhinitis**

#### *The Cochrane Review*

The Cochrane Review of SLIT for allergic rhinitis<sup>9</sup> was based on 22 randomized trials published between 1996 and 2002 comparing SLIT (from various companies) with placebo (Table 1). Because different studies employed different assessment scales and scoring systems, the Cochrane analysis was performed by the method of Standardized Mean Differences (SMD). The SMD range varied from -4.0 to +4.0, a value of 0 indicating no difference and a value of <0 favoring SLIT over placebo. From this extensive analysis based upon a large combined cohort (741 patients for symptom scores and 681 for medication scores), it was concluded that SLIT provides a significant improvement in rhinitis symptom scores and anti-allergic medication requirements compared to placebo.<sup>9</sup> The overall treatment-related effect being significant reductions in SMD for symptom score at -0.42 (95% CI -0.69 to -0.15,  $P=0.002$ ) and in medication score of -0.43 (95% CI -0.63 to -0.23,  $P=0.000003$ ) compared to placebo. This corresponds to treatment-related reductions in symptom and medication scores of 15-50%. When sub-analyses of studies involving adults and children were conducted the results remained significant for the former but not the latter group. However it was noted by the authors that the small number of children (218 patients for symptom score and 128 for medication score) included

**Table 1.** Studies Included in the Cochrane Review of Sublingual Immunotherapy (SLIT) versus Placebo in Allergic Rhinitis<sup>9</sup>

Study	Reference	Allergen/ Manufacturer	Number of		Reduction	Reduction
			Patients	Cohort	in Symptom Scores	in Medication Scores
Andre 2003	45	RG/Stallergenes	110	A	+	+
Guez 2000	46	HDM/Stallergenes	72	A/C	+	+
Mungan 1999	40	HDM/Stallergenes	26	A	+	+
Pradalier 1999	47	G/Stallergenes	126	A	+	+
Vourdas 1998	48	OL/Stallergenes	66	C	-	-
La Rosa 1999	49	PJ/Stallergenes	41	C	+	+
Bahceciler 2001	50	HDM/Stallergenes	15	C	-	+
D'Ambrosio 1999	51	P/ALK-Abelló	30	A	+	+
Feliziani 1995	52	G/ALK-Abelló	34	A	+	+
Lima 2002	53	G/ALK-Abelló656	A	-	+	
Passalacqua 1999	54	HDM/ALK-Abelló	30	A	+	+
Tari 1990	55	HDM/ALK-Abelló	66	C	+	NR
Troise 1995	56	P/ALK-Abelló	31	A	+	+
Voltolini 2001	57	Tree pollen/ALK-Abelló	30	A	-	-
Casanovas 1994	58	OLEA/NR	15	A	+	+
Ariano 2001	59	CUPRESSACEAE/NR	20	A	+	+
Hirsch 1997	60	HDM/Allergopharma	30	C	-	NR
Hordijk 1998	61	G/NR	57	A	+	+

A=adult; C=children; NR=not reported; RG=Ragweed; HDM=house dust mite; G=grass; P=parietaria; +=reduction in score for SLIT versus placebo; -=no difference in score between SLIT and placebo groups

in these studies was the most likely explanation for this lack of significance.

**Response to the Cochrane Review**

Similarly, results obtained in a recent analysis of SLIT for respiratory allergy in children found a non-significant reduction in nasal symptom scores and medication scores.<sup>13</sup> In that meta-analysis, 7 trials were included (232 patients for nasal symptoms and 146 for medical scores), of which 2 were not available for the Cochrane review, although it should be noted that their inclusion only added an additional 22 actively treated patients. The standardized mean difference in rhinitis symptom score was -0.44 (95% CI -1.22 to 0.35,  $P=0.27$ ) and for medication score -1.01 (95% CI -0.06 to 0.04,  $P=0.06$ ).

In a second response to the lack of significance noted in the Cochrane review, a meta-analysis of more recent

trials of allergic rhinitis in pediatric patients and including twice as many subjects (484 patients for symptom scores and 279 patients for medication scores) was conducted.<sup>14</sup> In that analysis the SMD for nasal symptom score was -0.56 (95% CI -1.01 to -0.10,  $P=0.02$ ) and for medication score -0.76 (95% CI -1.46 to -0.06,  $P=0.03$ ).

Thus, while the smaller analyses found marked improvements that failed to reach significance, when adequate numbers of patients were included in the analysis the significance of these reductions in symptom and medications scores for pediatric patients was evident. Therefore, the evidence is consistent for adult and pediatric cohorts, and supports the efficacy of SLIT in the reduction of both symptom and medication scores among patients presenting with allergic rhinitis. The uncertainty introduced by conducting trials in very small numbers

of patients could be avoided in future studies by recruiting more patients at the outset. Economic constraints would therefore place the onus for conducting such trials on the manufacturers of SLIT preparations. However, the importance of doing so is apparent when one considers that immunotherapy is the only treatment option currently available that has the potential to alter the course of allergy and SLIT in particular is the safest and most easily administered option for children. Providing evidence obtained from large, well-matched cohorts should be a priority in the future.

In an independent analysis of the studies included in the Cochrane review of SLIT but separated according to product manufacturer, it was observed that the products manufactured by ALK-Abelló (Hørsholm, Denmark) were associated with greater reductions in medication and symptom scores compared to the overall result of the Cochrane review.<sup>12</sup> The ALK-Abelló product-specific reductions for symptom and medication scores were -0.55 (95% CI -0.81 to -0.28) and -0.52 (95% CI -1.11 to 0.07), respectively. In the same sub-analysis, the trial results obtained with Stallergenes (Antony, France) preparations yielded reductions in medication score of -0.35 (95% CI -0.69 to -0.01) and symptoms score -0.13 (95% CI -0.32 to 0.5). Of those studies included in the Cochrane review approximately one-third were based upon use of ALK-Abelló products (8 studies with 154 subjects).

Although the product-specific analysis is noteworthy, the studies included in the Cochrane review also clearly differed with respect to the cohorts studied, allergens administered (grass pollens/house dust mite (HDM)/olive etc.), dose of allergen, and formulation. Therefore it is very difficult to determine to what extent the overall

between-trial heterogeneity can be attributed to specific product differences as opposed to trial differences. The effective relative-dose reported for SLIT in the literature ranges between 3 and 5 to 375 times the doses of SCIT, and both high and low doses have been associated with satisfactory and unsatisfactory results.<sup>11</sup> The American College of Allergy, Asthma and Immunology noted that despite reviewing more than 100 scientific papers they could not find sufficient evidence to define minimum and maximum effective doses for SLIT immunotherapy.<sup>15</sup> Therefore differences in administered relative-dose are unlikely to explain the between product differences.

However, a key limiting step in SLIT is the uptake of allergen across the mucosal barrier and into Langerhans-like dendritic cells,<sup>16</sup> differences at this point could affect efficacy by limiting the actual dose delivered to target cells. The uptake of allergen into dendritic cells is dependent on complex interactions, where age, mucosal permeability at the time, allergen dose, allergen quality, allergen form, and intervals between allergen administration may play a critical role.<sup>10</sup> Therefore, while comparing increasing doses of the same SLIT preparation to itself may reveal a 'dose-dependence' with respect to efficacy<sup>17,18</sup> similar comparisons cannot be made between different SLIT products because of potential variability in allergen quality and uptake. For example, an allergen formulation that readily penetrates the mucosal barrier to be taken up into the dendritic cells would deliver a greater effective dose to the target cells than an allergen preparation that, due to the presence of contaminants or aggregation of the allergen, is unable to efficiently cross the mucosal barrier. In the latter case administration of higher doses of allergen might overcome some of the resistance, however, it would also

increase cost by increasing the required dose of allergen.

Based on currently available data it is not possible to resolve the issue of variations in efficacy when comparing different products, therefore it would seem prudent to base future analyses of SLIT on a product-specific basis as is done in the following update, without generalizations.

### **Recent Trials**

In the Cochrane review the corresponding values for change in symptom and medication scores compared to placebo were -0.42 (95% CI -0.69 to -0.15) and -0.43 (95% CI -0.63 to -0.23), respectively.<sup>9</sup> Results obtained from large randomized trials published after 2003 (and therefore not included in the Cochrane review) generally concur with the Cochrane report findings in demonstrating SLIT-associated reductions in symptom and/or medication scores<sup>19,20</sup> (Table 2). Importantly, these more recent trials have, in many cases, enrolled greater numbers of patients compared to previous studies in which total cohort size (treatment plus control) often did not exceed 50 patients (Table 2), and therefore the newer trial data should be less prone to the influence of random variation.

The most recently reported study was a double-blind randomized trial which involved use of an ALK-Abelló grass pollen SLIT preparation among 114 adult patients suffering from rhinitis and asthma.<sup>21</sup> Treatment with grass pollen tablets pre-season and during the pollen season was associated with a significant 37% reduction in rhinoconjunctivitis score and a 41% reduction in medication score during the season. The end of trial symptom scores were 2.1 ( $\pm 1.7$ ) and 3.3 ( $\pm 2.2$ ) and medication scores were 2.4 ( $\pm 3.9$ ) and 4.2 ( $\pm 4.1$ ) for SLIT and placebo, respectively. These results are clearly in line with the findings of the Cochrane report.

Importantly, use of grass pollen tablets did not induce asthma symptoms. Although no difference in asthma onset could be detected, the low pollen count during the trial period may have influenced the low incidence of asthma symptoms in both treatment and placebo groups. The overall safety profile of SLIT was also confirmed in this study with equal proportions of patients in treatment and placebo groups reporting mild adverse events and no serious adverse events being reported by either.

A significant reduction in medication score was also observed in a randomized trial of mixed grass pollen SLIT (ALK-Abell) versus placebo, conducted among 97 children with allergic rhinitis but not asthma.<sup>22</sup> After 3 years of treatment, drug use and development of asthma were significantly reduced, but not symptom scores. The common relative risk of development of asthma was 3.8 (95% CI 1.5 to 10.0) in the control group. These improvements were again associated with a very low rate of side effects during the maintenance phase at 0.083/1000 doses. A second trial of grass pollen SLIT (ALK-Abelló) among children randomly allocated to treatment or placebo also noted a significant reduction in medication score (-33%,  $P=0.0025$ ) and a non-significant reduction in symptom score (-15%,  $P=0.22$ ).<sup>19</sup>

In another randomized trial of grass pollen extract (Stallergenes), it was demonstrated that despite a lack of between-treatment-group difference after the first year, significant differences were apparent after 2 years.<sup>20</sup> Treatment was associated with a 6.8 times greater likelihood of reduced nose running ( $P<0.001$ ) and a 2.5 times greater likelihood of reduced sneezing compared to placebo (Table 2). In that trial of 136 allergic rhinitis patients, subjects were randomized to either 2 years of active treatment, to receive placebo

**Table 2.** Recently Completed Studies of Sublingual Immunotherapy (SLIT) versus Placebo

Study	Reference	Allergen/ Manufacturer	Number of		Reduction	Reduction
			Patients	Cohort	in Symptom Scores	in Medication Scores
Tonnel 2004	24	HDM/stallergenes	32	A	+	-
Smith 2004	20	G/Stallergenes	136	A	+	+
Ippoliti 2003	25	DP/ALK-Abelló	86	C	+	NR
Rolinck 2004	19	G/ALK-Abelló	97	C	+(ns)*	+
Novembre 2004	22	Birch/ALK-Abelló	97	C	+(ns)	+
Dahl 2006	21	G/ALK-Abelló	114	A	+	+
Marogna 2005	23	Birch/Anallergo	79	A	+	+

HDM=house dust mite; G=grass; DP=Dermatophagoides pteronyssinus; NR=not reported; +=reduction in score for SLIT versus placebo; -=no difference in score between SLIT and placebo groups; \*ns=not significant

for 1 year prior to active treatment in the second year or to treatment with placebo only throughout the trial period. After 2 years only the first group showed improvement in sneezing and nose running, confirming the importance of long-term treatment with this preparation. After 2 years of treatment the use of antihistamine medication was also reduced in all groups, however while greater reductions were noted with active treatment compared to placebo, the significance of this difference was not indicated. In this trial minor side effects were reported by 70% of trial participants receiving active treatment compared to 44% of patients administered placebo. While most of these events were described as mild and well tolerated, it is noteworthy that 7 patients withdrew from the treatment group in the first year because of side effects and 4 were withdrawn because of non-life threatening systemic reactions with the Stallergenes grass pollen extract.

In a small randomized trial of birch-pollen sublingual drops (Anallergo; Florence, Italy), treatment was administered continuously to 29 adult patients and compared to 23 control patients receiving placebo.<sup>23</sup> In that trial significant treatment reductions in medication and symptom scores were observed over a 3.5-year period. The final rhinitis

symptom score was reduced by more than 50% and the use of salbutamol for asthma attacks decreased by over 80% (Table 2). The between-group differences were significant in the first season.

Similarly, significant reductions in symptom and/or medications scores have also been reported from other trials of SLIT immunotherapy.<sup>24,25</sup> Therefore, in line with the combined analyses of studies completed before 2002, these newer studies confirm the efficacy of SLIT in the treatment of allergic rhinitis. The reduction in symptom and medication scores in general terms were 30-50%, which is comparable to that documented previously with SLIT (20-50%) and close to the magnitude of effect associated with SCIT.<sup>11</sup> However, future consideration of efficacy with distinction being made between products is warranted based on the range of efficacy observed and possible differences in safety profiles suggested by results from some of the more recent trials.

### **SLIT in prevention of asthma development and progression**

The incidence of asthma in Western Europe has doubled in 10 years and in Germany there were an estimated 4 million asthmatics in the year 2000.<sup>26</sup> Among 13-14 year olds in Western

**Table 3.** Studies Assessing the Impact of Sublingual Immunotherapy (SLIT) on Asthma Symptoms Among Pediatric Patients Allergic to *Dermatophagoides pteronyssinus*: Summary of Results from a Meta-Analysis<sup>31</sup>

Study	Reference	Allergen	Allergen Manufacturer	Change in Asthmatic Symptoms
Tari 1990	55	D.pt	Neo Abelló	-40%
Pajno 2000	62	D.pt	ALK-Abelló	-57.1%
Ippoliti 2003	25	D.pt	ALK-Abelló	-61%
Hirsch 1997	60	D.pt	Allergopharma	-80%
Bahceciler 2001	50	D.pt	Stallergenes	-53%

D.pt = *Dermatophagoides pteronyssinus* major allergen

Europe, the prevalence of asthma is approximately 10% and the prevalence of allergic rhinoconjunctivitis is 10-15% according to the International Study of Asthma and Allergies in Childhood (ISAAC) committee.<sup>27</sup> Asthma and allergic rhinitis are also common comorbidities, with approximately 20% of all patients with allergic rhinitis developing asthma later in life. Therefore there is an increasing demand for effective and affordable treatment. Current treatment recommendations are generally based on the use of pharmacotherapy (steroids and bronchodilators) and immunotherapy to alleviate symptoms. However immunotherapy is the only treatment option that also addresses the underlying cause of asthma and has the potential to alter the course of allergy.

SCIT has been established as a valid treatment option for allergic asthma in adults and children. A number of reviews and meta-analyses have evaluated the use of SCIT in allergic asthma, one of the most comprehensive of which was a Cochrane review of 54 studies performed up until 1997.<sup>6</sup> In that analysis there was a significant, treatment-associated improvement in asthma symptom score (-0.53; 95% CI -0.7 to -0.35) compared to placebo and patients were less likely to require medication (odds ratio [OR] 0.28). Since publication of the first Cochrane review of SCIT,<sup>6</sup> a number of additional studies

and an update/expansion of the Cochrane review have been reported that continue to support the conclusion that SCIT treatment is associated with significant reductions in asthma symptom and medication scores.<sup>7,28-31</sup> Despite these favorable results, the association of SCIT with severe adverse reactions, particularly among those with severe asthma, as well as the difficulty of administering injection-based treatment to young children, limits the use and acceptance of SCIT.<sup>32</sup>

Due to its favorable safety profile, the potential value of SLIT-based immunotherapy in the treatment and prevention of asthma has generated considerable interest. In a systematic review of SLIT efficacy in pediatric patients suffering asthma and rhinitis, it was concluded from five papers published prior to 2003 that asthma due to HDM significantly improved with SLIT therapy.<sup>31</sup> The overall reductions in asthmatic scores were significant only in the active groups ( $\geq 40\%$  reduction) and this was the case for all tested SLIT products irrespective of dose or product utilized (Table 3).

In addition to these short-term studies (1-3 years), a 10-year prospective study of SLIT-based therapy for children suffering from HDM-induced rhinitis and asthma reported a significant reduction in the presence of asthma that persisted for at least 5 years after discontinuation of

SLIT.<sup>32</sup> In this long-term study, a total of 60 children were non-randomly allocated to treatment with SLIT (ALK-Abelló) or to the control group, and treatment was administered continuously throughout the year for a period of 4-5 years. At baseline, 86% of SLIT patients and 92% of controls had asthma; after completion of treatment the corresponding proportions were 11% of SLIT treated and 96% of controls. After 10 years (last 5 years without treatment) these significant between-group improvements were maintained. Therefore, this trial provides compelling evidence for the efficacy of SLIT in the treatment of allergic asthma.

With respect to prevention of asthma development, a recently reported 3-year-long randomized trial of co-seasonal SLIT treatment (ALK-Abelló) among 97 children with rhinitis but not asthma, provided evidence that treatment was associated with a significant reduction in the development of asthma.<sup>22</sup> The common relative risk of development of asthma in the placebo group was 3.80 (95% CI 1.5 to 10.0). In contrast, after 3 years, no between-treatment group difference in rhinitis symptom scores was observed, however medication scores were significantly different and favored use of SLIT. This trial with a relatively large cohort and long follow-up is one of the first to demonstrate the preventative potential of SLIT treatment among children prone to the development of asthma. Confirmation of these results with additional, similarly large cohorts of children and adolescents is now required, although ethical reasons will likely preclude the conductance of a blinded-trial over a long trial period. However, to date, the evidence supports the contention that SLIT treatment, as previously observed for SCIT,<sup>33</sup> prevents the development of asthma in children with allergic rhinitis.

Evidence is accumulating for the

efficacy of SLIT in both the treatment and prevention of allergic asthma. The long-term endurance of this effect has also been demonstrated in a 10-year-long trial with the ALK-Abelló SLIT preparation.<sup>22</sup> An important question raised by these trials is whether continuous SLIT treatment (as applied in the asthma treatment trials) as opposed to co-seasonal SLIT would provide even better protection. Future trials are needed to determine the most efficacious regimen. Importantly, the recent trials of SLIT in asthma have been conducted in pediatric cohorts and it is this group of patients for whom SCIT has raised the greatest safety concerns. This recent demonstration of long-term efficacy and safety with SLIT should translate into an increased acceptance and use of immunotherapy at an early stage of disease development. Thereby offering an opportunity to intervene before chronic disease is established with its long-term medication requirements.

### **Safety**

The impetus for SLIT and other alternative routes of immunotherapy was the association of SCIT with severe adverse reactions in a limited number of cases, therefore particular attention has been paid to safety in studies of SLIT. The occurrence of systemic reactions with SCIT ranges between 0.8% and 46.7%<sup>11,34</sup> while after 15 years of SLIT therapy, the corresponding rate is much lower<sup>11</sup> with estimates of 13 to 18%.<sup>35</sup> As noted throughout this report, the favorable safety profile of SLIT has been re-confirmed in recent trials, with low rates of systemic events being reported.

A recently reported meta-analysis sought to investigate a potential relationship between dose of allergen administered via SLIT and adverse events (local and systemic). After reviewing 25 studies (various SLIT preparations) it was concluded that the

overall rate of all adverse events associated with the use of SLIT was very low at 1.8 to 4.9 events per 1000 SLIT doses.<sup>35</sup> In a somewhat different survey of safety, the results of 8 controlled trials (472 adults and 218 children) using various SLIT preparations from a single manufacturer (Stallergenes) were analyzed for reported adverse events.<sup>36</sup> The conclusions from that review were that treatment with SLIT was not associated with any serious adverse event although mild gastrointestinal and buccal-cavity-associated events were more frequent with SLIT. However, while the demonstrated safety of SLIT in controlled trials is important, the safety profile of treatments obtained when SLIT is used in the everyday clinical situation is possibly of greater relevance. A survey of SLIT safety in the form of a post-marketing study was recently reported for the use of various ALK-Abelló SLIT preparations.<sup>37</sup> In total, 268 children receiving SLIT (ALK-Abelló) for respiratory allergies were followed for up to 3 years, and during that time 8 side effects were reported yielding an event rate of 0.083/1000 doses. No serious adverse events were reported. These results obtained from a realistic survey of actual use, confirm the excellent safety profile of SLIT previously observed in controlled trials.

### **Compliance**

One argument used to support the use of SCIT in preference to SLIT despite apparently similar efficacy is that the supervision of treatment by a physician might increase compliance and, therefore, overall treatment efficacy at a population level. However recent surveys of compliance fail to support that contention. In an Italian survey of 2774 children using various SLIT (n=1886), SCIT (n=806) and LNIT (n=82) products, compliance with treatment after 3 years was 78.5%, 89.1%, and 26.8% respec-

tively.<sup>38</sup> Although the between-group differences were significant, the difference between SLIT and SCIT is likely to represent an acceptable result in view of the favorable safety profile associated with SLIT. These results were also supported by a recent study of compliance among 443 patients (adults and adolescents) administered preseason SLIT (ALK-Abelló) and 223 patients receiving continuous SLIT (ALK-Abelló) over a 6-month observation period in a real life setting.<sup>39</sup> Overall compliance was satisfactory with more than 75% compliance in approximately 88% of the patients. It is interesting to note that in the latter study of ALK-Abelló SLIT the discontinuation rate at 6 months was 5%, while in the survey of Pajno et al<sup>38</sup> (which included various SLIT products) the proportion withdrawing after 12 months was 8.2% and 5.6% for SLIT and SCIT, respectively. As well as representing a very safe and efficacious mode of immunotherapy, SLIT is associated with good compliance that does not differ greatly from that associated with SCIT, even though patients are given the responsibility of self-administration.

### **SLIT VERSUS SCIT**

Direct comparison of SCIT and SLIT has been the subject of very few appropriately conducted randomized trials to date, and it is an area in need of greater attention. Of the 3 randomized trials conducted so far, 1 was marred by the failure to adequately blind patients<sup>40</sup> and another failed to include a placebo group and therefore could not conclude that active treatment (either with SCIT or SLIT) was better than no treatment.<sup>41</sup> The third trial conformed to the rigorous requirements of randomized controlled trials, although loss of patients to follow-up diminished the statistical power of that trial.<sup>42</sup> Nevertheless, in all 3 trials the efficacy of SCIT and SLIT was shown to be similar, with approxi-

mately 50% reductions in symptom and medication scores with either treatment regimen. For a review of these trials the reader is referred to the article of Malling.<sup>43</sup> With respect to safety, SLIT was clearly superior to SCIT in one trial<sup>42</sup> and comparable in another.<sup>40</sup> On the basis of currently available trial data, these treatment options would appear to be of comparable efficacy and any future trial aimed at differentiating between the 2 will need to be sufficiently powered to detect moderate differences.

### **FUTURE RESEARCH AND CONCLUSIONS**

The clinical efficacy and safety of SLIT in allergic rhinitis and asthma is now supported by numerous controlled trials, as is the case for SCIT. Between 2003 and 2006, data has been published that not only confirms the efficacy and safety of SLIT in rhinitis and asthma but also demonstrates the long duration of protection and excellent patient compliance with SLIT.

In this report we have highlighted results from recent trials with an emphasis on both efficacy and safety, but within the context of specific SLIT products. The impetus for this was apparent differences in the efficacy of SLIT treatments produced by different companies.<sup>12</sup> As we have discussed, the issue of product comparability is difficult to resolve based on the available information, however it cannot be dismissed and therefore it would seem reasonable to present future analyses in the context of specific products. A similar, product-specific approach was taken in the review published by Andre et al in which the safety of SLIT was assessed based upon trials administering SLIT allergens produced by a single manufacturer.<sup>36</sup>

In the brief review presented here and based on recent controlled trials, the

majority of publications centered on the use of ALK-Abelló products and therefore provided us with an opportunity to examine recent evidence without the added difficulty of accounting for between-manufacturer differences. The SLIT preparations of ALK-Abelló demonstrated efficacy and safety in both rhinitis and allergic asthma treatment that was at least comparable to estimates based upon meta-analyses of different SLIT products. The endurance of responses to SLIT therapy was also clearly demonstrated in the 10-year-long protection afforded by ALK-Abelló products against the development of asthma in children. In addition to this, the ALK-Abelló SLIT preparations were associated with excellent safety and compliancy rates in the surveys of real-life use. As reported here, recent trials have also demonstrated efficacy in the treatment of allergic rhinitis with SLIT products from other manufacturers. In the future, it would be helpful to perform similar product-specific reviews to monitor the consistency of efficacy/safety/compliance/duration data for these other SLIT products in both rhinitis and asthma.

Together with results from the Cochrane meta-analyses and trials directly comparing SCIT and SLIT, the current evidence also supports the contention that these alternative routes for immunotherapy are likely to be of comparable efficacy. While future studies directly comparing SLIT and SCIT under the same conditions and in comparable cohorts are needed, given the apparently similar efficacy it will be necessary to recruit large cohorts of patients to detect any differences in outcome. However the conductance of such trials should be placed as a priority because they are central to the clinical choice of the most appropriate treatment. If SCIT and SLIT were equivalent, then the improved safety of SLIT

would render it the obvious treatment option for all patients able to self administer medication (children obviously being under parental supervision). The overall rate of systemic reactions associated with SLIT is very low (0.13-0.18%). In contrast the dose-dependent rate of general systemic reactions with SCIT ranges between 0.8% and 46.7%.<sup>11</sup> However, if SCIT is moderately more effective than SLIT, then it is likely that SCIT would be more appropriate for adults while the safety profile of SLIT would make it more appropriate for young children and those suffering serious asthma, as well as those patients with a fear of needles or unable to fulfill the requirement for frequent visits to the physician to receive SCIT-based treatment.

The worldwide economic burden imposed by an increasing prevalence of asthma and allergic rhinitis is substantial. Estimates for the European Union revealed that total medical costs amounted to €3,011 million for the year 2004.<sup>44</sup> In Germany and the UK the respective estimates for annual direct costs alone were €661 and €216 per asthma patient, respectively, in 2004. Combining pharmacotherapy and immunotherapy, either in the form of SCIT or SLIT, offers the opportunity to treat the symptoms, reduce medication requirements, and restrict disease progression. However, given that there are at least 4 million asthma patients in Germany alone, the importance of performing rigorous cost-effectiveness analyses for the different treatment options is self-evident. Until appropriate head-to-head studies have been conducted under the rigorous demands of randomized controlled trials, it is not possible to conduct a realistic economic evaluation of SCIT versus SLIT. Nevertheless, in their review of immunotherapy Passalacqua et al<sup>11</sup> estimated that, even assuming that the

annual cost of SLIT extract is more than twice that of SCIT (\$360 versus \$150, respectively), after consideration of costs associated with visits to the physician, injections, and time lost, SLIT is likely to be less costly than SCIT (\$460 versus \$534 per year, respectively). More comprehensive analyses are clearly necessary, and, where possible, should include the long-term benefits of reduced asthma incidence and medication requirements, as well as improvements in patient quality of life. As new data becomes available and as the incidence of allergy and asthma continues to increase, conductance of these health economic analyses for individual SLIT products will be important.

In conclusion, current and emerging evidence continues to support the efficacy of immunotherapy in both allergic rhinitis and asthma. Similar rates of efficacy and compliancy are associated with SLIT and SCIT, however, it has been established that in many patients the safety profile of SLIT is improved compared to SCIT. While further trials are warranted, they should concentrate on the direct comparison of SLIT and SCIT with distinction being made between different products until comparability of preparations can be demonstrated. As the only treatment option available that can alter the course of allergy progression, the pursuit of further evidence relating to the clinical application of immunotherapy should be a future priority.

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