

# Will Sublingual Immunotherapy Offer Benefit for Asthma?

Carlos E. Baena-Cagnani · Désirée Larenas-Linnemann ·  
Alvaro Teijeiro · Giorgio Walter Canonica ·  
Giovanni Passalacqua

Published online: 11 September 2013  
© Springer Science+Business Media New York 2013

**Abstract** Evidence shows that sublingual immunotherapy (SLIT) is indicated in patients with allergic rhinitis (AR). In this article we discuss whether SLIT could offer benefit for children and adults with asthma. We reviewed individual trials on SLIT in asthmatic patients, but also asthma data reported in some SLIT trials conducted in AR patients. Findings were complemented with data from systematic reviews and meta-analysis on the subject since 2000 and some guidelines that mention immunotherapy for asthma treatment. In AR patients with concomitant persistent asthma, SLIT reduces medication needs while maintaining symptom control. This holds especially true for house dust mite SLIT. Data on pollen SLIT and lung symptom improvement with SLIT, however, are less convincing. Therefore, we suggest SLIT should be added as an optional add-on therapy for patients with asthma whenever

a causative allergen has been demonstrated and AR is associated with asthma. For the future, SLIT should be studied in specifically designed asthma studies in allergic asthmatics without AR.

**Keywords** Asthma · Immunotherapy · Sublingual · Children · Adults · SLIT · Pollen SLIT · House dust mite SLIT

## Introduction

Asthma is one of the most common chronic diseases, with an estimated 300 million individuals affected worldwide. Its prevalence is increasing, especially among children [1].

Asthma is a heterogeneous disease with several plausible causes leading to a chronic inflammation of the airways [2, 3]. One of the major causes being allergic inflammation, it is estimated that exposure to allergen(s) might be the triggering factor leading to the chronic airway condition in far more than half of the patients. In pediatric asthma, this percentage is even higher [4]. Historically, exposure to indoor allergens had already been shown to augment sensitization—as expressed by elevated levels of specific immunoglobulin (Ig) E—in a dose-dependent manner [5, 6] and in turn sensitization to indoor allergens to augment the risk of development of asthma [7]. These findings have been confirmed more recently [8]. For seasonal allergens such as pollens a relationship with seasonal asthma has been documented, although some argue this should not be considered real asthma.

As allergic inflammation is part of the pathophysiology of most asthmatic patients, immunotherapy should be a therapeutic option for asthma as for allergic asthmatics it is the only disease modifying treatment. Subcutaneous allergen immunotherapy in individuals with a single allergy reduced the number of new sensitizations that developed over a 3- to 4-year time-span [9]. For sublingual immunotherapy (SLIT) some

---

Carlos E. Baena-Cagnani and Désirée Larenas-Linnemann: Both authors contributed equally to this work.

C. E. Baena-Cagnani · A. Teijeiro  
CIMER (Research Center for Respiratory Medicine) Catholic  
University, Fundación LIBRA, Córdoba, Argentina

A. Teijeiro  
e-mail: [info@centropediatrica.com.ar](mailto:info@centropediatrica.com.ar)

D. Larenas-Linnemann (✉)  
Hospital Médica Sur, Mexico, DF, Mexico  
e-mail: [marlar1@prodigy.net.mx](mailto:marlar1@prodigy.net.mx)  
URL: [www.dr.larenas.com](http://www.dr.larenas.com)

C. E. Baena-Cagnani · G. W. Canonica · G. Passalacqua  
Allergy and Respiratory Diseases, Department of Internal Medicine,  
University of Genoa, Genoa, Italy

G. W. Canonica  
e-mail: [canonica@unige.it](mailto:canonica@unige.it)

G. Passalacqua  
e-mail: [passalacqua@unige.it](mailto:passalacqua@unige.it)

contradictory results were reported in this respect [10, 11]. In terms of asthma prevention the Preventive Allergy Treatment (PAT) studies [12, 13] opened a new avenue, and in this direction well designed and powered studies are now underway seeking the asthma preventive potential also for SLIT [14, 15••].

As such, GINA guidelines do indicate a role for immunotherapy in the treatment of asthma, be it a modest role. For immunotherapy to be indicated in the treatment of asthma, GINA guidelines stress the importance of the precise detection of the causative allergen and the balancing of efficacy against safety in the decision-making process [1]. A review by the Cochrane Airways Group of randomized controlled trials using various forms of injection allergen immunotherapy for asthma found 75 immunotherapy trials that fulfilled the inclusion criteria, 39 of which used a house dust mite extract. Overall, it would have been necessary to treat three patients with immunotherapy to avoid one deterioration in asthma symptoms [number needed to treat (NNT)=3] and four patients to avoid one requiring increased medication (NNT=4). These are excellent numbers compared to the NNTs with medical treatment, which are normally higher. However, as SCIT can have systemic reactions, the number needed to harm (NNH) was remarkable [16]. Moreover, a GRADE review of scientific evidence in the literature published between 2008–2012 concluded that for SCIT in pediatric asthmatic patients there exists high-quality evidence for improvement in asthma symptom and medication scores [17].

We here review the data available on the efficacy, safety and immunological changes with sublingual immunotherapy in patients with allergic asthma. We base our review on scientific evidence present in published literature and on personal experience of the authors. This article does not have the intention to be a complete systematic review of SLIT as several good reviews already exist on this subject [18–20, 21••, 22•].

## Methods

The data presented here are based on records from individual trials on SLIT in asthmatic patients and asthma data reported in some SLIT trials conducted in rhinitis patients. These findings are complemented by a discussion based on data from several systematic reviews on the subject [18–20, 21••, 22•], a Cochrane meta-analysis on sublingual immunotherapy in allergic rhinitis [23••] and data from the Practice parameter on House Dust Mite 2013 [24].

For the individual trials a PubMed search was conducted to identify original and review articles on SLIT in children and adults published between 1 January 2000 and 31 March 2013 and written in English or Spanish. Search terms and limits were all combinations of desensitization, immunologic

[medical subject heading (MeSH) terms] OR allergen immunotherapy AND administration, sublingual (MeSH terms) AND 2000/01/01-2013/03/31 AND (Review) (Randomized) (Controlled) (Clinical Trial) AND (English OR Spanish) AND the MeSH terms humans. We identified additional articles by manually searching references from the obtained articles and review articles. Study design was not a restriction; only full-text articles were included. Articles that were included in the meta-analysis and reviews we analyze in this articles were generally not commented on again individually.

## SLIT for Asthma: Efficacy

### Pollen SLIT: Adults

One high-quality DBPC trial investigated the safety and efficacy of a grass-pollen SLIT tablet (ALK, Denmark) given daily in a pre-coseasonal schedule to 114 asthmatic patients with rhinoconjunctivitis (RC). Although well days increased by 54 % in the active group ( $p=0.002$ ), the differences between active and placebo groups in asthma medication and symptom scores were negligible, probably because asthma was very mild. The reductions in RC scores on the contrary were clear (37 % for RC symptoms and 41 % for medication). No serious adverse events were reported [25].

Another pollen SLIT trial in adult asthmatic patients was conducted by Marogna et al. Here the design was open, randomized and controlled, comparing 5-year SLIT versus co-seasonal 800 µg/day inhaled budesonide in 51 mild-persistent adult asthmatic patients with grass pollen-induced asthma. In the long term, bronchial hyper-responsiveness improved significantly only in the SLIT group; SLIT was equally effective as inhaled budesonide in treating bronchial symptoms, but provided an additional benefit in treating rhinitis symptoms. Moreover, In the SLIT group vs. the budesonide group, a statistically significant decrease of nasal eosinophils was found at 3 and 5 years ( $p<0.01$ ) [26].

A year later another randomized open comparison of montelukast and birch pollen sublingual immunotherapy as add-on treatment in moderate persistent asthma was conducted. During five consecutive birch seasons, 33 patients with allergy solely due to birch pollen were randomized to receive either montelukast (10 mg/day) or co-seasonal birch SLIT, in addition to salmeterol/fluticasone (plus salbutamol and cetirizine as rescue medications). Asthma and rhinitis symptoms were recorded on diary cards from February to May and were lower at 3 and 5 years compared to baseline in the SLIT group. In-season bronchial hyper-responsiveness and bronchodilator use decreased significantly in both groups at 5 years, but only in the SLIT group at 3 years. In the SLIT group there was a significant decrease in in-season nasal eosinophils compared to the montelukast group and compared

to baseline. These results lead to the author's conclusion that in patients with birch pollen-induced moderate asthma and rhinitis, the addition of SLIT provides a greater clinical benefit than the addition of montelukast [27•].

Apart from these few pollen-SLIT trials in adult asthmatic patients, the great majority of articles on sublingual immunotherapy for pollen allergy are in patients with allergic rhinitis and rhinoconjunctivitis, most of them suffering simultaneously from intermittent asthma or mild persistent asthma. As such, the studies are designed to show efficacy in rhinitis/rhinoconjunctivitis scores. Asthma outcomes are only reported secondarily, thus leading to designs not optimally powered to show statistically significant differences with the asthma outcome parameters. Even so, favorable asthma results have been reported in most of the SLIT pollen trials, but should be interpreted with care as the design focused on rhinitis; thus, asthma evaluation was generally not complete and only based on subjective symptom and medication scores.

The use of co-seasonal grass pollen SLIT for 3 years in a DBPC of 183 patients with seasonal RC (and mild asthma in 13 %) showed, in a separate analysis of single asthma symptom scores, a trend for improvement even 1 year after treatment cessation [28].

In the US pre-coseasonal daily treatment with a grass pollen SLIT tablet in 439 subjects with allergic rhinoconjunctivitis (ARC), four asthma symptoms were also recorded and reported for the entire study population, without asthma subgroup analysis. There was a 24 % improvement in total asthma symptom scores for the grass allergen immunotherapy (AIT) group relative to the placebo group ( $p=0.04$ ). There was a 22 % improvement in asthma symptoms for the active group during the peak season relative to the placebo group ( $p=0.07$ ). In general, there was a limited need for asthma rescue medications; even so, the mean asthma medication score for the grass AIT treatment group was 46 % lower compared with that seen in the placebo group ( $p=0.01$ ). Fewer subjects receiving grass AIT treatment required treatment for worsening of asthma, which was defined as needing four or more inhalations of short-acting  $\beta_2$ -agonist per day at any point during the treatment period compared with subjects in the placebo group (2 subjects receiving grass AIT treatment and 13 subjects receiving placebo, respectively). However, the need for inhaled corticosteroids was similar in both groups [29•].

In a multinational European study with the same tablet, after 3 years of a continuous daily treatment, 238 patients with ARC (and asthma) were followed for 2 further years to study the long-term effect of SLIT. This prolonged DBPC design allowed the investigators to show the sustained improvement in rhino-conjunctivitis symptom and medication scores, but also data on asthma were analyzed. The weighted asthma combined score for participants with grass pollen-induced asthma at inclusion (SLIT=79; placebo=72) was reduced by

39 % in the active group relative to placebo over the entire grass pollen seasons ( $p=0.049$ ) and by 44 % over the peak seasons ( $p=0.030$ ) when combining all 5 years. No data were given for the post-SLIT period, though [30••].

The results of large-group phase IV, observational and retrospective studies have to be interpreted with greater caution because the study design implies several flaws. Even so, they can give the reader an idea of real-life situations. Milani et al. investigated the clinical relevance of respiratory allergies in Italy to pollens other than grasses and the effect of SLIT in the 3-year Rainbow Trial. One hundred sixty-two patients with rhinoconjunctivitis and/or mild moderate asthma were enrolled to receive an SLIT solution for two consecutive pollen seasons with pellitory (53 %), ragweed (14 %), olive (7 %), cypress (7 %) and other tree pollens (18 %). Forty percent had asthma at baseline, and this was more common in polysensitized patients. In patients with asthma, the mean clinical score decreased significantly from the baseline value of 2.7 to 0.3 at the end of the observation period [31].

In France, allergists and chest physicians prescribe immunotherapy, mostly SLIT, according to ARIA guidelines, and the fact that the patient is polysensitized or has intermittent or mild persistent asthma does not stop specialists from prescribing it, as shown in a nationwide prospective observational study [32]. We did not take into account the study by Cafferelli et al. [33] as the immunotherapy was given orally and not sublingually (personal communication from the investigator).

In conclusion, there is some low- to moderate-quality evidence that grass-pollen SLIT in adult seasonal asthmatic patients might be of benefit for symptom and medication scores. The evidence for improved bronchial hyper-responsiveness in season is stronger and of moderate quality. No major safety issues have been reported.

#### Pollen SLIT: Children

Concerning sublingual immunotherapy in children, two complete systematic reviews analyzed all published trials, no matter their design, and graded the quality of evidence. The first review ended in 2009 [20] and the second one included trials till December 2012 [21••].

Until 2009, the evidence for the efficacy of grass pollen SLIT for seasonal asthma in children was of low quality and based on just two trials: one with a grass-pollen tablet in RC children, which showed only improvement in asthma symptoms, whereas no statistically significant reduction in asthma medication scores was seen. This trial was a rhinitis study, not designed to evaluate all aspects of asthma [34]. The other trial used intermediate-dose daily pollen drops (120 IR=10  $\mu$ g group 5 major allergen) in a co-seasonal schedule on top of budesonide 400  $\mu$ g daily during the pollen season. Symptoms, medication and forced expiratory volume in 1 s (FEV<sub>1</sub>) improved significantly in the active group in comparison with

placebo. However, this DBPC study was of low quality because of the high dropout rate in the placebo group (25 recruited, 15 finished). Also, symptom and medication scores were adjusted to 1,000 pollen/m<sup>3</sup>. There were no data on long-term efficacy.

The 2012 systematic review and quality analysis showed that at this moment very low-quality evidence still exists for grass pollen SLIT in children improving asthma symptoms and low-quality evidence for improving medication scores, as some new studies were negative. As for bronchial hyperreactivity, SLIT does not provide any improvement (low-quality evidence), but bronchial inflammation—as expressed by FeNO—is reduced by SLIT in children (moderate-quality evidence). In conclusion, no trial of pollen SLIT in children has convincingly demonstrated any laudable effects of SLIT on asthma outcomes.

#### HDM SLIT: Adults

Australian investigators conducted a 12-month randomized DBPC trial with HDM SLIT in 30 house-dust mite-allergic subjects. In the subgroup with asthma (10 SLIT, 11 placebo), a statistically significant reduction in the total asthma score ( $p < 0.01$ , symptoms and medication) was demonstrated, even though this subgroup analysis was heavily underpowered [35]. Immunological results of this trial are discussed below.

A real-life observational study carried out in France among 139 specialists showed that of the 1,289 patients included (57 % under 18 years), 60 % were polysensitized and 51 % suffered from not only rhinoconjunctivitis but also asthma. Symptoms of rhinitis and/or asthma improved in 66 % and 63 % of the patients, respectively, with a concomitant reduction in medication intake: a quarter stopped using inhaled corticosteroids [36].

The long-lasting efficacy of HDM SLIT in allergic rhinitis with bronchial hyperreactivity was retrospectively studied in a 13-year study in real life by Marogna et al. The investigators concluded that the effects of a 4-year SLIT on clinical parameters but not bronchial reactivity and FEV<sub>1</sub> last 7–8 years after its discontinuation. They also concluded that SLIT shorter than 4 years yields proportionally less impressive results [37]. However, the retrospective and subjective nature of these data and the lack of a control group significantly weaken the quality of evidence.

To compare the economic impact of symptomatic pharmacologic therapy with sublingual immunotherapy (SLIT) over a long evaluation period, 70 patients with house dust mite-allergic asthma were enrolled; 50 of them were treated with HDM-SLIT, and 20 were treated with symptomatic drugs. The patients were evaluated for 2 years after discontinuing a 3-year SLIT course. Patients treated with SLIT plus drugs had a higher mean annual cost in the first year of SLIT treatment compared with patients only receiving drug treatment, but the

mean annual cost became significantly lower after the end of SLIT in both the whole population and the subgroups defined by disease severity [38].

Finally, an efficacy and safety trial in adults and adolescents with asthma was conducted with an HDM SLIT tablet. The primary efficacy endpoint was a significant reduction in inhaled corticosteroid dose compared to baseline after 1 year of daily treatment. A positive therapeutic effect on asthma was demonstrated by a reduction of more than 80 µg/day inhaled budesonide for a group receiving six developmental units daily compared to the placebo group [39•].

In conclusion, we can state that there is high-quality evidence that HDM SLIT in adults enhances the total asthma score based on the presence of symptoms and medication use. There is also some evidence suggesting SLIT might reduce asthma costs in the long run.

#### HDM SLIT: Children

The systematic review in 2009 concluded there was moderate Q evidence supporting that there was no improvement in symptoms with SLIT and the results for medication reduction were contradictory, as a high-dose SLIT trial showed no medication reduction, while a SLIT trial with lower doses of allergen did show positive results [20].

This situation has greatly improved. The 2013 review shows some evidence that HDM SLIT can result in asthma symptom reduction in children (very low quality). Better evidence, however, can be found at this point for asthma medication reduction with HDM SLIT in the pediatric population (moderate quality). Non-specific bronchial hyperreactivity does not improve with SLIT, as was shown by three independent trials.

Two HDM SLIT trials conducted in children with some special characteristics are worth discussing a bit more in detail. Keles et al. randomly divided 60 children into four groups to receive HDM SCIT, SLIT, SCIT buildup followed by SLIT maintenance (SCIT→SLIT) or pharmacotherapy alone. In comparison to the pharmaceutical group in the SCIT→SLIT group, rhinitis, asthma symptoms, asthma attacks and medication all improved at 12 months, reaching statistical significance even though the groups were small. In the SLIT-only group exclusively asthma medication scores improved. In the other trial, 68 children with intermittent asthma and a positive metacholine provocation test received SLIT or cetirizine. Half of each group consisted of children with exposure to high levels of home environmental tobacco smoke. After 3 years, in passive smokers the metacholine challenge greatly improved in the SLIT group vs. the cetirizine group (moderate quality evidence). The other clinical outcomes improved in the passive smoking SLIT group, whereas in the cetirizine group all parameters deteriorate. In the none-passive smoking groups, SLIT had improved clinical

scores and medication use, whereas there was no change with cetirizine. Unfortunately, no clear between-group comparisons were published, thus lowering the strength of the conclusion [40•]. Finally, a safety and tolerability study of an HDM SLIT tablet showed good tolerance in children, but no efficacy data on this tablet have been published yet [39•]. In summary, in children it is probable that HDM SLIT reduces medication use (moderate quality evidence), but evidence for improving asthma symptoms is still poor.

#### *Alternaria* SLIT

In a randomized DBPC moderate- to high-quality trial, 27 patients (14–42 years) suffering from AR (plus mild asthma) caused by *Alternaria* were assigned to 10 months of SLIT or placebo. In the active group, a significant improvement in symptoms and a reduction in medication intake vs. placebo and vs. the run-in season were confirmed, while no changes were noted in the placebo group. Oral itching and conjunctivitis were reported by one SLIT patient but only at the beginning of the trial. The asthma symptom score was part of this total symptom score. However, as only four patients had mild asthma, two in each group, no separate asthma analysis was done [41].

There is one randomized open 3-year trial in 52 adults with respiratory allergy (RC and/or asthma) to *Alternaria alternata*. Assessor-blinded, patient-reported outcomes with a once a year evaluation of symptoms and medication use showed positive results, but no separate asthma parameters were reported, and the design of the study makes this very low-quality evidence [42]. In summary, there is no clear evidence for the efficacy of *Alternaria* SLIT in asthmatic patients.

### SLIT for Asthma: Safety

#### Pollen SLIT

In a DBPC US trial of a grass-pollen SLIT tablet (ALK, Denmark) daily for 16 weeks in 439 patients, safety issues were closely observed. No SAE was reported, but in the grass AIT group, one subject received epinephrine after experiencing a possible grade 1 systemic reaction (local site reactions, chest discomfort and rash) [29•].

#### House Dust Mite SLIT

The safety of a high-dose ultra-rush up-dosing regimen (4 doses, every 30 min, maximum 120 IR) with a concentrated *Dermatophagoides sp.* extract was well tolerated in 218 patients with RC, some with concomitant asthma. Adverse reactions were monitored, and asthmatic patients underwent

spirometry testing at baseline and after each dose. Of a total of eight systemic reactions, all of mild-moderate severity, one was asthma and one dyspnea [43].

The next study went one step further. In a multi-center German DBPC trial 54 asthmatic children were given ultra-rush up dosing, but this time until the dose of 300 IR was reached with a 90-min protocol. Close follow-up with peak expiratory flow measurements showed a 95 % probability that SLIT does not decrease PFR during ultra-rush titration, and no serious or severe adverse events were documented [44].

### SLIT for Asthma: Immunological Changes

#### Pollen SLIT

None of the two studies with grass-pollen SLIT in asthmatic children reported any differences between active and placebo groups in specific IgE, total IgG4 or the induction in peripheral blood of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>−</sup> cells [45, 46•].

The pediatric grass-pollen SLIT tablet trial in subjects with ARC, which reported improvement in seasonal asthma, found an increase in IgG4 ( $p < 0.001$ ) and in IgE-blocking factor ( $p < 0.001$ ); moreover, the seasonal IgE peak was blunted in the actively treated group (NS).

#### HDM SLIT

A 12-month DBPC trial with HDM SLIT in 30 patients established the novel finding that TGF-beta mediates the immunological suppression seen early in clinically effective sublingual house dust mite immunotherapy in addition to an increase in regulatory T cells with suppressor function. After 24 months, SLIT mechanisms seemed to change, and a major rise in IgG4 was seen. An allergen-induced CD4<sup>+</sup> T cell division and IL-5 production were significantly decreased following 6 and 12 months active treatment but not placebo. sTGF-betaRII blocked immunotherapy-induced suppression of allergen-specific T-cell proliferation, maximally at 6 months. Decreased allergen-specific CD4<sup>+</sup> T-cell proliferation and increased IL-10 secretion and serum Der p 2-specific IgG4 were maximal at 24 months of active treatment. Regulatory T-cell (CD4<sup>+</sup>CD25<sup>+</sup>CD127lo/Foxp3<sup>+</sup>) function was demonstrated by suppression of allergen-specific effector T cell (CD4<sup>+</sup>CD25<sup>−</sup>CD127hi) proliferation and cytokine production [35]. Most other studies have confirmed the initial rise in specific IgE and the augmented specific IgG4, TGF-beta and IL-10 for HDM SLIT [47•], but not all [48••]. A SLIT-SCIT comparative trial confirmed a previous finding that the rise in specific IgG4 was less in SLIT than in SCIT [49•].

## Discussion

Only recently, after the first Cochrane meta-analysis for SCIT in asthma showed clearly positive results [50], has allergic asthma begun to be accepted as an indication for SLIT. Thus, the development of well-designed SLIT asthma trials is only starting to become a reality now that lessons have been learned from the small first-generation studies, which were highly heterogeneous in their design [18]. We here present data found in individual trials of SLIT in subjects with asthma published since 2000, which were not already included in a meta-analysis. Only a few trials of pollen SLIT in asthmatic patients have been conducted, as most are in subjects with RC. There is evidence of low/moderate quality that grass-pollen SLIT in adult asthmatic patients might be of benefit for symptom and medication control, especially if there is reasonable evidence

for improved bronchial hyper-responsiveness in season. In children, the 2013 systematic review and quality analysis showed that at this time only low-quality evidence exists for pollen SLIT improving asthma medication scores, while evidence for symptom improvement is of very low quality, since some new studies were negative. However, bronchial inflammation, as expressed by FeNO, was reduced by SLIT in children.

Many more trials have been conducted with HDM-SLIT for asthma, and at this point we can state that there is high quality-evidence for HDM SLIT in adults enhancing the total asthma score based on the presence of symptoms and medication use. There is also some evidence suggesting SLIT might reduce asthma costs in the long run. In children, it is probable that HDM SLIT reduces medication use (moderate-quality evidence), but evidence for improving symptoms of

**Table 1** Systematic reviews of sublingual immunotherapy

| Author, year                | Coch? | No. included trials (patients) | Findings                                                                                                                                                                                                         |
|-----------------------------|-------|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Asthma</b>               |       |                                |                                                                                                                                                                                                                  |
| Calamita 2006               | No    | 25 (1,706 patients)            | SMD: non-significant reduction in asthma symptoms. However, analyzing by categorical outcomes: significant reduction in asthma severity                                                                          |
| Penagos 2008                | No    | 9 (411 patients)               | Pediatric. High heterogeneity. Significant reduction in both symptoms (SMD -1.14; 95 % CI, -2.10 to -0.18; $p=0.02$ ) and medication use (SMD, -1.63; 95 % CI, -2.83 to -0.44; $p=0.007$ ) following SLIT        |
| Hoeks 2008                  | No    | 13                             | Pediatric, asthma and AR: not enough evidence because of poor quality of the studies                                                                                                                             |
| <b>Allergic rhinitis</b>    |       |                                |                                                                                                                                                                                                                  |
| Wilson 2005                 | Yes   | 22 (979 patients)              | No analysis of asthma                                                                                                                                                                                            |
| Penagos 2006                | No    | 10 (577 patients)              | Pediatric. There are still too few trials in asthma to allow an efficient meta-analysis                                                                                                                          |
| Roder 2007                  | No    | 11                             | Pediatric. No analysis of asthma                                                                                                                                                                                 |
| Di Bona 2010                | No    |                                | SAR                                                                                                                                                                                                              |
| Radulovic 2011              | Yes   | 60 (49 MA)                     | No analysis of asthma                                                                                                                                                                                            |
| Di Bona 2012                | No    | 22                             | SAR grass-pollen SLIT vs. SCIT: No analysis of asthma                                                                                                                                                            |
| <b>Respiratory allergy</b>  |       |                                |                                                                                                                                                                                                                  |
| Olaguibel 2005              | No    |                                |                                                                                                                                                                                                                  |
| Larenas-Linnemann 2008–2009 | No    | 12, Asthma (2,173 patients)    | Pollen SLIT, asthma: low Q evidence for symptom or medication reduction. HDM SLIT, asthma: moderate Q evidence there is no symptom improvement, results for medication reduction contradictory                   |
| Compalati 2009              | No    | 9 (532 patients)               | HDM. Reduction in symptoms (SMD -0.95; CI 95 % -1.74 to -.15 ( $p=0.02$ )). Reduction in rescue medication (SMD -1.48; CI 95 % -2.70 to -0.26 ( $p=0.02$ ))                                                      |
| Larenas-Linnemann 2013      | No    | 27 (2,468 patients)            | Pollen SLIT, asthma: very low Q evidence for symptom reduction, low Q for medication reduction. HDM SLIT, asthma: very low Q evidence there is symptom improvement, moderate Q evidence for medication reduction |
| Lin 2013                    | No    | 63 (5,131 patients) 13 asthma  | SLIT improves asthma symptoms (strong evidence) and medication (moderate evidence)                                                                                                                               |

Coch?: if the analysis is a Cochrane Respiratory Workgroup analysis

MA mild asthma

asthma is still poor. As for *Alternaria* SLIT in asthmatic patients, good evidence is still lacking.

Some meta-analyses have analyzed the efficacy of SLIT; see Table 1. The first meta-analysis on SLIT in pediatric asthma dates back to 2008. It started with an initial scanning that identified 92 articles, 49 of which were potentially relevant trials on SLIT use in pediatric patients with allergic asthma. Eight studies met the inclusion criteria for the meta-analysis. All randomized clinical trials included 412 participants (215 SLIT). Even though heterogeneity was high among the trials, the investigators were able to show a reduction of both symptoms and medication scores as expressed by the standard mean difference below -0.8, reflecting a high impact of the treatment on the disease [18]. Although not all initial reviews were positive [51], the most recent systematic analyses are definitely promising, especially in showing a reduction in medication use while asthma control is maintained; see Table 1.

In the 2009 World Allergy Organization Position Paper on Sublingual Immunotherapy, experts in the field observed that there were two randomized open controlled studies suggesting that SLIT reduces the risk of asthma onset in children with rhinitis. In the chapter on SLIT in children, the paper also states that SLIT can be used for allergic rhinitis in children with asthma, but not as monotherapy for treating asthma [52].

As a result of all the above evidence, SLIT in asthma is mentioned in several of the latest guidelines. The BTS/SIGN guideline is favorable with respect to immunotherapy, even though SLIT is not mentioned specifically; it points out that trials on SLIT have consistently demonstrated beneficial effects compared with placebo in the management of allergic asthma. Moreover, BTS/SIGN experts recognized the positive outcome of the Cochrane reviews on immunotherapy [53, 54]. Contrarily, for the Global Initiative on Asthma (GINA), the role of AIT in asthma is limited because of the marginal effect on the syndrome. NAEPP is more positive in its recommendation for AIT in asthma: “Consider SCIT for patients who have persistent asthma when there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive. Evidence is strongest for use of SCIT for single allergens, particularly HDM, animal dander, and pollen. The role of allergy in asthma is greater in children than in adults.”

The International Consensus on Pediatric Asthma (ICON), an international consortium formed by WAO, EAACI, AAAA&I and ACAAI, has published a document addressing pediatric asthma in 2012. SLIT is included in the section addressing therapeutic aspects: “Sublingual immunotherapy (SLIT) is painless and child friendly in terms of administration route, offering the desirable option of home dosing and a more favorable safety profile compared to SCIT. Most documents require additional evidence of efficacy before recommending SLIT as a valid therapeutic option in asthma management. Nevertheless, a relevant meta-analysis confirmed significant

efficacy in children with asthma” (our ref. 18). ICON suggests 3 to 5 years as the starting age in children [55].

As for the practicing clinician in the US, a recent survey among US allergists showed that if approved, 77.9 % (401/515) of respondents would consider using SLIT for allergic rhinitis compared with 56.3 % (290/515) of respondents for mild asthmatics, 37.1 % (191/515) for 60 moderate-severe asthmatics and 20.2 % (104/515) for food allergy [56•].

## Conclusions

Currently available evidence shows that SLIT is indicated in patients with AR. In patients with concomitant persistent asthma, it has been demonstrated to be efficacious in reducing medication needs while maintaining symptom control. Lung symptom improvement is less clear, though. Therefore, we suggest considering SLIT as an add-on medication in the treatment of asthmatic patients with concomitant AR in whom a causative allergen has been demonstrated. For the future, SLIT should be studied in specifically designed asthma studies in patients with the allergic phenotypes of asthma, but without AR. More head-to-head studies comparing SLIT versus controller medications—specifically ICS—might be of interest, particularly with a well-powered long-term design seeking to show medication reduction and a long-term benefit of SLIT.

## Compliance with Ethics Guidelines

**Conflict of Interest** Désirée Larenas-Linnemann has served on advisory boards for Novartis and Pfizer; has served as a consultant for Hollister-Stier Laboratories (allergen manufacturer); has received honoraria from Merck Sharp & Dohme (distributor of allergen tablets), AstraZeneca, Novartis, Pfizer, GlaxoSmithKline and Almirall; and has had travel/accommodations expenses covered/reimbursed by Merck Sharp & Dohme (distributor of allergen tablets), Pfizer, Novartis, UCB, Senosiain and Almirall.

Giovanni Passalacqua has served as a consultant for Stallergenes and Lofarma (both allergen manufacturers).

Carlos E. Baena-Cagnani, Alvaro Teijeiro, and Giorgio Walter Canonica declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. b. Global strategy on asthma management and prevention. 2012 [cited 2013 11th May]; Available from: [http://www.ginasthma.org/local/uploads/files/GINA\\_Report\\_2012Feb13.pdf](http://www.ginasthma.org/local/uploads/files/GINA_Report_2012Feb13.pdf).

2. • Lazic N, Roberts G, Custovic A, Belgrave D, Bishop CM, Winn J, et al. Multiple atopy phenotypes and their associations with asthma: similar findings from two birth cohorts. *Allergy*. 2013. Epub 2013/04/30. *Importance of the different asthma phenotypes; those linked to allergy will probably best benefit from allergen-specific immunotherapy*.
3. Custovic A, Lazic N, Simpson A. Pediatric asthma and development of atopy. *Curr Opin Allergy Clin Immunol*. 2013;13(2):173–80. Epub 2013/02/07.
4. 2008 EcG. Global strategy for the diagnosis and management of asthma in children 5 years and younger. 2009 [cited 11 May 2013]; Available from: [http://www.ginasthma.org/local/uploads/files/GINA\\_Under5](http://www.ginasthma.org/local/uploads/files/GINA_Under5).
5. Wahn U, Bergmann R, Kulig M, Forster J, Bauer CP. The natural course of sensitisation and atopic disease in infancy and childhood. *Pediatr Allergy Immunol*. 1997;8(10 Suppl):16–20. Epub 1997/01/01.
6. Huss K, Naumann PL, Mason PJ, Nanda JP, Huss RW, Smith CM, et al. Asthma severity, atopic status, allergen exposure and quality of life in elderly persons. *Ann Allergy Asthma Immunol*. 2001;86(5):524–30. Epub 2001/05/31.
7. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. *N Engl J Med*. 1990;323(8):502–7. Epub 1990/08/23.
8. Holt PG, Rowe J, Kusel M, Parsons F, Hollams EM, Bosco A, et al. Toward improved prediction of risk for atopy and asthma among preschoolers: a prospective cohort study. *J Allergy Clin Immunol*. 2010;125(3):653–9. Epub 2010/03/17.
9. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol*. 1997;99(4):450–3. Epub 1997/04/01.
10. Inal A, Altintas DU, Yilmaz M, Karakoc GB, Kendirli SG, Sertdemir Y. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. *J Investig Allergol Clin Immunol*. 2007;17(2):85–91. Epub 2007/04/28.
11. Harmanci K, Razi CH, Toyran M, Kanmaz G, Cengizlier MR. Evaluation of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. *Asian Pac J Allergy Immunol*. 2010;28(1):7–13. Epub 2010/06/10.
12. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol*. 2002;109(2):251–6. Epub 2002/02/14.
13. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. 2007;62(8):943–8. Epub 2007/07/11.
14. Valovirta E. Effect of AIT in children including potential to prevent the development of asthma. *Allergy*. 2011;66 Suppl 95:53–4. Epub 2011/06/28.
15. • Valovirta E, Berstad AK, de Blic J, Bufer A, Eng P, Halken S, et al. Design and recruitment for the GAP trial, investigating the preventive effect on asthma development of an SQ-standardized grass allergy immunotherapy tablet in children with grass pollen-induced allergic rhinoconjunctivitis. *Clin Ther*. 2011;33(10):1537–46. Epub 2011/10/18. *Design of one of the most interesting studies to come out in the area of preventive effect of SLIT. If the preventive effect can be shown, this might mark a change in conduct and a widening of the indication for SLIT in the future*.
16. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev*. 2010;8, CD001186. Epub 2010/08/06.
17. Larenas-Linnemann DE, Pietropaolo-Cienfuegos DR, Calderon MA. Evidence of effect of subcutaneous immunotherapy in children: complete and updated review from 2006 onward. *Ann Allergy Asthma Immunol*. 2011;107(5):407–16. Epub 2011/10/25.
18. Penagos M, Passalacqua G, Compalati E, Baena-Cagnani CE, Orozco S, Pedroza A, et al. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest*. 2008;133(3):599–609. Epub 2007/10/24.
19. Compalati E, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. *Allergy*. 2009;64(11):1570–9. Epub 2009/10/03.
20. Larenas-Linnemann D. Sublingual immunotherapy in children: complete and updated review supporting evidence of effect. *Curr Opin Allergy Clin Immunol*. 2009;9(2):168–76. Epub 2009/03/28.
21. • Larenas Linnemann D, Blaiss M, Van Beever H, Compalati E, Baena-Cagnani C. Pediatric sublingual immunotherapy efficacy: evidence analysis, 2009–2012. *Ann Allergy Asthma Immunol*. 2013;110. Epub 18 april 2013. *Recent complete review of published trials on SLIT in pediatric allergy. Each article is also analyzed on quality of evidence according to GRADE. Clinical and immunological outcomes are presented*.
22. • Lin SY, Ereksom N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA*. 2013;309(12):1278–88. *Evidence for SLIT in respiratory allergy*.
23. • Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy*. 2011;66(6):740–52. Epub 2011/03/30. *Second Cochrane meta-analysis of SLIT for respiratory allergy*.
24. Frati F, Scurati S, Puccinelli P, Justicia JL, Adamec T, Sieber HJ, et al. Development of an allergen extract for sublingual immunotherapy—evaluation of Staloral. *Expert Opin Biol Ther*. 2009;9(9):1207–15. Epub 2009/07/16.
25. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy*. 2006;61(2):185–90. Epub 2006/01/18.
26. Marogna M, Spadolini I, Massolo A, Berra D, Zanon P, Chiodini E, et al. Long-term comparison of sublingual immunotherapy vs inhaled budesonide in patients with mild persistent asthma due to grass pollen. *Ann Allergy Asthma Immunol*. 2009;102(1):69–75. Epub 2009/02/12.
27. • Marogna M, Colombo F, Spadolini I, Massolo A, Berra D, Zanon P, et al. Randomized open comparison of montelukast and sublingual immunotherapy as add-on treatment in moderate persistent asthma due to birch pollen. *J Investig Allergol Clin Immunol*. 2010;20(2):146–52. Epub 2010/05/14. *SLIT versus montelukast as add-on treatment in patients with moderate persistent asthma, showing greater benefit for SLIT as it also reduces nasal symptoms*.
28. Ott H, Sieber J, Brehler R, Folster-Holst R, Kapp A, Klimek L, et al. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. *Allergy*. 2009;64(9):1394–401. Epub 2009/09/22.
29. • Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol*. 2011;127(1):72–80. Epub 2011/01/08. *The first big grass tablet SLIT trial in the US*.
30. • Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol*. 2012;129(3):717–25. Epub 2012/01/31. *Long-term effect of grass tablet SLIT for allergic rhinitis, 2 years after discontinuation of a 3 years' treatment*.

31. Milani M, Pecora S, Rainbow Study Investigator G. Clinical relevance of non-grass pollens respiratory allergies in Italy and effects of specific sublingual immunotherapy: The Rainbow Trial, a multicentre 3-year prospective observational study. *Eur Ann Allergy Clin Immunol.* 2011;43(4):111–6.
32. Miguères M, Fontaine JF, Haddad T, Grosclaude M, Saint-Martin F, Bern David D, et al. Characteristics of patients with respiratory allergy in France and factors influencing immunotherapy prescription: a prospective observational study (REALIS). *Int J Immunopathol Pharmacol.* 2011;24(2):387–400. Epub 2011/06/11.
33. Caffarelli C, Sensi LG, Marcucci F, Cavagni G. Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial. *Allergy.* 2000;55(12):1142–7. Epub 2000/12/16.
34. Buñe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol.* 2009;123(1):167–73 e7. Epub 2009/01/10.
35. O'Hehir RE, Gardner LM, de Leon MP, Hales BJ, Biondo M, Douglass JA, et al. House dust mite sublingual immunotherapy: the role for transforming growth factor-beta and functional regulatory T cells. *Am J Respir Crit Care Med.* 2009;180(10):936–47. Epub 2009/08/22.
36. Trebuchon F, David M, Demoly P. Medical management and sublingual immunotherapy practices in patients with house dust mite-induced respiratory allergy: a retrospective, observational study. *Int J Immunopathol Pharmacol.* 2012;25(1):193–206. Epub 2012/04/18.
37. Marogna M, Bruno M, Massolo A, Falagiani P. Long-lasting effects of sublingual immunotherapy for house dust mites in allergic rhinitis with bronchial hyperreactivity: a long-term (13-year) retrospective study in real life. *Int Arch Allergy Immunol.* 2007;142(1):70–8. Epub 2006/10/04.
38. Ariano R, Berto P, Incorvaia C, Di Cara G, Boccardo R, La Grutta S, et al. Economic evaluation of sublingual immunotherapy vs. symptomatic treatment in allergic asthma. *Ann Allergy Asthma Immunol.* 2009;103(3):254–9. Epub 2009/10/01.
39. • Mosbech H. Tolerability and efficacy of house dust mite AIT. *Allergy.* 2011;66 Suppl 95:55–6. Epub 2011/06/28. *First data on house-dust mite tablet SLIT.*
40. • Marogna M, Massolo A, Colombo F, Isella P, Bruno M, Falagiani P. Children passive smoking jeopardises the efficacy of standard anti-allergic pharmacological therapy, while sublingual immunotherapy withstands. *Allergol Immunopathol (Madr).* 2011;39(2):60–7. Epub 2011/01/11. *SLIT did reduce bronchial hyper-responsiveness and symptoms even in children with passive smoking and asthma symptoms as opposed to pharmacotherapy where hyperreactivity did not improve.*
41. Cortellini G, Spadolini I, Patella V, Fabbri E, Santucci A, Severino M, et al. Sublingual immunotherapy for *Alternaria*-induced allergic rhinitis: a randomized placebo-controlled trial. *Ann Allergy Asthma Immunol.* 2010;105(5):382–6. Epub 2010/11/09.
42. Pozzan M, Milani M. Efficacy of sublingual specific immunotherapy in patients with respiratory allergy to *Alternaria alternata*: a randomised, assessor-blinded, patient-reported outcome, controlled 3-year trial. *Curr Med Res Opin.* 2010;26(12):2801–6. Epub 2010/11/06.
43. Roger A, Justicia JL, Navarro LA, Eseverri JL, Ferres J, Malet A, et al. Observational study of the safety of an ultra-rush sublingual immunotherapy regimen to treat rhinitis due to house dust mites. *Int Arch Allergy Immunol.* 2011;154(1):69–75. Epub 2010/07/29.
44. Mosges R, Graute V, Christ H, Sieber HJ, Wahn U, Niggemann B. Safety of ultra-rush titration of sublingual immunotherapy in asthmatic children with tree-pollen allergy. *Pediatr Allergy Immunol.* 2010;21(8):1135–8. Epub 2010/12/02.
45. Stelmach I, Kaczmarek-Wozniak J, Majak P, Olszowiec-Chlebna M, Jerzynska J. Efficacy and safety of high-doses sublingual immunotherapy in ultra-rush scheme in children allergic to grass pollen. *Clin Exp Allergy.* 2009;39(3):401–8. Epub 2009/01/13.
46. • Stelmach I, Kaluzinska-Parzyszek I, Jerzynska J, Stelmach P, Stelmach W, Majak P. Comparative effect of pre-coseasonal and continuous grass sublingual immunotherapy in children. *Allergy.* 2012;67(3):312–20. Epub 2011/12/07. *Both pre-coseasonal and continuous treatments were more efficacious than placebo. Pre-coseasonal treatment was even a bit better than continuous treatment on the nose symptoms.*
47. • Eifan AO, Akkoc T, Yildiz A, Keles S, Ozdemir C, Bahceciler NN, et al. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. *Clin Exp Allergy.* 2010. Epub 2010/01/27. *Both SLIT and SCIT demonstrated clinical improvement compared with pharmacotherapy in asthma/rhinitis children sensitized to HDM.*
48. •• Keles S, Karakoc-Aydiner E, Ozen A, Izgi AG, Tevetoglu A, Akkoc T, et al. A novel approach in allergen-specific immunotherapy: combination of sublingual and subcutaneous routes. *J Allergy Clin Immunol.* 2011;128(4):808–15 e7. Epub 2011/06/07. *Up-dosing with SCIT to speed up efficacy and then switching to maintenance treatment with SLIT gave the best results compared to SLIT alone or SCIT alone.*
49. • Yukselen A, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. *Int Arch Allergy Immunol.* 2012;157(3):288–98. Epub 2011/11/02. *At the end of 1-year immunotherapy, the clinical efficacy of SCIT on rhinitis and asthma symptoms was more evident than SLIT when compared with the placebo. However, the study was heavily underpowered. SLIT did show improvement, but not statistically significantly.*
50. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev.* 2003;4, CD001186. Epub 2003/10/30.
51. Roder E, Berger MY, de Groot H, van Wijk RG. Immunotherapy in children and adolescents with allergic rhinoconjunctivitis: a systematic review. *Pediatr Allergy Immunol.* 2008;19(3):197–207. Epub 2008/01/29.
52. Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy.* 2009;64 Suppl 91:1–59. Epub 2010/02/06.
53. Turner S, Paton J, Higgins B, Douglas G. British Guidelines on the Management of A. British guidelines on the management of asthma: what's new for 2011? *Thorax.* 2011;66(12):1104–5.
54. Levy ML, Thomas M, Small I, Pearce L, Pinnock H, Stephenson P. Summary of the 2008 BTS/SIGN British Guideline on the management of asthma. *Prim Care Respir J: J Gen Pract Airways Group.* 2009;18 Suppl 1:S1–16. Epub 2009/02/12.
55. Papadopoulos NG, Arakawa H, Carlsen KH, Custovic A, Gern J, Lemanske R, et al. International consensus on (ICON) pediatric asthma. *Allergy.* 2012;67(8):976–97. Epub 2012/06/19.
56. • Sikora JM, Tankersley MS, Immunotherapy A, Diagnostics C. Perception and practice of sublingual immunotherapy among practicing allergists in the United States: a follow-up survey. *Ann Allergy Asthma Immunol.* 2013;110(3):194–7 e4. Epub 2013/04/04. *US allergist perception of SLIT as found in a recent survey among ACAAI members.*