

## Allergen Specific Immunotherapy in Asthma

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### Abstract

The use of allergen Specific Immunotherapy (SIT) to treat allergic asthma is still a matter of scientific debate. Currently, there are few studies specifically designed to evaluate asthma, and few studies had a formal sample size calculation, or objective parameters of pulmonary function assessed. On the other hand, there are good quality trials with both Subcutaneous Immuno-therapy (SCIT) and Sublingual Immunotherapy (SLIT) in allergic rhinitis, where asthma symptoms were also evaluated, if present. These studies consistently reported positive results. Moreover, several favourable meta-analyses are available, although their validity is limited by the great heterogeneity of the trials included. The disease modifying effect of SIT that is the capacity of preventing asthma onset should be also taken into account.

Concerning the safety, fatalities seem to be an exceptional event, and in Europe no fatality has been reported over the last two decades. Uncontrolled asthma is universally recognized as the most important risk factor for severe adverse events.

In conclusion, both SLIT and SCIT can be used in asthma associated with rhinitis (which is the most common condition), provided that asthma is adequately controlled by pharmacotherapy. In such case, a measurable clinical benefit on asthma symptoms can be expected. Nonetheless, SIT cannot be presently recommended as single therapy when asthma is the unique manifestation of respiratory allergy.

**Keywords:** Allergen-specific immunotherapy; Allergic asthma; Efficacy; Safety

### Introduction

The use of allergen-Specific Immunotherapy (SIT) to treat asthma remains one of the most debated aspects in the field since several decades. The available guidelines provide no clear or unequivocal indication, stating only that SIT is specific for the allergen causing the allergic disease (rhinitis and/or asthma) and not for the disease itself [1]. Nonetheless, in the majority of the clinical trials, the efficacy of SIT has been evaluated separately for the two disorders, rhinitis and asthma, [2-7] and only few trials were specifically designed to evaluate the impact of SIT on asthma. This is due to the fact that in real life, isolated allergic asthma without rhinitis is infrequent and more than 30% of patients with allergic rhinitis also suffer from allergic asthma [8]. Another problem is that none of the trials evaluating asthma symptoms has been adequately designed and reported. A sample size calculation and a power analysis based on asthma symptoms alone were not ever used as primary outcome in any trial [9]. Moreover, a formal consensus on which measurement parameter for evaluating asthma should be chosen is still missing. In this regard, asthma symptoms, rescue medications intake, combined scores, asthma-free days, asthma exacerbations are all equally reasonable choices [10], however, objective functional pulmonary measurements such as Forced Expiratory Volume in one second (FEV1) were carried out only sporadically [11].

Currently, our knowledge on the use of SIT in asthma is based mostly on old clinical trials with SCIT, and on few recent trials conducted with SLIT, in rhinitis patients with concomitant asthma. Regardless of these limits, and the possible confounding factors, there is some evidence available to derive at least provisional conclusions.

### SCIT and SLIT in Asthma

There are numerous clinical trials of SCIT in asthma published before 1990, most of them, involving a small number of patients. The largest review concerning asthma includes 88 clinical trials [12]. Many of these studies were not specifically designed for asthma, but had

asthma symptoms reported. Although there are heavy methodological limitations (small samples, no power calculation, variable inclusion criteria) the above mentioned studies substantially agree on the clinical efficacy of SCIT in asthma induced by the most common allergens (grass, mite, pet dander), while about 25% of the studies mentioned in the reviews [1,13,14] failed to demonstrate a significant difference in clinical efficacy between placebo and active groups. The studies performed more recently, continued to have design limitations, without a formal sample size calculation, with inclusion criteria and outcomes largely variable and with a methodological quality often low [11]. Nonetheless the majority of the recent trials of SCIT including also asthmatic patients were able to show an improvement of asthma symptoms, and some also demonstrated a reduction in antiasthma drugs consumption. Lung function parameters (either FEV1 or PEFr) were measured only in few trials [15-20] with controversial results, but some trials reported a significant decrease in bronchial specific and non-specific responsiveness [11,12]. The first meta-analysis of SCIT in asthma took into account of 20 studies either controlled or not [21]. The same meta-analysis was updated again very recently expanded in 88 trials (70 randomized and placebo controlled) [12], with only 6 trials receiving the maximum score of 5 points at the Jadad scale, which considers the quality of blinding, randomisation, allocation of patients (from 0 to a maximum of 5). The effect of SCIT on asthma

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medication was also significant and a significant reduction in allergen-specific bronchial responses (measured by the threshold eliciting dose) was consistently shown. The heterogeneity of the studies was high, thus limiting the strength of the conclusions that could be drawn from the meta-analysis.

Sublingual immunotherapy has been introduced more recently as an alternative route of allergen administration. At present more than 70 randomized controlled trials are available [12], none of them formally sized and adequately powered for asthma. Some trials, conducted mainly in pediatric population (Table 1), were explicitly designed to include also the effects on asthma symptoms [22-27]. Regarding those trials, three of them [22,24,27] failed to detect any effect on asthma symptoms due to the randomization of almost symptom-free patients (active patients and controls had almost no asthma symptoms at baseline or during the trial). Despite the high heterogeneity of the trials, as previously mentioned, various meta-analyses confirmed the clinical effect over placebo also for SLIT in asthma [28,29]. One of the major problems of SIT meta-analyses is that they often put together studies using different allergens (i.e. mites and pollens). Very recently, this aspect was addressed by two analyses, one restricted to mite extracts [30] and one to grass extracts [31]. The meta-analysis for dust mites included 9 trials that evaluated asthma symptoms and medication requirements. The results demonstrated a significant reduction versus placebo in both symptom scores (p=0.02) and medication use (p=0.02). Similar to other analyses, there was a high heterogeneity (I<sup>2</sup>>90%) across studies. On the other hand the meta-analysis for grasses did not report specific results for asthma. As a matter of fact, it remains clear that there are differences in term of clinical response among different allergens, and that pollen-based SIT usually perform better than mite-based SIT [1].

### SIT versus Pharmacotherapy

The clinical effects of SIT, at variance with those using pharmacological treatment (bronchodilators, inhaled corticosteroids), cannot immediately be observed or measured. On the other hand SIT possesses an immuno-modulatory effect, that is profound and long-lasting (Figure 1). Based on these observations, it is currently stated that SIT does not replace drugs but must be used in addition to them, in order to achieve a maximal therapeutic benefit [1]. However, a direct comparison between drugs and SIT remains a matter of debate. The main problems are that the clinical benefits of SIT appear only over a long time period, and that a rigorous head-to-head comparison would require a 3-5 year double blind and double dummy design. Thus, few studies have been performed, and none specifically designed for asthma. Rak et al. [32] demonstrated the superiority of nasal corticosteroids versus SIT in rhinitis but found that SIT could decrease the seasonal

BHR in asthmatic patients. In another open study [33] it was shown that that inhaled corticosteroids produced a more rapid and relevant benefit than SIT (based on symptoms' grading), but SIT maintained its effects after discontinuation. A trial conducted in asthmatic children [34] demonstrated that the clinical efficacy of SLIT plus fluticasone was equal to that of fluticasone alone, but that the addition of SLIT resulted in improvement in non-bronchial symptoms. Finally, a direct open randomized trial of SLIT versus inhaled budesonide as an add-on therapy in asthmatic patients, demonstrated an overall superiority of immunotherapy versus inhaled budesonide over time [35]. Certainly, all of these studies that were not randomized or designed as open trials which limit the methodological value of these observations.

### Other Effects?

It is well known that patients affected by rhinitis have a major risk for the development of asthma [36]. The preventive effect of SIT was suggested more than 40 years ago in an observational open prospective study [37] in children and adolescents. SIT (either SCIT or SLIT) profoundly modifies the immune response to allergens (Figure 1), and was therefore hypothesized that it may alter the progression of the disease, reducing the risk of asthma onset. The effect was confirmed in more rigorous trials only during the last decades. The Preventative Allergy Treatment study enrolled 205 children (aged 6-10 years) suffering from allergic rhinitis randomized in two groups, one only with drug therapy alone and the other treated with drugs plus SCIT. After 3 years, the SCIT-treated patients had developed significantly less asthma than the control group, with an odds ratio of 2.5 [38]. The beneficial effect of SCIT lasted several years after discontinuation. A 10-year follow-up demonstrated significantly few numbers of patients with asthma in the SCIT-treated group [39]. The same effect was demonstrated in a randomized open trial with SLIT. The first open controlled study [40] involved 113 children aged 5-14 years affected by seasonal rhinitis due to grass pollen, randomly allocated to medications plus SLIT or medications only. After 3 years, 8/45 SLIT subjects and 18/44 controls had developed asthma, with a relative risk of 3.8 for untreated patients. The other randomized open controlled trial [41] involved 216 children (5-17 years) suffering from rhinitis with/without intermittent asthma, randomly allocated 2:1 to drugs plus SLIT or drugs only. The prevalence of persistent asthma after 3 years of observation was 1.5% in the SLIT group and 30% for the control group.

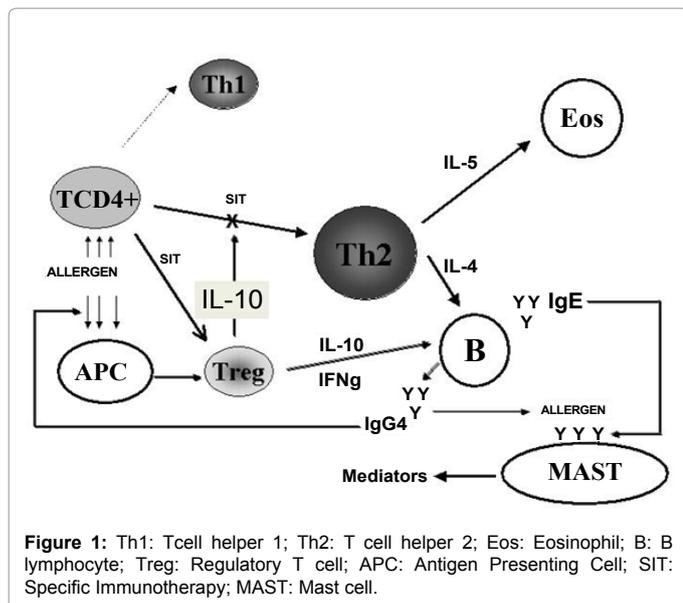
### The Safety of SLIT and SCIT in Asthma

In the published studies, the frequency of SIT-induced Systemic Reactions (SRs) is variable, according to the allergen, the administration schedule, the extract and the dose. The majority of the data on the safety of SCIT pertain the surveys performed regularly in the United

Author, year	Allergen	Active/placebo	Duration	Jadad score	Main results
Hirsch, 1997	Mite	13/14	1 yr	5/5	↓ asthma symptom score; no change in bronchial reactivity
Niu, 2006	Mite	56/54	6 months	4/5	↓ asthma symptom score, daytime, nighttime symptoms and medication score; no change FEV1 and oral steroids
Lue, 2006	Mite	10/10	8 months	4/5	↓ nighttime symptoms, ↑FEV1 vs baseline; no change total symptom score, medications and FEV1 vs placebo
Dahl, 2006	Grass	74/40	5 months	5/5	no change symptoms and medications
Pham Ti, 2007	Mite	55/56	18 months	4/5	no change symptoms, medications, FEV1, well days
Stelmach, 2009	Grass	25/25	2 season	5/5	↓ asthma symptoms and medications
Bufe, 2009	Grass	126/127	6 months	5/5	↓ asthma symptoms; no change medications

↓: decrease/reduction; ↑: increase; FEV1: Forced Expiratory Volume in one second; PEFr: Peak Expiratory Flow Rate; QoL: Quality of Life.

**Table 1:** The most recent randomized controlled trials of SLIT considering also asthma symptoms in patients with concomitant rhinitis.



States [42-47], recording about 50 deaths over a 50 year period with a risk of one death every 2.500.000 injections and one near-fatal reaction per million injections. Fortunately, in the period 2008-2011 no further fatality due to SCIT was reported in the United States and SRs were about 0.1% of injection visits [48]. It must be underlined that the practice of SCIT differs between Europe and United States. In the USA, allergen mixtures and more concentrated allergen preparations are commonly used [49]. Thus, caution should be applied in transferring the USA data to other countries [50]. Less systematically collected data is available from Europe. Other than the well-known study that reported approximately 26 SCIT-induced deaths in UK in 1986 [51], fatalities have subsequently become extremely rare, without no report in the last two decades. An Italian survey [52], stated an overall rate of systemic reactions in about 5% of patients, and a Spanish survey, which included 423 patients [53] showed a prevalence of 3.7% reactions per patient. A recent multi-centre observational study [54] suggested that systemic reactions are slightly more frequent in rhinitis with asthma than in patients with rhinitis alone, although another retrospective study [55] found no significant association between SRs and asthma. According to the more recent meta-analysis of clinical trials [12], the occurrence of systemic reactions with SCIT (of any type and severity) is about 1 per 9 patients. Despite the overall rarity of deaths, all surveys agree that uncontrolled asthma is the predominant risk factor for adverse events, including asthma itself [1,12]. The safety of SLIT is overall superior to that of SCIT [13,56], at least because no fatality has been reported until now, and only 12 cases of suspect/ascertained anaphylaxis have been described after 25 years of clinical use [57]. A controlled dose-finding study [58], involving 48 grass-allergic patients outside the pollen season and receiving daily up to 200 mcg Phl p 5, (about 40 times the amount given with one monthly injection) reported an occurrence of side effects in 74% patients, almost all local and mild or moderate in intensity. Dahl et al [24] specifically assessed the safety of SLIT in asthma. More than 100 grass-allergic asthmatics were enrolled and treated before the pollen season. The number of side effects possibly related to asthma (wheezing cough, dyspnoea) was similar between the active and placebo group, and there was no evidence of asthma aggravation. Only few large-scale surveys can assure reliable data on the prevalence, the nature and the severity of side effects. The lack of a universally accepted classification and grading system for SRs has

recently been addressed by the World Allergy Organization, proposing a new classification for systemic reactions due to SCIT/SLIT [59] and for local reactions due to SLIT [60]. According to the available data, severe or uncontrolled asthma remains the principal risk factor for side effects due to SCIT. For practical reasons, this concept has been transferred to SLIT, although the clinical data do not clearly indicate severe asthma as a specific contraindication to SLIT [13]. In general, asthma is not an absolute contraindication to SCIT/SLIT, provided that the patient is well controlled with pharmacotherapy.

### Concluding Remarks. Where Do We Stand?

Since year 2000, many guidelines and recommendations were prepared according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [61], which takes into account not only the assessment of the efficacy of a given intervention, but also the safety and the patient's preferences. Certainly, the first essential requirement is an adequate study methodology (e.g. sample size, outcome, selection criteria, randomization), not always respected in SIT trials in asthma, since many of the randomized controlled trials had important limitations (small number of patients, absence of objective measurement of lung function, no sample size calculation based on the objective parameters, variability of doses and protocols, lack of a true placebo control group). This is reflected in meta-analyses, where the overall positive clinical results are counterbalanced by the high heterogeneity of the studies. In fact, according to the GRADE rules, physicians and researchers are generally reluctant to clearly recommend the use of SIT in asthma [62], with few exceptions [63]. On the other hand, it would not be reasonable to neglect all the positive clinical data, produced so far in trials where asthma symptoms were adequately recorded. What we presently know is that for SCIT, uncontrolled asthma represents the only contraindication, although the same has not been clearly demonstrated for SLIT. Moreover, the disease-modifying and long-lasting effects of SIT in asthma prevention should be taken into account [64]. Also, the pharmaco-economical aspects should be taken into account, since it was suggested that SIT may result produce relevant saving (direct and indirect costs) in patients with allergic rhinitis and comorbid asthma [65,66]. What is clearly lacking is a predictive (either clinical or biological) parameter to anticipate the clinical outcomes of SIT in allergic patients, although attempts are ongoing to better define a phenotype-oriented profile [67]. According to the available evidence it should be stated that either SLIT or SCIT can be used together with asthma medications in patients affected by rhinitis and asthma, when the causal role of the allergen (pollens, mite or pets) is clearly confirmed. The recommendation of not giving SIT in patients with severe or uncontrolled asthma remains valid. Some unresolved questions remain: the optimal treatment schedule (pre-seasonal or continuous) [68], the optimal maintenance dose administered for SLIT for allergens other than grasses, the duration of treatment to obtain a satisfactory long term effect [69], and the appropriate use of objective outcomes in asthma. Finally, the most important question is to whose children with rhinitis only, SIT should be prescribed to achieve the relevant clinical effect of preventing the on future development of asthma.

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