

## 23 Sublingual Immunotherapy for Allergic Rhinoconjunctivitis, Allergic Asthma, and Prevention of Allergic Diseases

Moisés A. Calderón, Martin Penagos, and Stephen R. Durham

*Allergy and Clinical Immunology, National Heart and Lung Institute,  
Imperial College London, London, U.K.*

### INTRODUCTION

Sublingual immunotherapy (SLIT) is an efficacious and safe alternative to subcutaneous immunotherapy (SCIT). During the last three decades, SLIT has been widely used in many countries, primarily in central and southern Europe, where more than 50% of the current population of patients receiving specific immunotherapy are on SLIT (1).

The sublingual route has emerged as an effective alternative to SCIT. The clinical indications are broadly similar, and where both treatments are available, patient preference becomes an important determinant of choice. Selection of patients for SLIT should always be in the hands of physicians trained and experienced in allergy and immunotherapy. The favorable safety profile makes this treatment suitable for ambulatory use and, therefore, more accessible to a broader range of patients (2–4).

Efficacy of SLIT has been mainly assessed by evaluation of patients' symptom scores and medication scores before and after treatment compared with placebo. There is no general agreement as to what degree of improvement, either individually or in combination, might indicate clinically relevant efficacy (2).

This review examines all 46 double-blind, placebo-controlled randomized trials (DB PC RCT) published in peer-reviewed journals up to August 1, 2007. Cochrane and Pubmed databases were searched for studies that assessed the efficacy of SLIT in adults and children with allergic rhinitis and asthma. The review focuses only on those outcomes provided in quantitative terms.

### HISTORICAL BACKGROUND

The first clinical trials on mucosal specific immunotherapy were reported by Black (5) and Feinberg (6) almost 70 years ago. However, it was not until 1986 that the first DB PC crossover randomized trial using low doses of dust-mite allergen for SLIT was published (7). The authors found that SLIT was effective in reducing symptoms in 72% of cases compared with placebo. Since then, the potential for SLIT in the treatment of respiratory allergies has been investigated by several different researchers, mostly from European centers. In 1998, the World Health Organization reported that there are sufficient efficacy and safety data available to conclude that SLIT is an acceptable method of specific immunotherapy administration (1). A subsequent publication by the European Academy of Allergy and Immunology, as well as the Allergic Rhinitis and Its Impact on Asthma (ARIA) document, endorsed the use of SLIT in adults and children (8,9) (Fig. 1).

Interest in immunotherapy has grown rapidly, on the basis of clinical evidence that supports its long-term benefits. For example, clinical efficacy remains evident up to at least three years following cessation of treatment (10). The risks of developing asthma in children with seasonal allergic rhinitis are reduced two- to threefold. Immunotherapy also prevents both the number and degree of sensitization to novel allergens following successful treatment of monosensitized children, even during a long-term follow-up (11–13). The efficacy of immunotherapy is reflected in numerous well-designed clinical studies that follow international standardized recommendations.

| 1911 <sup>(5)</sup>                                                                       | 1939 <sup>(5,6)</sup>                  | 1986 <sup>(7)</sup>                                                               | 1990 <sup>(7)</sup>                                                                 | 1998 <sup>(1)</sup> | 1995 <sup>(8)</sup> | 2003 <sup>(22)</sup>                         | 2006    |
|-------------------------------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------|---------------------|----------------------------------------------|---------|
| Pollen antigen quantification allowed a safe and reproducible antigen dose administration | Oral administration of ragweed pollen. | First randomized double-blind placebo controlled study using SLIT-Mites in adults | First randomized double-blind placebo controlled study using SLIT-Mites in children | WHO document        | ARIA                | First meta-analysis evaluating SLIT efficacy | Tablets |

**Figure 1** Chronology of sublingual immunotherapy.

## SUBLINGUAL IMMUNOTHERAPY IN CLINICAL PRACTICE

SLIT is a self-administered treatment, which can be taken at home. The vaccine is administered orally and held under the tongue for one to two minutes prior to being swallowed or spat out. Sublingual protocols used for vaccination vary considerably, although these may contain up to 50- or even 500-fold more allergens than those doses used for SCIT (4,14–16). Different formulations of allergen are used, including oral drops, dissolving tablets, or a combination of the two.

Treatment duration and frequency of dosing may vary widely, from daily to weekly administrations, depending on the geographical location (study center), where treatment is given and the type of preparation administered. Duration of treatment can vary from two months to five years, according to the protocol and allergen used. SLIT has been administered preseasonally only, preseasonal continuing through the season, and continuously throughout the whole year, without regard to season. In one study, SLIT for grass pollen allergy had a better effect in reducing symptom and medication scores during the pollen season when preseasonal treatment was started at least 16 weeks before the pollen season (17).

## EVIDENCE-BASED MEDICINE APPROACH TO SLIT

Evidence-based medicine (EBM) has gained in popularity. On the basis of EBM, conclusions from meta-analyses of DB PC RCT represent the most solid sources of evidence to assess the efficacy of a therapeutic intervention. Meta-analysis is a statistical procedure that incorporates the results of pooled independent studies. This allows a more objective appraisal of the evidence than a traditional narrative. A meta-analysis also provides a quantitative estimate of treatment effect sizes and may explain and quantify any heterogeneity among individual studies. Analysis is performed by the method of the weighted or standardized mean differences (SMD) and by use of fixed or random effect models (REMs). This depends on the study design, distribution of effect sizes, and outcome characteristics (18–21).

At present, four systematic reviews and meta-analyses assessing the efficacy of SLIT are published (22–25). The first systematic review and meta-analysis regarding the effects of SLIT on allergic rhinitis was published by Wilson et al. in 2003 (22). This review was conducted following Cochrane group methodology. The efficacy of SLIT was compared with placebo-assessing symptoms and medication requirements. Twenty-two trials involving 959 participants (484 SLIT and 475 placebo) were included. There was a significant reduction in both symptoms [SMD  $-0.42$ ; 95% confidence interval (95% CI),  $-0.69$  to  $-0.15$ ;  $p = 0.002$ ] and rescue medication requirements (SMD  $-0.43$ ; 95% CI,  $-0.63$  to  $-0.23$ ;  $p = 0.00003$ ) following immunotherapy (Fig. 2). A subgroup analysis failed to identify any preference for particular allergens administered. In those studies involving only children ( $n = 5$ ), there was no significant reduction in symptoms (SMD  $-0.31$ ; 95% CI,  $-1.32$  to  $0.7$ ;  $p = 0.5$ ) and medication scores (SMD  $0.02$ ; 95% CI,  $-0.34$  to  $0.37$ ;  $p = 0.9$ ), although this could reflect the relative paucity of pediatric studies when this review was performed (22).

This systematic review and meta-analysis has been updated (26). Thirty-nine DB PC RCT studies were included; of them, 19 were newly identified and 20 were from the previous

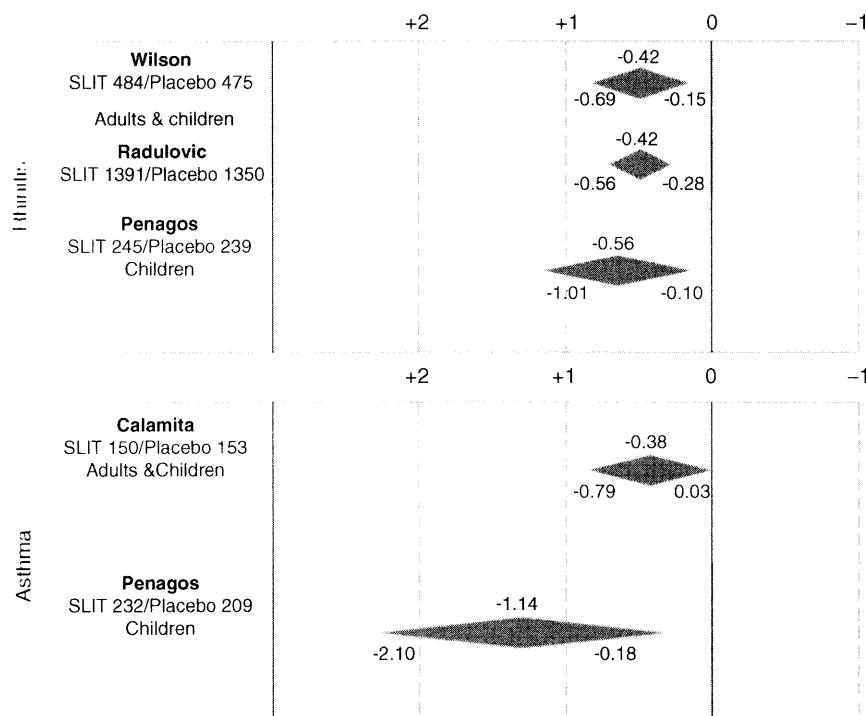


**Figure 2** Meta-analyses summary.

review (1393 received SLIT and 1353 placebo). It confirmed previous findings of a significant reduction, with narrower CIs than in the original review for both symptoms (SMD  $-0.43$ ; 95% CI,  $-0.57$  to  $-0.28$ ;  $p < 0.00001$ ) and medication requirements (SMD  $-0.41$ ; 95% CI,  $-0.55$  to  $-0.28$ ;  $p < 0.00001$ ).

The predetermined subgroup analyses performed in this review show that SLIT is highly effective in both seasonal and perennial allergic rhinitis and that treatment is effective, whatever the duration, although the effect size is greatest with the treatment lasting more than 12 months for both symptoms (SMD  $-0.70$ ; 95% CI,  $-1.19$  to  $-0.21$ ;  $p = 0.005$ ) and medication scores (SMD  $-0.44$ ; 95% CI,  $-0.84$  to  $-0.04$ ;  $p = 0.03$ ). Similarly to the previous review, the authors were unable to identify a significant reduction in both symptoms and medication scores in children (26).

The efficacy of SLIT in the treatment of allergic rhinitis in children was evaluated in a meta-analysis of 10 DB PC RCTs published between 1990 and 2004 (23). Four hundred eighty-four participants (245 SLIT and 239 placebo) had a final clinical evaluation and were assessed. Overall, there was a significant reduction in both symptoms (SMD  $-0.56$ ; 95% CI,  $-1.01$  to  $-0.10$ ;  $p = 0.02$ ) and medication use (SMD  $-0.76$ ; 95% CI,  $-1.46$  to  $-0.06$ ;  $p = 0.03$ ) after immunotherapy compared with placebo (Fig. 2). Subanalysis of treatment duration shows that SLIT for more than 18 months versus shorter courses is more effective. The authors conclude that SLIT with standardized vaccines is effective in pediatric patients with allergic rhinitis when compared with placebo (23). The observed discrepancy between the effect sizes reported in the pediatric subanalysis by Radulovic (26) and those reported by the Penagos meta-analysis (23) is perhaps due to the use of different studies and different data extraction methods.

Another systematic review evaluated the effect of SLIT for asthma (24). Nine studies, including 303 participants (150 SLIT and 153 placebo), assessed asthmatic symptoms, and six studies of 254 participants (132 SLIT and 122 placebo) evaluated specific asthma medication. There was a tendency toward the improvement of asthma symptom scores (SMD  $-0.38$ ; 95% CI,  $-0.79$  to  $0.03$ ;  $p = 0.07$ ) and reduction of asthma medication use (SMD  $-0.91$ ; 95% CI,  $-1.94$  to  $0.12$ ;  $p = 0.08$ ) in favor of SLIT, but without statistical significance. The 95% CI includes the zero, thus indicating a nonsignificant reduction in asthmatic symptoms (Fig. 2). We found some methodological issues, which make interpretation difficult. First, there are no restrictive inclusion criteria for trial selection; this review includes open-labeled and double-blind

studies. Second, the outcomes analyzed are not clearly defined. Authors analyzed different allergic symptom scores in a collective manner. Finally, statistical analysis includes qualitative assessments instead of a quantitative approach for some outcomes (24).

A meta-analysis on the efficacy of SLIT in allergic asthma in pediatric patients, aged 3 to 18 years, also has been published (25). Nine DB PC RCTs, all published from 1990 to May 2006, fulfil the selection criteria. Four hundred and forty-one patients (232 SLIT and 209 placebo) had a final assessment and are included in the analysis. Overall, there is a 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 compared with placebo (Fig. 2). The authors conclude that SLIT with standardized vaccines reduces both symptom scores and rescue medication use in children with allergic asthma compared with placebo (25). Nonetheless, in this meta-analysis, the heterogeneity is very significant ( $>94\%$ ), with a wide 95% CI for SMD in both outcomes. This indicates the diverse methodology used throughout studies. More studies are required to give a robust conclusion.

In a systematic review, as expected, studies brought together will differ in their outcomes for rhinoconjunctivitis symptom and medication use. In all four meta-analyses on SLIT, a significant interstudy heterogeneity is found. This may be due to the fact that diverse allergens were used and different age groups included in the analyses. Methodological diversity is also evident in the study sample sizes. Finally, variability in the treatment effects evaluated in the different trials was observed. This is known as "statistical heterogeneity," and it is a consequence of clinical and/or methodological diversity among the studies (21).

All authors analyzed their data with the REM to estimate the treatment effects. Even though REM explicitly accounts for the heterogeneity of studies through a statistical parameter representing the interstudy variation, further evaluations should be conducted to determine the impact of this variability on the global effect size (20,21).

In all four meta-analyses, a significant interstudy heterogeneity is found. This is most likely due to widely differing scoring systems for rhinoconjunctivitis symptoms and medication use, among studies. In the light of the heterogeneity, one should be cautious in the interpretation, particularly when the studies included are small. This highlights the need for more definitive studies, including dose-response studies involving large numbers of well-defined patients (21).

## SLIT FOR ADULTS

Quantitative data have been identified from 31 DB PC RCT studies in adults assessing the efficacy of SLIT (Table 1) (27–57). Age ranged from 18 to 60 years. All studies include subjects with symptomatic sensitization to only one aeroallergen, but some individuals were polysensitized to other aeroallergens.

The allergens studied include seasonal pollens, such as grasses (12 studies), trees (5 studies), both grasses and trees (1 study), and weeds (5 studies) and, perennial allergens, such as house-dust mites (HDM) (5 studies) and cats (2 studies). Twenty studies used drops, seven studies tablets, and three studies both drops and tablets.

All studies assessed the clinical efficacy of SLIT in patients with moderate to severe allergic rhinoconjunctivitis; 14 of these also included patients with mild to moderate allergic asthma. Only one study investigated the efficacy of SLIT in asthmatics (29). The main clinical outcome was reduction of rhinoconjunctivitis symptoms and medication scores. In most studies, it was possible to retrieve the cumulative dose in micrograms. A wide dose range was used, which makes it difficult to perform a global analysis of the effects of the dose on the outcomes.

In Tables 1 and 2, the effect size ( $\delta$ ) of each of the studies is demonstrated. As defined by Cohen, this is the difference in the means between two groups divided by the standard deviation. The most usual interpretation of  $\delta$  is to consider:  $0.0 < \delta < 0.2$ , trivial effect size;  $0.2 < \delta < 0.5$ , small effect size;  $0.5 < \delta < 0.8$ , moderate effect size, and  $\delta > 0.8$ , strong effect size (58).

The clinical efficacy and safety of a new fast-dissolving, once-daily oral lyophilisate tablet for sublingual administration has been investigated in adults with seasonal allergic rhinitis due to grass pollen. The tablet contains 75,000 SQ-T standardized allergen extract of grass pollen,

Table 1 Efficacy of Sublingual Immunotherapy in Adults: Evidence Review

| Author, yr               | Diagnosis | SLIT | Placebo | Allergen                                                                                                                                   | Units     | Presentation | Duration (mo) | Cumulative dose                       | Effect size             | Dropout rate (%) |
|--------------------------|-----------|------|---------|--------------------------------------------------------------------------------------------------------------------------------------------|-----------|--------------|---------------|---------------------------------------|-------------------------|------------------|
| Andre et al., 2003       | R, A, C   | 48   | 51      | Amb a 1                                                                                                                                    | IR        | Tablets      | 6.5           | 1300–30,500                           | R: -0.45 (-0.84, -0.05) | 10               |
| Ariano et al., 2001      | R, A      | 10   | 10      | <i>Cupressus arizonica</i>                                                                                                                 | U RAST    | Drops        | 8             | 250,000 U RAST                        | R: -2.06 (-3.19, -0.93) | 0                |
| Bousquet et al., 1999    | A         | 23   | 27      | <i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides. farinae</i>                                                                 | IR        | Drops        | 25            | Der p 1–4.2 mg<br>Der f 1–7.3 mg      | A: -0.04 (-0.60, 0.51)  | 41               |
| Bowen et al., 2004       | R, A, C   | 37   | 39      | Amb a 1                                                                                                                                    | IR        | Drops        | 3.5           | 18.26 mg                              | R: -0.43 (-0.88, 0.03)  | 31               |
| Casanovas et al., 1994   | R, A, C   | 9    | 6       | <i>Olea europaea</i>                                                                                                                       | HEP (w/v) | Drops        | 4             | n/s                                   | R: -1.00 (-2.11, 0.12)  | 0                |
| Clavel et al., 1998      | R, C, A   | 62   | 58      | Mixed grasses (Orchard, meadow, ryegrass, sweet vernal, and timothy)                                                                       | IR        | Drops        | 6             | 2.6 mg/Phl p 5s                       | R: -0.42 (-0.82, -0.02) | 12               |
| Dahl et al., 2006a       | A, R, C   | 61   | 32      | <i>Phleum pratense</i>                                                                                                                     | SQ-T      | Tablet       | 5             | 2.0 mg                                | R: -0.63 (-1.07, -0.19) | 18               |
| Dahl et al., 2006b       | R, C, A   | 282  | 286     | <i>Phleum pratense</i>                                                                                                                     | SQ-T      | Tablet       | 8             | 2.7 mg                                | R: -0.52 (-0.69, -0.35) | 10               |
| Didier et al., 2007      | R, C      | 133  | 146     | Mixed grasses (Orchard, meadow, ryegrass, sweet vernal, and timothy)                                                                       | IR        | Tablet       | 6             | 4.125 mg                              | R: -0.43 (-0.67, -0.20) | 11               |
| Di Rienzo, 2006          | R, C      | 18   | 14      | <i>Juniperus ashei</i>                                                                                                                     | IR        | Drops        | 4             | 12.6 mcg                              | R: -0.98 (-1.72, -0.23) | 6                |
| Drachenberg et al., 2001 | R, C      | 37   | 12      | Birch and grass/rye                                                                                                                        | AU        | Drops        | 5             | Phl p 1 1914 µg                       | R: -0.26 (-0.92, 0.39)  | 28               |
| Durham et al., 2006      | R, C, A   | 131  | 129     | <i>Phleum pratense</i>                                                                                                                     | SQ-T      | Tablets      | 9             | Bet v 1 1535 µg<br>15 µg Phl p 5/day  | R: -0.23 (-0.47, 0.02)  | 8                |
| Feliziani et al., 1995   | R, C, A   | 18   | 16      | Grass ( <i>Dactylis glomerata</i> , <i>Festuca pratensis</i> , <i>Lolium perenne</i> , <i>Phleum pratense</i> , and <i>Poa pratensis</i> ) | BU        | Drops        | 3             | 19.2 µg major grass allergen/mo       | R: -1.00 (-1.72, -0.28) | 0                |
| Guez et al., 2000        | R, C      | 36   | 36      | <i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides. farinae</i>                                                                 | IR        | Drops        | 24            | Der p 1 = 2.2 mg;<br>Der f 1 = 1.7 mg | R: -0.41 (-0.88, 0.06)  | 46               |

(Continued)

Table 1 Efficacy of Sublingual Immunotherapy in Adults: Evidence Review (Continued)

| Author, yr                      | Diagnosis | SLIT | Placebo | Allergen                                                                  | Units | Presentation      | Duration (mo) | Cumulative dose                       | Effect size             | Dropout rate (%) |
|---------------------------------|-----------|------|---------|---------------------------------------------------------------------------|-------|-------------------|---------------|---------------------------------------|-------------------------|------------------|
| Hordijk et al., 1998            | R, C      | 35   | 36      | Mixed grasses (Orchard, meadow, ryegrass, sweet vernal, and timothy)      | BU    | Drops             | 3             | 760,000 BU                            | R: -0.57 (-1.04, -0.09) | 20               |
| Lima et al., 2002               | R, C      | 28   | 28      | <i>Phleum pratense</i>                                                    | µg    | Drops             | 12-18         | 16.3 mg                               | R: 0.01 (-0.51, 0.54)   | 12               |
| Nelson et al., 1993             | R, C      | 20   | 21      | Fel d 1                                                                   | AU    | Drops             | 3.5           | 4,500,000 AU or 450-900 Fel d 1 Units | R: -0.56 (-1.18, 0.07)  | 7                |
| Palma-Carlos AG                 | R, A, C   | 13   | 7       | Grass pollen                                                              | AU    | Tablets           | 24            | Maintenance 2000 AU/week              | NA                      | 39               |
| Passalacqua et al., 1998        | R, C      | 10   | 9       | <i>Dermatophagoides pteronyssinus</i> and <i>Parietaria judaica</i>       | AU    | Tablets           | 24            | 4000 AU/wk                            | R: -1.27 (-2.28, -0.26) | 5                |
| Passalacqua et al., 1999        | R, C, A   | 15   | 15      | <i>Dermatophagoides farinae</i>                                           | BU    | Drops             | 6             | 16 µg                                 | R: -0.02 (-0.73, 0.70)  | 10               |
| Passalacqua et al., 2006        | R, C      | 28   | 28      | <i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides farinae</i> | AU    | Tablets           | 24            | 2000 AU/wk                            | R: -1.65 (-2.26, -1.04) | 18               |
| Pradaliar et al., 1999          | R, C, A   | 63   | 63      | Mixed grasses (Orchard, meadow, ryegrass, sweet vernal, and timothy)      | IR    | Drops and Tablets | 4.5           | 0.935 mg Phl p 5                      | R: -0.18 (-0.53, 0.17)  | 6                |
| Purello-D'Ambrosio et al., 1999 | R, C, A   | 14   | 16      | <i>Parietaria judaica</i>                                                 | BU/mL | Drops             | 9             | 12.77 µg (Par j 1)                    | R: -0.62 (-1.36, 0.12)  | 0                |
| Sabbah et al., 1994             | R, C      | 29   | 29      | Mixed grasses (Orchard, meadow, ryegrass, sweet vernal, and timothy)      | IR    | Drops             | 4             | 4500 IR                               | NA                      | 0                |

|                       |      |    |    |                                                                                                                                                        |     |                   |    |                                                      |                        |    |
|-----------------------|------|----|----|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-------------------|----|------------------------------------------------------|------------------------|----|
| Sabbah et al., 1994   | R, C | 29 | 29 | Mixed grasses (Orchard, meadow, ryegrass, sweet vernal, and timothy)                                                                                   | IR  | Drops             | 4  | 4500 IR                                              | NA                     | 0  |
| Sanchez-Palacios 2001 | R, A | 20 | 20 | Fel d 1                                                                                                                                                | HEP | Drops             | 12 | 3.6 mg                                               | NA                     | 0  |
| Smith et al., 2004    | R, C | 45 | 51 | Mixed grasses (Orchard, meadow, ryegrass, sweet vernal, and timothy)                                                                                   | IR  | Drops and tablets | 24 | 6264 µg Lolp1                                        | R: 0.12 (-0.28, 0.52)  | 27 |
| Tonnel et al., 2004   | R, C | 10 | 12 | <i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides farinae</i>                                                                              | IR  | Drops and tablets | 24 | 3654 µg Dacg5<br>1.28 mg Der p 1;<br>1.47 mg Der f 1 | R: -0.61 (-1.47, 0.25) | 44 |
| Troise et al., 1995   | R, C | 15 | 16 | <i>Parietaria judaica</i>                                                                                                                              | BU  | Drops             | 10 | 6.3 µg Parij1                                        | R: -0.22 (-0.92, 0.49) | 0  |
| Vervioet et al., 2007 | R, C | 19 | 19 | <i>Juniperus ashei</i>                                                                                                                                 | IR  | Drops             | 4  | 27.36 mg                                             | R: 0.13 (-0.51, 0.76)  | 8  |
| Vololini et al., 2001 | R, C | 15 | 15 | Alder, birch, hazel                                                                                                                                    | BU  | Drops             | 12 | 445 µg Betv1                                         | R: 0.37 (-0.35, 1.10)  | 10 |
| Worm, 2006            | R, C | 41 | 48 | <i>Holcus lanatus</i> , <i>Dactylis glomerata</i> , <i>Lolium perenne</i> , <i>Phleum pratense</i> , <i>Poa pratensis</i> , and <i>Festuca elatior</i> | µg  | Drops             | 20 | 24 mg                                                | NA                     | 52 |

Abbreviations: R, rhinitis; C, conjunctivitis; A, asthma.

Table 2 Efficacy of Sublingual Immunotherapy in Children: Evidence Review

| Author, yr               | Diagnosis | SLIT | Placebo | Allergen                                                                                                                      | Units | Presentation | Duration (mo) | Cumulative dose                  | Effect size                                        | Dropout rate (%) |
|--------------------------|-----------|------|---------|-------------------------------------------------------------------------------------------------------------------------------|-------|--------------|---------------|----------------------------------|----------------------------------------------------|------------------|
| Bahcecioglu et al., 2001 | R, A      | 7    | 7       | Dpt and Df extract 50/50                                                                                                      | IR    | Drops        | 6             | Dpt 0.56 mg; Df 0.98 mg          | R: 0.31 (-0.71, 1.34)<br>A: 0.33 (-0.73, 1.39)     | 0                |
| Bufe et al., 2004        | R, A      | 63   | 63      | Grass pollen extracts                                                                                                         | AU    | Drops        | 36            | 9.6 mg                           | R: -0.06 (-0.40, 0.28)                             | 18               |
| Caffarelli, 2000         | R, A, C   | 24   | 20      | <i>Holcus lanatus</i> , <i>Phleum pratense</i> , and <i>Poa pratensis</i>                                                     | AU    | Tablets      | 3             | 37 250 AU                        | R: -0.98 (-1.69, -0.26)<br>A: -3.51 (-4.50, -2.53) | 8                |
| Hirsch et al., 1997      | R, A      | 14   | 15      | Mites extract                                                                                                                 | µg    | Drops        | 12            | 570 µg                           | R: 0.51 (-0.36, 1.39)<br>A: -0.53 (-1.40, 0.35)    | 5                |
| Ippoliti et al., 2003    | R, A, C   | 18   | 15      | <i>Dermatophagoides pteronyssinus</i>                                                                                         | BU    | Drops        | 6             | 12 mg                            | R: -0.61 (-1.32, 0.09)<br>A: -2.57 (-3.14, -1.99)  | 0                |
| La Rosa et al., 1999     | R         | 16   | 17      | <i>Parietaria judaica</i>                                                                                                     | IR    | Drops        | 24            | 52.5 mg                          | R: -0.24 (-0.93, 0.44)                             | 19               |
| Lue et al., 2006         | A         | 10   | 10      | <i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides farinae</i>                                                     | IR    | Drops        | 6             | 1.7 mg Dpt<br>3.0 mg Df          | A: -1.15 (-2.11, -0.19)                            | 0                |
| Niu et al., 2006         | R, A      | 49   | 48      | Dpt and Df extract 50/50                                                                                                      | IR    | Drops        | 6             | 1.7 mg Dpt<br>3.0 mg Df          | A: -1.26 (-1.70, -0.82)                            | 12               |
| Pajno et al., 2000       | A         | 12   | 9       | Der p 1, Der p 2                                                                                                              | BU    | Drops        | 24            | 250 µg Der p 1<br>125 µg Der p 2 | A: -1.24 (-2.20, -0.28)                            | 13               |
| Röder E et al., 2007     | R         | 82   | 72      | <i>Lolium perenne</i> , <i>Phleum pratense</i> , <i>Dactylis glomerata</i> , <i>Holcus</i> , and <i>Anthoxanthum odoratum</i> | BU    | Drops        | 24            | 4.5 mg Lol p 5                   | R: -0.17 (-0.49, 0.15)                             | 25               |

|                                  |         |    |    |                                                                                                                                                    |      |       |    |                                           |                                                    |    |
|----------------------------------|---------|----|----|----------------------------------------------------------------------------------------------------------------------------------------------------|------|-------|----|-------------------------------------------|----------------------------------------------------|----|
| Röder E et al., 2007             | R       | 82 | 72 | <i>Lolium perenne</i> , <i>Phleum pratense</i> , <i>Dactylis glomerata</i> , <i>Holcus</i> , and <i>Anthoxanthum odoratum</i>                      | BU   | Drops | 24 | 4.5 mg Lol p 5                            | R: -0.17 (-0.49, 0.15)                             | 25 |
| Rolnick-Werninghaus et al., 2004 | R, A    | 39 | 38 | Mixed grasses ( <i>Dactylis glomerata</i> , <i>Festuca pratensis</i> , <i>Lolium perenne</i> , <i>Phleum pratense</i> , and <i>Poa pratensis</i> ) | STU  | Drops | 32 | 188 µg                                    | H: 0.05 (0.40, 0.49)<br>A: 0.01 (-0.62, 0.64)      | 17 |
| Tari et al., 1990                | R, A    | 30 | 28 | Mites extract                                                                                                                                      | STU  | Drops | 18 | 365 STU                                   | R: -2.24 (-2.91, -1.58)<br>A: -2.53 (-3.23, -1.83) | 12 |
| Valovirta et al., 2006           | R, A, C | 27 | 29 | <i>Brachydesmiella verrucosa</i> , <i>Corylus avellana</i> , and <i>Alnus glutinosa</i>                                                            | SQ-U | Drops | 19 | Low dose: 67.5 µg<br>High dose: 562.87 µg | R: -0.49 (-1.03, 0.04)<br>A: -0.31 (-0.84, 0.22)   | 14 |
| Vourdas et al., 1998             | R, A, C | 34 | 32 | <i>Olea europaea</i>                                                                                                                               | IR   | Drops | 24 | Ole e 1 (8.1 mg)                          | R: -0.17 (-0.65, 0.32)<br>A: 0.99 (0.46, 1.52)     | 3  |
| Wüthrich et al., 2003            | R, C    | 10 | 12 | Mixed grasses ( <i>Dactylis glomerata</i> , <i>Festuca pratensis</i> , <i>Lolium perenne</i> , <i>Phleum pratense</i> , and <i>Poa pratensis</i> ) | µg   | Drops | 24 | 139.88 µg                                 | R: -0.11 (-0.95, 0.73)                             | 21 |

Abbreviations: R, rhinitis; C, conjunctivitis; A, asthma.

*Phleum pratense* (equivalent to 2800 BAU or 15 mcg of major allergen protein), and it is recommended as safe for home administration with no up dosing phase. Over 2400 subjects have been included in the tablet evaluation. The mean rhinoconjunctivitis symptom scores and medication scores were reduced by 30% and 38%, (median results 34% and 53%), respectively, in the SLIT group as compared with placebo in the first year (38) and, by 36% and 46%, (median results 44% and 73%), respectively, in the second year (59). These reductions are highly statistically significant, ( $p < 0.0001$ ). Furthermore, the subjects in the SLIT group report improved quality of life as assessed using Juniper's Rhinoconjunctivitis Quality-of-Life Questionnaire (60).

Another DB PC RCT study evaluated the efficacy and safety of a different sublingual tablet in adults (57). Six hundred and twenty-eight participants with grass pollen rhinoconjunctivitis were randomized into three groups, receiving 100-, 300-, and 500-IR of five-grasses pollen immunotherapy. Treatment started four months before the pollen season and was given until the end of the pollen season. Significant improvements in symptom and medication scores were found in both 300- and 500-IR groups compared with placebo. Furthermore, a very good safety profile was identified (57,61).

### SLIT FOR CHILDREN

Over the last two decades, the interest on efficacy of SLIT in children has increased. Due to its good safety profile and convenience, SLIT seems to be an efficacious route to administer specific immunotherapy to children. At present, 15 DB PC RCT studies evaluating the efficacy of SLIT in children compared with placebo provide quantitative data (62-76) (Table 2). Age range varies from 3 to 18 years. The youngest age reported in DB PC RCT assessing efficacy of SLIT compared with placebo is three years (25). Moreover, in a safety survey of SLIT, the investigators included subjects as young as 23 months (77), with no severe adverse effects.

The allergens studied include seasonal pollens such as grasses (6 studies), trees (2 studies), and weeds (1 study) and perennial allergens such as dust mites (6 studies). All studies used drops, except one (64), which investigated the effect of sublingual tablets.

Thirteen studies assessed the clinical efficacy of SLIT in patients with moderate to severe allergic rhinitis. Ten of these also included patients with mild to moderate allergic asthma. Two studies (68,70) exclusively evaluate the effect of SLIT in mild to moderate allergic asthma. The main clinical outcome is reduction of rhinitis symptoms and medication scores. The effect size of each study is summarized in Table 2, where the data have been analyzed according to Cohen's method. Even though most of the studies conducted in asthmatics report a reduction in clinical scores, a statistical significant effect of SLIT was observed in seven studies.

The efficacy of preseasonal monomeric allergoid SLIT tablets was investigated in a DB PC study in children with asthma, rhinitis, and/or rhinoconjunctivitis due to grass pollen (64). Twenty-four patients received SLIT for three months before the pollen season and 24 matched patients received identically appearing placebo. Patients in the SLIT group showed a significant reduction in the symptom-medication score compared with the placebo group during the pollen season. The authors conclude that SLIT is effective for the treatment of asthma due to grass pollen in children (64).

A study in a primary care setting evaluated the efficacy of SLIT in children aged 6 to 18 years with hay fever. Participants were randomly assigned to receive grass pollen mix ( $n = 91$ ) or placebo ( $n = 77$ ) for two years. The authors concluded that both symptom and medication scores do not differ between those subjects allocated to SLIT or placebo. However, this study has limitations. Patients with mild disease are included, at least 70% of patients are polysensitized, a retrospective score is considered as a substitute for baseline evaluation, and study withdrawals are more than 20%; for these reasons, results have to be interpreted with care (71).

### SLIT VS. SCIT

The efficacy of SLIT and SCIT in patients with respiratory allergy has been compared by various authors (78-84). Allergic rhinoconjunctivitis was evaluated in all studies; in addition, three studies included mild to moderate allergic asthma (80,81,83). Different allergens have

protein), and it is  
over 2400 subjects  
symptom scores and  
( $p < 0.001$ ), respectively,  
by 36% and 46%,  
the reductions are  
SLIT group report  
Quality-of-Life

erent sublingual  
h grass pollen  
-, and 500-IR of  
ne pollen season  
in symptom and  
d with placebo.

ased. Due to its  
e to administer  
ating the efficacy  
(Table 2). Age  
essing efficacy of  
ey of SLIT, the  
dverse effects.  
udies), trees (2  
ies). All studies  
ts.

oderate to severe  
allergic asthma.  
allergic asthma.  
cores. The effect  
ed according to  
port a reduction  
studies.

stigated in a DB  
rass pollen (64).  
and 24 matched  
oup showed a  
placebo group  
he treatment of

ldren aged 6 to  
pollen mix ( $n =$   
and medication  
r, this study has  
polysensitized, a  
dy withdrawals  
(71).

n compared by  
es; in addition,  
allergens have

been used, such as grass-mixed pollens, birch pollen, HDM, and multiple allergen extracts. The design of the studies also varies. Some are open (78,79,83), while others are randomized (81,84) or randomized placebo-controlled studies (80,82). All studies report no significant differences between SCIT and SLIT for improvement in symptom scores and medication scores. Thus, out of nine studies, seven do not involve a double-blind randomized protocol such that there are clear limitations in their interpretation. Two studies (80,82) are designed as DB PC RCT double-dummy studies. The first is small and does not include a placebo arm, and in view of the inevitable large placebo effect in immunotherapy trials (35), it is unclear whether the lack of difference between SCIT and SLIT implies any benefit for either treated group. The Khinchi study, although optimally designed and showing a convincing difference for both SLIT and SCIT compared with placebo, is, nonetheless, inadequately powered to detect a difference between SLIT and SCIT. On reviewing the data in the Khinchi study (82), there is a clear trend in favor of SCIT over SLIT, even though significance was not achieved.

At present, the meta-analysis data suggest that SCIT may be more effective than SLIT, although in view of heterogeneity among trials and overlap of the CIs, no firm conclusions can be drawn. More head-to-head comparisons of SLIT versus SCIT are needed, since, with the exception of the Kinchi study (82), the lack of a proper study design and the limited statistical power of the studies does not allow for a firm conclusion (2).

## LONG-TERM EFFECT OF SLIT

Five studies evaluated the long-lasting effect of SLIT (70,85–88). In a DB PC RCT study, 24 children (8–15 years) with mild to moderate asthma, with single sensitization to mite allergen, were evaluated. After a one-year observation phase, patients were randomly allocated to receive SLIT (sublingual-spit immunotherapy) as drops with a standardized extract of *Dermatophagoides pteronyssinus*. After two years of SLIT, there was a significant reduction in asthma symptom scores (SMD  $-1.24$  95% CI,  $-2.20$  to  $-0.28$ ;  $p = 0.0001$ ) and medication use (SMD  $-8.10$ ; 95% CI,  $-10.95$  to  $-5.25$ ;  $p = 0.0001$ ) in the active compared with placebo group (70).

A DB RCT, not placebo controlled, of one or three years of SLIT and three years of observation, was conducted in 137 patients (10–51 years) with perennial rhinitis due to HDM (88). Efficacy of SLIT was evaluated with symptom scores, skin prick tests, and the nasal allergen challenge score. The authors found a greater improvement in the three years of SLIT group compared with the two years of treatment when they compared results over six years. However, the lack of a placebo group during discontinuation of treatment makes the validity of these results difficult to interpret (88).

A 13-year retrospective study evaluated the long-lasting effect of SLIT and also assessed if this effect could be related to the duration of treatment (87). Patients had HDM-allergic rhinitis and also had a retrospective positive methacholine challenge performed at baseline. However, the study design means that the results are difficult to interpret. Long-term well-designed DB PC RCTs in large populations are needed to assess the long-term effects of SLIT after discontinuing treatment.

## PROGRESSION OF ATOPY

The progression from allergic rhinitis to allergic asthma was specifically evaluated in an open study conducted by Novembre et al. in 113 children aged 5 to 14 years (89). These children had hay fever limited to grass pollen. This was an open study in which patients were randomized to receive preseasonal and coseasonal SLIT for three years or to observation only with standard symptomatic therapy. At recruitment, none of the children reported more than three episodes of seasonal asthma per year. The SLIT-treated group used less medication in the second and third years of therapy, and their symptom scores tended to be lower. From the second year of SLIT, subjective evaluation of overall allergy symptoms was favorable in the actively treated children. Development of asthma after three years was 3.8 times more frequent in the control subjects.

In an open, controlled, two parallel group study, 511 patients, with allergic rhinitis with or without intermittent asthma, were randomized to drugs only or drugs and SLIT for three years (90). At the end of the treatment period, one or more new sensitizations to allergens as determined by skin tests versus those existing at the time of randomization appeared in 16 of 271 (5.9%) patients in the SLIT group and 64 of 170 (38%) patients in the control group ( $p = 0.01$ ).

The long-lasting effects of SLIT in children (mean age 8.5 years) with asthma due to HDM was evaluated in a 10-year prospective open study by Di Rienzo et al. (85). The authors found that the mean peak expiratory flow result was significantly higher in the active than in the control group. They concluded that SLIT is effective and maintains the clinical efficacy for four to five years after discontinuation. Although these studies are encouraging, at present, there is insufficient evidence to draw firm conclusions on the long-term effects of SLIT on the development of new sensitizations.

### DOSE EFFICACY

Evaluation of efficacy by dose response has been evaluated in three large multicenter DB PC RCT studies (38,57,74). The literature was reviewed to determine whether the allergen SLIT dose is related to clinical outcomes. Studies that reported allergen dose in mass units and symptom and/or medication scores were reviewed. Of the 46 RCT DB PCT identified, clinical scores were available in 42 and the allergen dose in mass units in 35 studies. Thirty-one studies were included in this analysis. Twelve studies used grasses, nine HDM, five tree pollens, and five weeds. The median administration time for SLIT was 10 months (range 3–36 months) (Fig. 3). Cumulative dose was variable, ranging from a monthly dose of 0.6 to 6840  $\mu\text{g}$ . Allergen dose was not significantly correlated with lower clinical scores.

We are currently conducting a meta-regression analysis to corroborate these findings. Nonetheless, the data imply that large definitive trials will be needed to determine dose-response relationships for SLIT. There are currently two reported. Durham et al. evaluated the

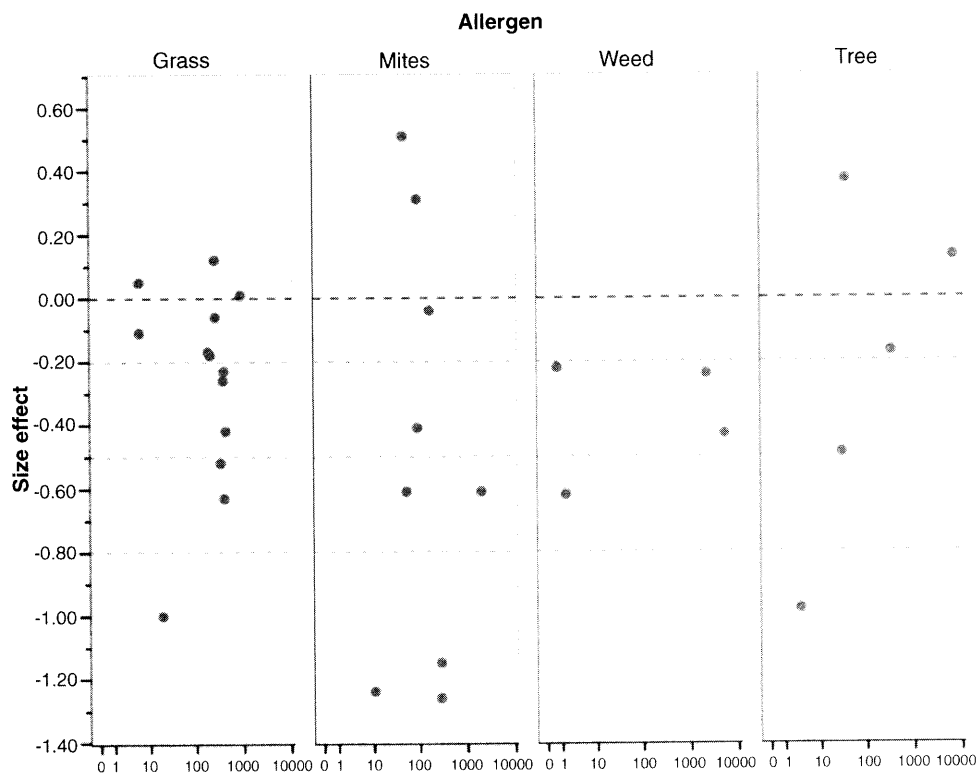


Figure 3 Effect of the allergen dose on clinical efficacy.

**Table 3** Efficacy of Sublingual Immunotherapy: In Vivo Studies

| Author, yr                       | Immediate skin reactivity | Nasal provocation test | Immediate conjunctival reactivity |
|----------------------------------|---------------------------|------------------------|-----------------------------------|
| Ariano et al., 2001              |                           | 2.00 (0.88, 3.12)      |                                   |
| Bahceciler et al., 2001          | -1.22 (-2.36, -0.09)      |                        |                                   |
| Bufe et al., 2004                | 0.05 (-0.29, 0.39)        |                        |                                   |
| Drachenberg et al., 2001         | 0.65 (-0.02, 1.31)        |                        |                                   |
| Lue et al., 2006                 | 0.34 (-0.55, 1.22)        |                        |                                   |
| Marcucci et al., 2003            |                           | 0.36 (-0.45, 1.17)     |                                   |
| Rolinck-Werninghaus et al., 2004 | 0.51 (0.05, 0.96)         | -0.31 (-0.76, 0.14)    | 0.17 (-0.28, 0.62)                |
| Sanchez-Palacios, 2001           | 0.15 (-0.47, 0.77)        |                        |                                   |
| Troise et al., 1995              |                           | 0.66 (-0.06, 1.39)     |                                   |
| Vourdaz et al., 1998             | -0.46 (-0.94, 0.03)       |                        |                                   |
| Vessner et al., 2003             |                           | 0.36 (-0.35, 1.06)     |                                   |
| Wuthrich, 2003                   |                           | -0.45 (-1.30, 0.40)    |                                   |

effect of three doses of a grass pollen tablet (2500, 25,000, and 75,000 SQ-T units of *P. pratense*) in 855 adults. Treatment was administered daily for a mean duration of 18 weeks. The authors found a significant improvement in medication and symptom scores only in the highest-dose treatment group, 75,000 SQ-T (equivalent to 15 mg of Phl p 5) compared with the placebo group (38). Similarly, in another study, 628 adults with grass pollen rhinoconjunctivitis were randomized in three groups, receiving 100-, 300-, and 500-IR of a five-grass pollen SLIT tablet. Treatment started four months before the grass pollen season and was given until the end of the pollen season. Significant improvements in symptom and medication scores were found in both 300- and 500-IR groups compared with placebo (57). These two studies confirm a dose-response relationship and the need for high doses of grass pollen SLIT using preseasonal protocols of up to four months. Whether more prolonged courses of SLIT, for example, one to three years, will require lower doses than for preseasonal protocols, remains to be determined.

## IN VIVO TESTS

Twenty-nine studies carried out in vivo tests to evaluate the efficacy of SLIT compared with placebo. Only 12 studies provided quantitative data suitable for statistical analysis (Table 3). Seven studies reported results of immediate skin reactivity by means of skin prick tests (37,50,62,63,68,72,75). A significant increase of skin reactivity was found by Bufo (63) and Rolinck-Werninghaus (72) in children treated with SLIT. Those children who clinically improved by SLIT did not show a significant reduction of sensitivity in skin prick tests.

Nasal provocation tests were carried out in six studies (28,53,72,76,91,92). Only in Ariano's study (28) did the challenge tests result in a significant increase in the allergen dose required to develop a positive test. Immediate conjunctival reactivity was evaluated by Rolinck-Werninghaus (72). Even though an increase in allergen dose was found, the difference is not statistically significant. A significant heterogeneity exists in all studies, because most of the trials are designed to assess clinical efficacy as the primary end point.

## CONCLUSION

Evidence-based medicine demonstrates that SLIT is effective in reducing symptoms and there is need for rescue medication in patients with allergic rhinoconjunctivitis due to grass pollen. This clinical effect is associated with an excellent safety profile and makes SLIT suitable for home administration. SLIT offers efficacy, safety, and convenience, and therefore provides the ideal characteristics for allergen immunotherapy to be given to a wider population of allergic people. More studies are needed to confirm the optimal dose and schedule to be used and to clarify indications for SLIT in children. Evaluation of the influence of SLIT on long-term efficacy and progression of atopic diseases requires further well-designed clinical studies in large cohorts.

## SALIENT POINTS

- EBM shows that SLIT is efficacious in improving symptom and medication scores.
- SLIT has a very good safety profile.
  - Minor local side effects (itching and swelling of the oral mucosa) were reported almost universally, but were rarely of significance.
- The good clinical effect of SLIT associated with its excellent safety profile makes it suitable for home administration.
- Long-term efficacy and progression of atopy of SLIT needs to be confirmed with further well-designed clinical studies in large cohorts.
- More studies are needed to confirm the optimal dose and schedule to be used.
- SLIT can be considered as an alternative to SCIT.

## REFERENCES

1. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO Position Paper. *J Allergy Clin Immunol* 1998; 102:558-562.
2. Durham SR. Tradition and innovation: finding the right balance. *J Allergy Clin Immunol* 2007; 119:792-795.
3. Canonica GW, Passalacqua G. Non-injection routes for immunotherapy. *J Allergy Clin Immunol* 2003; 111:437-448.
4. Cox LS, Linnemann DL, Nolte H, et al. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006; 117:1021-1035.
5. Black JH. The oral administration of ragweed pollen. *J Allergy* 1939; 10:156-158.
6. Feinberg SM, Foran FL, Lichtenstein M. Oral pollen therapy in ragweed pollinosis. *J Am Med Assoc* 1940; 115:23-39.
7. Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house-dust mite. *Clin Allergy* 1986; 16:483-491.
8. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108:S147-S334.
9. Brozek JL, Baena-Cagnani C, Bonini S, et al. Methodology for development of the Allergic Rhinitis and its Impact on Asthma Guideline 2008 update. *Allergy* 2008; 63(1):38-46.
10. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999; 341:468-475.
11. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002; 109: 251-256.
12. Niggemann B, Jacobsen L, Dreborg S, et al. PAT Investigator Group: Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy* 2006; 61(7): 855-859.
13. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; 62:943-948.
14. Passalacqua G, Guerra L, Pasquali M, et al. Efficacy and safety of sublingual immunotherapy. *Ann Allergy Asthma Immunol* 2004; 93:3-12.
15. Bousquet J, Demoly P. Specific immunotherapy—an optimistic future. *Allergy* 2006; 61:1155-1158.
16. Leatherman BD, Owen S, Parker M, et al. Sublingual immunotherapy: past, present, paradigm for the future? A review of the literature. *Otolaryngol Head Neck Surg* 2007; 136:S1-S20.
17. Calderon MA, Birk AO, Andersen JS, et al. Prolonged preseasonal treatment phase with Graza sublingual immunotherapy increases clinical efficacy. *Allergy* 2007; 62:958-961.
18. Akobeng AK. Principles of evidence based medicine. *Arch Dis Child* 2005; 90:837-840.
19. Sackett DL. Clinical epidemiology. What, who, and whither. *J Clin Epidemiol* 2002; 55:1161-1166.
20. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ* 1997; 315:1533-1537.
21. Higgins JPT, Green S, eds. Formulating the problem. *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.6 (updated September 2006); Section 6b.2. In: *The Cochrane Library*, Issue 4. Chichester, UK: John Wiley, 2006.
22. Wilson DR, Torres-Lima M, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005; 60:4-12.
23. Penagos M, Compalati E, Tarantini F, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. *Ann Allergy Asthma Immunol* 2006; 97:141-148.

24. Calamita Z, Saconato H, Pela AB, et al. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. *Allergy* 2006; 61: 1162–1172.
25. Penagos M, Passalacqua G, Compalati E, et al. Meta-analysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest* 2007; [Epub ahead of print]: DOI:10.1378/chest.06-1425.
26. Radulovic S, Calderon M, Wilson S, et al. Sublingual immunotherapy for allergic rhinitis: an updated Cochrane systematic review and meta-analysis. *Allergy* 2007; 62(s83):167–551.
27. Andre C, Perrin-Fayolle M, Grosclaude M, et al. A double-blind placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed extract in patients with seasonal rhinitis. Evidence for a dose-response relationship. *Int Arch Allergy Immunol* 2003; 131:111–118.
28. Ariano R, Spadolini I, Panzani RC. Efficacy of sublingual specific immunotherapy in Cupressaceae allergy using an extract of *Cupressus arizonica*. A double blind study. *Allergol Immunopathol (Madr)* 2001; 29:238–244.
29. Bousquet J, Scheinmann P, Guinépain MT, et al. Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study. *Allergy* 1999; 54:249–260.
30. Bowen T, Greenbaum J, Charbonneau Y, et al. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 2004; 93:425–430.
31. Casanovas M, Guerra F, Moreno C, et al. Double-blind, placebo-controlled clinical trial of preseasonal treatment with allergenic extracts of *Olea europaea* pollen administered sublingually. *J Invest Allergol Clin Immunol* 1994; 4:305–314.
32. Clavel R, Bousquet J, André C. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. *Allergy* 1998; 53:493–498.
33. Purello-D'Ambrosio F, Gangemi S, Isola S, et al. Sublingual immunotherapy: a double-blind, placebo-controlled trial with *Parietaria judaica* extract standardized in mass units in patients with rhinoconjunctivitis, asthma, or both. *Allergy* 1999; 54:968–973.
34. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablet for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; 118:434–440.
35. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006; 61:185–190.
36. Di Rienzo V, Pagani A, Parmiani S, et al. Postmarketing surveillance study on the safety of sublingual immunotherapy in children. *Allergy* 1999; 54:1110–1113.
37. Drachenberg KJ, Pfeiffer P, Urban E. Sublingual immunotherapy—results from a multi-centre, randomised, double-blind, placebo-controlled study with a standardised birch and grass/rye pollen extract. *Allergologie* 2001; 24:525–534.
38. Durham SR, Yang WH, Pedersen MR, et al. Sublingual once-daily grass-pollen immunotherapy: a randomised controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; 117: 802–809.
39. Feliziani V, Lattuada G, Parmiani S, et al. Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts. A double blind study. *Allergol Immunopathol (Madr)* 1995; 23(5):224–230.
40. Guez S, Vatrinet C, Fadel R, et al. House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. *Allergy* 2000; 55:369–375.
41. Hordijk GJ, Antvelink JB, Luwema RA. Sublingual immunotherapy with a standardised grass pollen extract; a double-blind placebo-controlled study. *Allergol Immunopathol (Madr)* 1998; 26:234–240.
42. Lima MT, Wilson D, Pitkin L, et al. Grass pollen sublingual immunotherapy for seasonal rhinoconjunctivitis: a randomized controlled trial. *Clin Exp Allergy* 2002; 32:507–514.
43. Nelson HS, Oppenheimer J, Vatsia GA, et al. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. *J Allergy Clin Immunol* 1993; 92:229–236.
44. Palma-Carlos AG, Santos AS, Branco-Ferreira M, et al. Clinical efficacy and safety of preseasonal sublingual immunotherapy with grass pollen carbamylated allergoid in rhinitic patients. A double-blind, placebo-controlled study. *Allergol Immunopathol (Madr)* 2006; 34:194–198.
45. Passalacqua G, Albano M, Fregonese L, et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet* 1998; 351:629–632.
46. Passalacqua G, Albano M, Riccio A, et al. Clinical and immunologic effects of a rush sublingual immunotherapy to *Parietaria* species: a double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 1999; 104:964–968.
47. Passalacqua G, Pasquali M, Ariano R, et al. Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. *Allergy* 2006; 61:849–854.
48. Pradaliere A, Basset D, Claudel A, et al. Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. *Allergy* 1999; 54:519–528.

49. Sabbah A, Hassoun S, Le SJ, et al. A double-blind, placebo-controlled trial by the sublingual route of immunotherapy with a standardized grass pollen extract. *Allergy* 1994; 49(5):309-313.
50. Sánchez Palacios A, Schamann F, García JA. Sublingual immunotherapy with cat epithelial extract. Personal experience. *Allergol Immunopathol (Madr)* 2001; 29:60-65.
51. Smith H, White P, Annala I, et al. Randomized controlled trial of highdose sublingual immunotherapy to treat seasonal allergic rhinitis. *J Allergy Clin Immunol* 2004; 114:831-837.
52. Tonnel AB, Scherpereel A, Douay B, et al. Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. *Allergy* 2004; 59:491-497.
53. Troise C, Voltolini S, Canessa A, et al. Sublingual immunotherapy in Parietaria pollen-induced rhinitis: a double-blind study. *J Investig Allergol Clin Immunol* 1995; 5:25-30.
54. Vervloet D, Birnbaum J, Laurent P, et al. Safety and efficacy of Juniperus ashei sublingual-swallow ultra-rush pollen immunotherapy in cypress rhinoconjunctivitis. A double-blind, placebo-controlled study. *Int Arch Allergy Immunol* 2007; 142:239-246.
55. Voltolini S, Modena P, Minale P, et al. Sublingual immunotherapy in tree pollen allergy. Double-blind, placebo-controlled study with a biologically standardised extract of three pollens (alder, birch and hazel) administered by a rush schedule. *Allergol Immunopathol (Madr)* 2001; 29:103-110.
56. Worm M. Efficacy and tolerability of high dose sublingual immunotherapy in patients with rhinoconjunctivitis. *Allerg Immunol (Paris)* 2006; 38:355-360.
57. Didier A, Mallng HJ, Worm M, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007; 120(6):1338-1345.
58. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. New Jersey: Lawrence Erlbaum, 1988.
59. Emminger W, Dahl R, Kapp A, et al. Progressive effect of grass tablet immunotherapy during long-term treatment in patients with rhinoconjunctivitis. *Allergy* 2007; 62(S83): 240 (abstr).
60. Rak S, Yang WH, Pedersen MR, et al. Once-daily sublingual allergen-specific immunotherapy improves quality of life in patients with grass pollen-induced allergic rhinoconjunctivitis: a double-blind, randomised study. *Qual Life Res* 2007; 16(2):191-201; [Epub 2006, Oct 11].
61. Mallng H, Mélaç M, de Beaumont O, et al. Efficacy of sublingual immunotherapy (SLIT) tablets for grass pollen rhinoconjunctivitis in patients with or without mild asthma, mono- or polysensitized. *Allergy* 2007; 62(supp 83):167-551.
62. Bahceciler NN, Isik U, Barlan IB, et al. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. *Pediatric Pulmonology* 2001; 32:49-55.
63. Bufe A, Ziegler-Kirbach E, Stoeckmann E, et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 2004; 59:498-504.
64. Caffarelli C, Sensi LG, Marcucci F, et al. Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial. *Allergy* 2000; 55:1142-1147.
65. Hirsch Th, Sähn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. *Pediatr Allergy Immunol* 1997; 8:21-27.
66. Ippoliti F, De Sanctis W, Volterrani A, et al. Immunomodulation during sublingual therapy in allergic children. *Pediatr Allergy Immunol* 2003; 14:216-221.
67. La Rosa M, Ranno C, Andre C, et al. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized Parietaria judaica in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999; 104:425-432.
68. Lue KH, Lin YH, Sun HL, et al. Clinical and immunologic effects of sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, randomized, placebo-controlled study. *Pediatr Allergy Immunol* 2006; 17:408-415.
69. Niu CK, Chen WY, Huang JL, et al. Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: A multi-center, double-blind, randomized, and placebo-controlled study in Taiwan. *Respir Med* 2006; 100(8):1374-1383. (Epub 2006, Jan 5.).
70. Pajno GB, Morabito L, Barberio G, et al. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study. *Allergy* 2000; 55:842-849.
71. Röder E, Berger MY, Hop WC, et al. Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care. *J Allergy Clin Immunol* 2007; 119:892-898.
72. Rolinck-Werninghaus C, Wolf H, Liebke C, et al. A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy* 2004; 59:1285-1293.
73. Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. *Allergol Immunopathol (Madr)* 1990; 18(5):277-284.
74. Valovirta E, Jacobsen L, Ljorring C, et al. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. *Allergy* 2006; 61:1177-1183.

- sublingual route of  
helial extract.  
immunotherapy  
evaluation of the  
pollen-induced  
sublingual-swallow  
placebo-controlled  
study. Double-  
blind (alder, birch  
pollen) 103–110.  
patients with  
only sublingual  
Clin Immunol  
Key: Lawrence  
during long-  
immunotherapy  
rhinitis: a double-  
blind (IT) tablets for  
polysensitized.  
patients with asthma  
study. Allergy  
grass pollen in  
immunotherapy  
study. Allergy  
study in allergic  
of sublingual-  
rhinoconjunctivitis  
immunotherapy in  
study. Pediatr  
high-dose mite  
study in  
long-term sublingual  
controlled study.  
not effective in  
double-blind, placebo-  
controlled study (SLIT) in  
rhinitis and  
asthma 18(5):277–284.  
immunotherapy
75. Vourdas D, Syrigou E, Potamianou P, et al. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. *Allergy* 1998; 53:662–672.
  76. Wüthrich B, Bucher Ch, Jörg W, et al. Double-blind placebo-controlled study with sublingual immunotherapy in children with seasonal allergic rhinitis to grass pollen. *J Invest Allergol Clin Immunol* 2003; 13:145–148.
  77. Agostinis F, Tellarini L, Canonica GW, et al. Safety of sublingual immunotherapy with a monomeric allergoid in very young children. *Allergy* 2005; 60:133.
  78. Piazza I, Bizzaro N. Humoral response to subcutaneous, oral, and nasal immunotherapy for allergic rhinitis due to *Dermatophagoides pteronyssinus*. *Ann Allergy* 1993; 71:461–469.
  79. Bernardis P, Agnoletto M, Puccinelli P, et al. Injective versus sublingual immunotherapy in *Alternaria tenuis* allergic patients. *J Invest Allergol Clin Immunol* 1996; 6:55–62.
  80. Quirino T, Iemoli E, Siciliani E, et al. Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study. *Clin Exp Allergy* 1996; 26:1253–1261.
  81. Mungan D, Misirligil Z, Gurbuz L. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma—a placebo controlled study. *Ann Allergy Asthma Immunol* 1999; 82:485–490.
  82. Khinchi MS, Poulsen LK, Carat F, et al. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy* 2004; 59:45–53.
  83. Herrscher RF. Evaluation of three allergen specific immunotherapy methods: standard injection, rush injection and sublingual. In: Proceedings of the annual meeting of American College of Allergy, Asthma, and Immunology; 2005 Nov 5–7; Anaheim: ACAAI; 2005. Abstract nr 54.
  84. Mauroa M, Russelloa M, Incorvaia C, et al. Comparison of efficacy, safety and immunologic effects of subcutaneous and sublingual immunotherapy in birch pollinosis: a randomized study. *Eur Ann Allergy Clin Immunol* 2007; 39:119–122.
  85. Di Rienzo V, Marcucci F, Puccinelli P, et al. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy* 2003; 33(2):206–210.
  86. Cingi C, Aynaci S, Cakli H, et al. Efficacy of long-term sublingual-oral immunotherapy in allergic rhinitis. *Acta Otorhinolaryngol Ital* 2005; 25:214–219.
  87. Marogna M, Bruno M, Massolo A, et al. 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; 142:70–78.
  88. Tahamiler R, Saritzali G, Canakcioglu S. Long-term efficacy of sublingual immunotherapy in patients with perennial rhinitis. *Laryngoscope* 2007; 117:965–969.
  89. Novembre E, Galli E, Landi F, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004; 114:851–857.
  90. Marogna M, Spadolini I, Massolo A, et al. Randomized controlled open study of sublingual immunotherapy for respiratory allergy in real-life: clinical efficacy and more. *Allergy* 2004; 59:1205–1210.
  91. Wessner D, Rakoski J, Ring J. Efficacy of sublingual immunotherapy in grass pollen allergy. *Chem Immunol Allergy* 2003; 82:53–61.
  92. Marcucci F, Sensi L, Frati F, et al. Effects on inflammation parameters of a double-blind, placebo controlled one-year course of SLIT in children monosensitized to mites. *Allergy* 2003; 58:657–662.