

Immunotherapy: The Meta-Analyses. What have we Learned?

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- Specific allergen immunotherapy • Meta-analysis • Rhinitis
- Asthma

Since the first publication of clinical experimental work on the efficacy of specific allergen immunotherapy (SIT) in humans 100 years ago,¹ the interest of the medical community in this particular kind of treatment for allergic diseases has increased.

SIT is being delivered and investigated for a variety of allergic conditions, including rhinitis, conjunctivitis, asthma, Hymenoptera venom allergy, eczema, food allergy, latex allergy, and drug allergy. SIT is targeted at a large and variable range of allergens. The use of SIT as therapy for allergic respiratory diseases has been recognized in different international guidelines²⁻⁵ and by the World Health Organization.^{2,6}

Different routes for SIT have been evaluated, such as the subcutaneous, sublingual, oral, nasal, bronchial, and intralymphatic,⁷ the first 2 of these routes being the most commonly used today in clinical practice. Subcutaneous immunotherapy (SCIT) is still the most commonly used route for the treatment of allergic rhinitis and allergic asthma in adults and children. Sublingual immunotherapy (SLIT) was introduced as an alternative to SCIT in the late 1970s. Allergen extracts for SLIT can be administered as drops

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or fast-dissolving tablets. At present, its prescription by allergists is becoming more frequent in several countries worldwide, mainly within Europe.⁸

The increased interest of the medical community in the use of SIT is reflected by the large number of published randomized double-blind, placebo-controlled trials (RCTs) using standardized products and validated outcome measures that have been published in recent years. These publications have enabled the undertaking of systematic reviews investigating the effectiveness of SIT.^{9,10} Some of the data in these systematic reviews have been found to be suitable for meta-analysis. Several different clinical and research/laboratory outcomes have been evaluated in each review. The selection of specific outcomes was established according to the interests of the reviewers, the most commonly used being symptom scores and rescue medication scores.

The clinical area that has received the greatest attention in relation to systematic reviews and meta-analyses is that of chronic allergic respiratory disease, in particular allergic rhinoconjunctivitis and allergic asthma; therefore, these areas represent the focus of this review. While concentrating on SIT for allergic airway disease, the authors nonetheless, where relevant, seek to draw lessons from systematic reviews and meta-analyses in other clinical areas. In other allergic diseases a small number of systematic reviews have been undertaken: there is a Cochrane review and one other systematic review of SIT for eczema in progress^{11,12} but none published; there are 2 published meta-analyses of SIT for venom allergy^{13,14} and one Cochrane review in progress¹⁵; there is one published Cochrane review of desensitization for drug allergy¹⁶; and there is one published meta-analysis of immunotherapy for food allergy recently.¹⁷ These other allergic conditions are not discussed directly in this article, which aims to describe the lessons learned from meta-analyses of allergic rhinitis and asthma.

SYSTEMATIC REVIEWS AND META-ANALYSES

The terms systematic review and meta-analysis are often used interchangeably, but they do not mean exactly the same thing. A systematic review attempts to bring together all empirical evidence that fits specific inclusion criteria to answer a research question. It uses explicit, reproducible methods that are selected with a view to minimizing bias, thus generating valid findings.¹⁸ Not all systematic reviews include meta-analysis, but this step may be included as part of a systematic review if data can meaningfully be combined and are furthermore available in an appropriate form. A meta-analysis comprises the use of statistical methods to estimate an average, or common effect, over several studies.^{18,19} By combining information from all relevant clinical trials, meta-analyses can increase the precision of the summary estimates that is typically obtained through small studies, thus allowing a more objective appraisal of the evidence than a traditional narrative synthesis of findings. Meta-analysis also facilitates investigations of the consistency of evidence and the exploration of differences across studies, and enables exploration of controversies arising from apparently conflicting studies.¹⁸ A meta-analysis also allows exploration of, and in some cases explanation of, heterogeneity between studies.

The effect size of the intervention is extracted/calculated for each study and for each outcome. The effect size is a statistical measure for the magnitude of the difference between two interventions adjusted by some estimate of variability. Outcomes are commonly reported using categorical (most commonly dichotomous) and continuous data.^{18,20} For dichotomous outcomes, the main options are relative risks (RR), odds ratios (OR), or risk differences (RD). For continuous outcomes, the options are the mean difference (MD) or standardized mean difference (SMD) between the interventions tested.¹⁹ This latter measure is important because different scales are

commonly used by different investigators, and if this is so the results derived from these different scales need to be standardized to be able to combine the different studies in a meta-analysis by a common unit. The disadvantage of SMDs is that they are difficult to interpret: one commonly used interpretation of the SMD is to consider the effect size as trivial if the SMD is between 0.0 and 0.2, small for 0.2 to 0.5, moderate for 0.5 to 0.8 and large for greater than 0.8.^{18,20,21}

Meta-analyses are usually displayed in graphical form by using “forest plots,” which present the findings for all studies plus the combined results. The combined effect appears as a diamond at the bottom of the forest plot. The center of the diamond is equal to the average effect and the extremes of the diamond are equal to the 95% confidence interval (CI) of the average effect. The diamond or average effect is obtained from combining the summary measures collected for all included studies.¹⁹

Fig. 1 summarizes the main features of a meta-analysis presented in the form of a forest plot.

There are two models for combining studies: the fixed-effect model and the random-effects model. The fixed-effect model considers the variability between the studies as exclusively due to random variation. In other words, the assumption is that if the individual studies were infinitely large they would all produce the same result. By contrast, the random-effects model assumes a different underlying effect for each study and takes this into consideration as an additional source of variation. Under this assumption, if the studies were infinitely large they would still give different results of the effect of the intervention. The effects of the studies are assumed to be randomly distributed, and the central point of this distribution is the focus of the combined (pooled) effect estimate.¹⁹

HETEROGENEITY

Any kind of variability among studies in a systematic review may be termed “heterogeneity.” There are different sources of heterogeneity: (1) clinical heterogeneity (variability in the participants, interventions and outcomes), (2) methodological heterogeneity (variability in study design and risk of bias), and (3) statistical heterogeneity (a consequence of clinical or methodological diversity, or both, among the studies) (**Box 1**). Statistical heterogeneity manifests itself in the observed intervention effects being more different from each other than one would expect if due to random error alone.¹⁸

If the results of the studies differ greatly then it may not be appropriate to combine the results using meta-analysis. There are available tests to assess heterogeneity across studies. The chi-squared (χ^2 or Chi^2) test assesses whether observed differences in results are compatible with chance alone. A low *P* value provides evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance). Because of the low power of this test, a *P* value of .10, rather than the conventional level of .05, is sometimes used to determine statistical significance.¹⁸

A useful statistic for quantifying inconsistency is the I^2 test. This test describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). I^2 lies between 0% and 100%; a value of 0% indicates no heterogeneity, and larger values show increasing heterogeneity. Thresholds for the interpretation of I^2 can be misleading, because the importance of inconsistency depends on several factors. A rough guide to interpretation is as follows: 0% to 40%: might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity, and 75% to 100% considerable heterogeneity.¹⁸ If the I^2 test shows homogeneous results (<40%) then the differences between studies are assumed to be a consequence of sampling variation, and

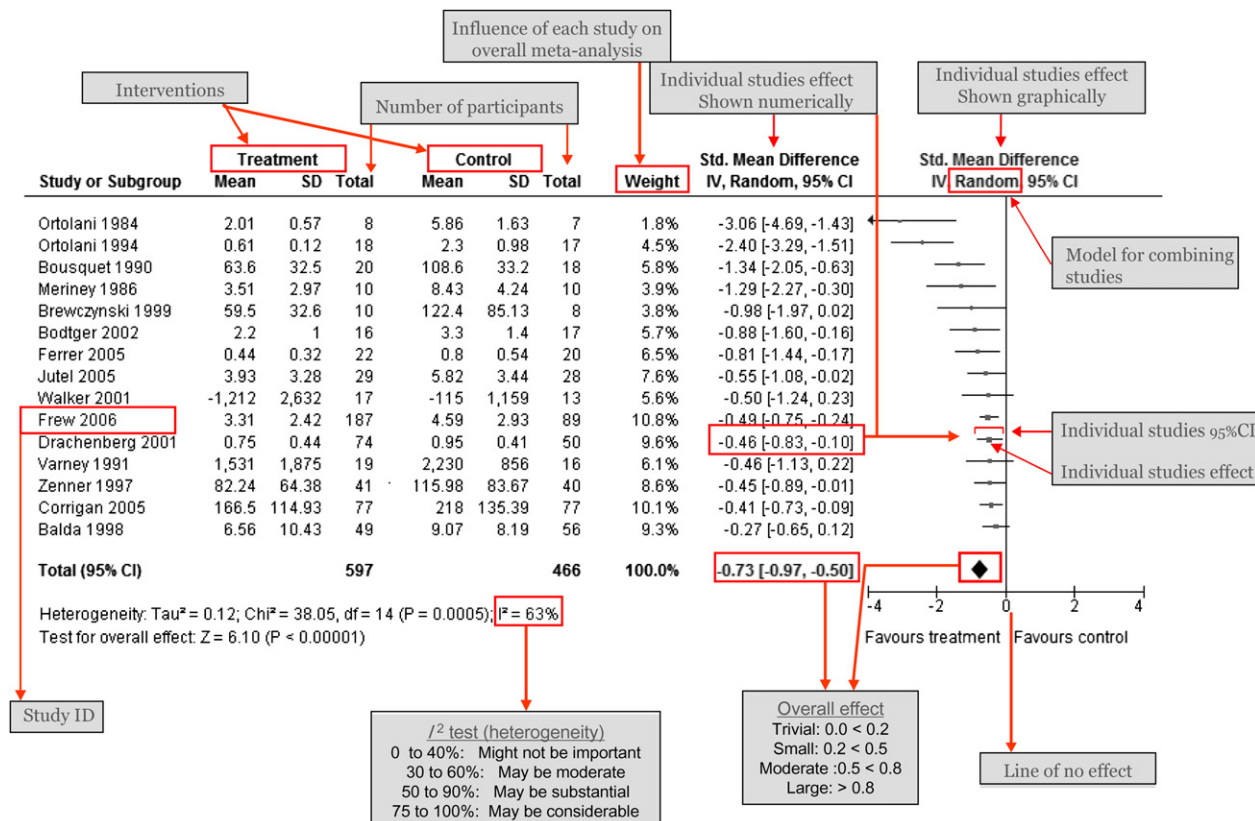


Fig. 1. Summary of the main features of a meta-analysis presented in the form of a forest plot.

Box 1**Types of heterogeneity**

1. Clinical heterogeneity
 - Variability in the participants
 - Variability in interventions
 - Variability in outcomes
2. Methodological heterogeneity
 - Variability in trial design
 - Variability in study quality
 - Variability in allergen extracts
 - Variability in dose schedules
3. Statistical heterogeneity
 - Due to clinical and/or methodological diversity

the use of a fixed-effect model is appropriate. If, however, the test shows that significant heterogeneity exists between study results, a random-effects model is advocated.^{18,22}

Heterogeneity should not simply be ignored after a statistical test is applied; rather, it should be scrutinized, with an attempt to explain it.^{18,22} For example, sensitivity analyses may identify specific causes of statistical heterogeneity in a meta-analysis.

META-ANALYSES OF SIT

At present, 12 meta-analyses evaluating the effect of SIT on allergic rhinitis^{23–31} and allergic asthma^{29,30,32–37} have been published.

Allergic Rhinitis

The results of meta-analyses of SCIT or SLIT for treating allergic rhinitis are summarized in **Table 1**, and are described in detail here.

SCIT

The first “meta-analysis” on SCIT was published in German and included 43 RCTs published between 1980 and 1997 investigating the effect of SCIT on clinical and immunologic treatment used in patients with allergic rhinoconjunctivitis.²³ SCIT was shown to be an effective treatment in allergic rhinoconjunctivitis, decreasing symptoms, the need for medication, and reactivity in specific nasal and conjunctival provocation tests, as well as inflammatory markers. This study was more a “general literature review” rather than a formal systematic review, as no search design methodology was presented and no statistical meta-analyses were conducted. However, the investigators did thoroughly review possible mechanisms involved in SIT and concluded that the efficacy of SIT is dependent on the allergen to which the individual patient is sensitive, the quality and total amount of the allergen applied, and the SIT schedule.

A second “analysis” of SIT for treating allergic rhinitis was conducted on 16 prospective, single-blind or double-blind, placebo-controlled studies published between 1966 and 1996. This review included 759 patients (546 adults, 53 children, 160 all ages).²⁴ The investigators explained that because experimental designs varied considerably from one study to another, it was not possible to reduce the entire

Table 1
Meta-analyses of RCTs of SIT for treating allergic rhinitis

Study, ^{Ref.} Year	Patients	Allergens	Symptom Scores SMD (95% CI)	Medication Scores SMD (95% CI)	Comment
Calderon et al, ²⁵ 2007	2871 adults	SCIT Seasonal	−0.73 (−0.97, −0.50) I ² = 63%	−0.57 (−0.82, −0.33) I ² = 64%	No children included No fatalities reported Moderate heterogeneity
Radulovic et al, ²⁷ 2010	4589 adults & children	SLIT Seasonal and perennial	−0.49 (−0.64, −0.34) I ² = 81%	−0.32 (−0.43, −0.21) I ² = 50%	Considerable heterogeneity despite inclusion of large trials
Penagos et al, ²⁸ 2006	484 children	SLIT Seasonal and perennial	−0.56 (−1.01, −0.10) I ² = 81%	−0.76 (−1.46, −0.06) I ² = 86%	Considerable heterogeneity
Olaguibel and Alvarez Puebla, ²⁹ 2005	232 children	SLIT Seasonal and perennial	−0.44 (−1.22, 0.35) I ² = not reported	Not reported	Small numbers Heterogeneity not reported
Compalati et al, ³⁰ 2009	382 adults and children	SLIT House dust mite	−0.95 (−1.77, −0.14) I ² = 92%	−1.88 (−3.65, −0.12) I ² = 95%	Considerable heterogeneity despite focus on a single allergen
Di Bona et al, ³¹ 2010	2971 adults and children with rhinitis	SLIT Grass pollen	−0.32 (−0.44, −0.21) I ² = 56%	−0.33 (−0.50, −0.16) I ² = 78%	Moderate heterogeneity

database to a single format for statistical analysis. Therefore, OR and 95% CI were calculated using a random-effects model for a variety of clinical outcomes. All but one study concluded that SIT was effective in terms of reducing symptoms of allergic rhinitis (OR 1.81, 95% CI 1.48–2.23) compared with placebo.

At present, there is only one Cochrane meta-analysis evaluating the effect of allergen injection immunotherapy on seasonal allergic rhinitis.²⁵ This review examined 51 RCTs published between 1984 and 2006 and included a total of 2871 patients (1645 active, 1226 placebo), each receiving on average 18 injections. A wide range of allergens were administered in these studies: ragweed ($n = 12$ trials), mixed grass ($n = 16$ trials), timothy ($n = 5$ trials), *Parietaria* ($n = 6$ trials), birch ($n = 4$ trials), orchard ($n = 2$ trials), cedar ($n = 3$ trials), bermuda ($n = 1$ trial), *Juniperus ashei* ($n = 1$ trial), and *Cocos nucifera* ($n = 1$ trial). Six studies specified that patients did not experience coexistent asthma; in 27 studies patients had mild to moderate seasonal allergic asthma; 18 studies did not specify the asthmatic status of their participants. The types of vaccines used were extracts ($n = 38$ studies), allergoids ($n = 12$ studies), and non-specified ($n = 1$ study). The duration of maintenance treatment and the period of follow-up varied considerably between studies, largely reflecting preseasonal, coseasonal, and postseasonal administration. Duration of immunotherapy varied from 3 days (minimum duration) to 3 years (maximum duration). Six studies did not mention the duration of treatment. It was not possible from most of the studies to determine accurately the dose of allergen given in terms of micrograms of major allergen. Doses given were quantified in many different units including BU, PNU, BU, SQ-U, $\mu\text{g Ag}$, SE-U, AUeq, SU/mL, TU, wt/vol, and HEP. Symptom score data from 15 trials were suitable for meta-analysis and showed an overall reduction in the immunotherapy group (SMD -0.73 , 95% CI -0.97 to -0.50 ; $I^2 = 63\%$). Medication score data from 13 trials showed an overall reduction in the immunotherapy group (SMD -0.57 , 95% CI -0.82 to -0.33 ; $I^2 = 64\%$).

SLIT

The effectiveness of SLIT has been studied in 5 meta-analyses.^{26–31} The first Cochrane analysis looked at 22 studies published between 1990 and 2002.²⁶ This systematic review and meta-analyses was updated in 2010²⁷ to include 49 RCTs (involving a total of 4589 participants: 2333 active and 2256 placebo), 34 studies were performed in adults and 15 in children. Allergens used were grass pollen ($n = 23$ trials); *Parietaria* ($n = 5$ trials), ragweed ($n = 2$ trials); trees ($n = 9$ trials): olive ($n = 2$ trials), cypress ($n = 3$ trials), birch pollen ($n = 2$ trials), mixed trees ($n = 2$ trials); house dust mite ($n = 8$ trials); and cat ($n = 1$ trial). Symptom score data showed an overall reduction in the immunotherapy group (SMD -0.49 , 95% CI -0.64 to -0.34 , $P < .00001$); there was significant heterogeneity between the studies ($\text{Chi}^2 = 256.76$, $P < .00001$, $I^2 = 81\%$). Medication score data from 38 trials showed an overall reduction in the immunotherapy group (SMD -0.32 , 95% CI -0.43 to -0.21 , $P < .00001$). Significant heterogeneity was indicated ($\text{Chi}^2 = 73.32$, $P = .0003$, $I^2 = 50\%$). 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) and medication scores (SMD -0.44 , 95% CI -0.84 to -0.04). Similarly to the previous version of this Cochrane review, the investigators were unable to identify a significant reduction in either symptoms or medication scores in children.

A separate systematic review focused only on the pediatric use of SLIT in studies published between 1990 and 2004.²⁸ Ten studies provided enough data for meta-analyses

and included 484 children (245 SLIT and 239 placebo). Allergens included were mites ($n = 4$ trials), grass mix ($n = 3$ trials), olive ($n = 1$ trial), *Parietaria* ($n = 1$ trial), and *Phleum poa* ($n = 1$ trial). There was a significant reduction in both symptoms (SMD -0.56 , 95% CI -1.01 to -0.10 , $I^2 = 81\%$) and medication use (SMD -0.76 , 95% CI -1.46 to -0.06 , $I^2 = 85\%$) after SLIT compared with placebo. The subgroup analyses performed for treatment duration and type of allergen showed that SLIT for longer than 18 months and with pollen extracts was effective compared with SLIT courses shorter than 18 months and with mites. Duration of treatment varied between 3 and 36 months.

Six pediatric trials were included in a systematic review and meta-analysis to assess the effect of SLIT compared with placebo (117 children in SLIT and 115 placebo).²⁹ Allergens included were house dust mite ($n = 3$ trials), grass mixed ($n = 1$ trial), olive ($n = 1$ trial), and *Parietaria* ($n = 1$ trial). Using a random-effect model there was a reduction in nasal symptoms scores (SMD -0.44 , 95% CI -1.22 to 0.35 ; $I^2 =$ not reported).

The effectiveness of SLIT with house dust mite extracts for allergic rhinitis was independently meta-analyzed in 9 trials published up to March 1, 2008 with a total of 403 participants (194 active, 209 placebo).³⁰ A significant reduction in symptoms of allergic rhinitis (SMD -0.95 , 95% CI -1.77 to -0.14 , $I^2 = 92\%$) and rescue medication (SMD -1.88 , 95% CI -3.65 to -0.12 , $I^2 = 95\%$) was found in the SLIT group compared with the placebo group.

More recently, the effect of SLIT with grass allergens in adults and children with seasonal allergic rhinitis was separately evaluated in 19 trials; this review included 2971 patients (1518 receiving SLIT and 1453 placebo).³¹ In this analysis there was a significant reduction in both symptoms (SMD -0.32 , 95% CI -0.44 to -0.21 , $I^2 = 56\%$) and medication use (SMD -0.33 , 95% CI -0.50 to -0.16 , $I^2 = 78\%$) compared with placebo. The investigators concluded that the treatment seems to be more efficacious in adults than in children, and prolonging the duration of preseasonal treatment for more than 12 weeks improves the treatment efficacy.

Allergic Asthma

The results of meta-analyses of SCIT or SLIT for treating allergic asthma are summarized in **Table 2**, and are described in detail here.

SCIT

The clinical efficacy of SCIT in asthma was firstly summarized by a meta-analysis of 20 trials for asthma published between 1954 and 1990.³² Subsequently this systematic review was updated as a Cochrane meta-analysis to include 75 trials published between 1954 and 2001.³³ The last update looked at 81 trials.³⁴ Allergens used were house dust mite ($n = 42$ trials), pollen ($n = 27$ trials), animal dander ($n = 10$ trials), *Cladosporium* mold ($n = 2$ trials), latex (2 trials), and multiple allergens ($n = 6$). Overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity following immunotherapy. There was a significant improvement in asthma symptom scores (SMD -0.59 , 95% CI -0.83 to -0.35) and it would have been necessary to treat 3 (95% CI 3–5) patients with immunotherapy to avoid one deterioration in asthma symptoms. Overall, it would have been necessary to treat 4 (95% CI 3–6) patients with immunotherapy to avoid one requiring increased medication. Allergen immunotherapy significantly reduced allergen specific bronchial hyperreactivity, with some reduction in nonspecific bronchial hyperreactivity as well. There was, however, no consistent effect on lung function. The investigators stated that the benefits of allergen immunotherapy could be overestimated because of unpublished negative studies, and suggested that additional studies would be necessary to overturn these results. It was concluded that

Table 2
Meta-analyses of RCTs of SIT for treating allergic asthma

Study	Patients	Allergens	Symptom Scores SMD (95% CI)	Medication Scores SMD (95% CI)	Comment
Abramson et al, ³⁴ 2010	3459 children and adults	SCIT Seasonal or perennial	−0.59 (−0.83, −0.35) I ² = 90%	−0.53 (−0.80, −0.27) I ² = 67%	Open trials included No detailed evaluation of safety Considerable heterogeneity
Calamita et al, ³⁶ 2006	1706 adults and children	SLIT Seasonal and perennial	−0.38 (−0.79, 0.03) I ² = 64%	−0.91 (−1.94, 0.12) I ² = 92%	Considerable heterogeneity Weak methodology Open trials included
Penagos et al, ³⁷ 2008	441 children	SLIT Seasonal and perennial	−1.14 (−2.10, −0.18) I ² = 94%	−1.63 (−2.83, −0.44) I ² = 95%	Considerable heterogeneity
Olaguibel and Alvarez Puebla, ²⁹ 2005	193 children	SLIT Seasonal and perennial	−1.42 (−2.51, −0.34) I ² = not reported	Not reported	Small numbers Heterogeneity not reported
Compalati et al, ³⁰ 2009	476 adults and children	SLIT House dust mite	−0.95 (−1.74, −0.15) I ² = 93%	−1.48 (−2.70, −0.26) I ² = 96%	Considerable heterogeneity despite focus on a single allergen

allergen immunotherapy is a treatment option in highly selected patients with extrinsic ("allergic") asthma.

Ross and colleagues³⁵ extracted data from 24 prospective trials published between 1966 and 1998 in allergic asthmatics. Using a random-effects model, the SCIT patients group showed an improvement compared with the placebo group for symptoms of asthma (OR 2.76, 95% CI 2.22–3.42), for pulmonary function (OR 2.87, 95% CI 1.82–4.52), protection against bronchial challenge (OR 1.81, 95% CI 1.32–2.49), and reduced need for medications (OR 2.00, 95% CI 1.46–2.72).

SLIT

The efficacy of SLIT in mild to moderate asthmatics was evaluated in a meta-analysis of 25 studies published between 1991 and 2005 (total 1706 patients).³⁶ The effect of SLIT on asthma symptoms (SMD -0.38 , 95% CI -0.79 to 0.03 ; $I^2 = 64\%$) and asthma medication use (SMD -0.91 , 95% CI -1.94 to 0.12 , $I^2 = 92\%$) were not statistically significant. This review has some methodological issues, which make interpretation difficult. First, there were no restrictions in relation to inclusion criteria for trial selection; the review thus included both open and blinded trials. Second, the outcomes analyzed were not clearly defined. Finally, statistical analysis included qualitative assessments instead of a quantitative approach for some outcomes.

Another meta-analysis focused on allergic asthma in children (3–18 years of age)³⁷ and included 9 studies published between 1990 and May 2006 with total of 441 patients. The effect of SLIT was significant for both improvement of asthma symptoms (SMD -1.14 , 95% CI -2.10 to -0.18 , $I^2 = 94\%$) and reduction in asthma medication use (SMD -1.63 , 95% CI -2.83 to -0.44 , $I^2 = 95\%$) compared with placebo. The investigators concluded that SLIT with standardized vaccines reduces both symptom scores and rescue medication use in children with allergic asthma compared with placebo.²⁴ Nonetheless, in this meta-analysis the heterogeneity was very significant ($>94\%$), with a wide 95% CI for SMD in both outcomes. This variation indicates the diverse methodology used throughout studies. More studies are required to make a robust conclusion.

Five pediatric RCTs were included in another systematic review and meta-analysis to assess the effect of SLIT compared with placebo.²⁹ Allergens included were house dust mite (4 trials) and olive (1 trial). Using a random-effects model, there was a significant reduction in bronchial symptoms scores (SMD -1.42 , 95% CI -2.51 to -0.34 ; $I^2 =$ not recorded).

Compalati and colleagues³⁰ undertook a review of the effect of house dust mite SLIT for treating allergic asthma. These investigators found a significant reduction for symptom scores (SMD -0.95 , 95% CI -1.74 to -0.15 , $I^2 = 93\%$) and rescue medication use (SMD -1.48 , 95% CI -2.70 to -0.26 , $I^2 = 96\%$) in the SLIT group compared with the placebo group.

COMPARING SCIT WITH SLIT USING META-ANALYSES

There are very few trials comparing SCIT with SLIT for the same allergen within the same study; a direct comparison is not possible because of the absence of well-designed primary studies. It is also problematic, however, to use the results obtained in one systematic review and meta-analysis for comparison with the results obtained in separate meta-analysis, for example of SCIT versus SLIT for treating allergic rhinoconjunctivitis. The effect size of one particular outcome is related to that particular meta-analysis, which is based on the data extracted from a specific systematic review. The high clinical and methodological heterogeneity (more than 50%) found in the various meta-analyses makes comparisons even more difficult. However, efforts

have been made to quantify any differences in clinical efficacy between SLIT and SCIT. For example, a set of parallel meta-analyses of SCIT ($n = 6$ trials), SLIT (drops; $n = 12$ trials) and SLIT (tablets; $n = 6$ trials) in a total of 3629 patients with grass pollen rhinitis found the level of efficacy was greater for SLIT tablets (SMD -0.41 , 95% CI -0.51 to -0.31) and SCIT (SMD -0.46 , 95% CI -0.62 to -0.31) than for SLIT drops (SMD -0.14 , 95% CI -0.25 to -0.02). Tests for heterogeneity were nonsignificant for SLIT tablets and SCIT ($P = .23$ and $P = .99$, respectively), but significant for the SLIT drop analysis ($P = .002$). Results were similar with a random-effects model.³⁸

SAFETY EVALUATIONS IN META-ANALYSES

Systematic reviews have shown that SCIT is safe when prescribed to selected patients in a specialist clinic with adequate facilities and trained health personnel. SCIT can produce both local and systemic adverse reactions; however, in the majority of cases these symptoms are readily reversible if recognized early and with prompt treatment. Adverse effects may occur with all allergen preparations whether using standardized extracts, allergoids, or recombinant allergens.³⁹ In the only Cochrane systematic review and meta-analyses on SCIT for seasonal allergic rhinitis,²⁵ 22% of SCIT versus 8% of placebo had mild (European Academy of Allergy and Clinical Immunology [EAACI] Grade II) and 7% of SCIT versus 1% had moderate to severe (EAACI Grade III) allergic reactions at some time during their course of SCIT. Anaphylaxis (EAACI Grade IV) was reported only in 3 cases in the SCIT group (0.72%) versus 1 case in the placebo group (0.33%). Adrenaline was used in 3.4% of participants (19/557 patients; 0.13% of 14,085 injections) in the SCIT group versus 0.25% (1/404 patients; 0.01% of 8278 injections) in the placebo group. This review suggests that adverse reactions serious enough to require treatment with adrenaline (epinephrine) occur approximately once in every 770 immunotherapy injections. There were no fatalities.²⁵

The safety profile of SLIT seems to be superior to that for SCIT; however, it is difficult to compare safety data between different meta-analyses, because different trials and meta-analyses use different grading systems for severity. Although there is recent consensus on an immunotherapy adverse event grading system, this was not used for the studies included in the meta-analyses published to date.^{39,40}

WHAT HAVE WE LEARNED FROM THE META-ANALYSES?

It is important to step back and reflect on what this body of work has contributed to advancing our understanding of the management of people with allergic airway disease. Some key over-arching lessons include the following observations.

- *Systematic reviews and meta-analyses are powerful tools for synthesizing clinical trial data in a format that is easily accessible to trained clinicians.* One hundred years after the discovery of SIT, there is now a substantial body of trial evidence available to draw on in this field, and investigators have on the whole been very generous in sharing their data for meta-analysis.
- *Meta-analyses have shown that SCIT and SLIT are effective in the treatment of allergic rhinitis and allergic asthma.* Meta-analyses of SIT based on properly well performed systematic reviews represent the highest level of evidence. Meta-analyses of SCIT and SLIT for allergic rhinitis^{23–31} and allergic asthma^{29,30,32–37} show that these forms of treatment are clinically efficacious when compared with placebo. Because of the high level of heterogeneity present in the meta-analyses of SLIT and SCIT particularly for allergic asthma, caution is needed in

drawing conclusions. Some of this heterogeneity can be attributed to variation in study design and methodological limitations in the clinical trials themselves. The inclusion of weak study designs (eg, open trials) in systematic reviews and meta-analyses would bias in favor of demonstrating a beneficial effect associated with treatment.

- *SIT is a relatively safe form of treatment for allergic rhinitis.* In the modern age and with appropriate safeguards in place, SIT is a relatively safe form of treatment, particularly if given through nonparenteral routes. However, clinical trials and meta-analyses are not a good way to assess the risk of rare adverse events such as fatal anaphylaxis, due to insufficient statistical power and less than optimal safety monitoring, which usually occur within a clinical trial setting. Moreover, reporting of safety outcomes has been limited in many clinical trials and some meta-analyses of SIT, particularly meta-analysis of SCIT for treating allergic asthma.
- *Future SIT meta-analyses should focus on specific allergens, populations, and outcomes.* SIT is being delivered and investigated for a variety of allergic conditions such as asthma, allergic rhinitis, eczema, and food allergy through a variety of routes (mainly subcutaneous and sublingual). It is important that some boundaries are drawn and a focus is found when researchers conduct a systematic review and meta-analyses, due to the unavoidable clinical and methodological heterogeneity in reviews that include a wide range of differing studies. This approach will allow us to reach conclusions that are more specific and with less heterogeneity.
- *The quality of systematic reviews and meta-analyses is critical for making reliable and valid conclusions about the therapeutic intervention.* The need for high-quality RCTs is well recognized, but the literature on quality assessment for systematic reviews and meta-analyses is at an earlier stage of development. Poor published quality reviews and meta-analyses can be misleading, and criteria have been developed for the assessment of systematic review quality.^{41,42} Common weaknesses include lack of a priori systematic review design, a comprehensive literature review, a quality assessment of included studies (for example using GRADE criteria⁴³), and inappropriate statistical methods for meta-analysis. Considering that meta-analysis is a statistical procedure that incorporates the results of pooled independent studies, the reader must be critical and objective in the interpretation of its results, and data should be carefully scrutinized for adequate study design.^{39,44}
- *Selection and grading of the primary end points in SIT trials is necessary.* There are clear discrepancies in the selection and grading of the primary end points for assessing the response to SIT in allergic rhinitis and allergic asthma. Recommendations have been made to unify these criteria⁴⁵; however, many of the studies included in the systematic reviews and therefore in the meta-analyses were conducted prior to these recommendations. There is a need for further trials and meta-analyses that report more global outcome measures than symptom and medication scores, such as quality of life and health economic assessments. There is also a lack of studies looking at long-term outcomes (eg, immune tolerance), health economic evaluations, and head-to-head studies with other active treatments (eg, intranasal steroids).
- *Adequate study size and power calculations are needed for future SIT trials, to limit heterogeneity between trials included in meta-analyses.* Inclusion of multiple small trials in a single meta-analysis may increase the risk of overestimating or

underestimating the true treatment effect.⁴⁵ Many studies of small numbers of participants are included in the current systematic reviews and in meta-analyses. Power calculation should be determined before initiation of any particular therapeutic intervention.

- *There may be a need for a publicly accessible immunotherapy trials data repository, to facilitate updates/follow-on systematic reviews and meta-analyses.* It is very important that the results of both positive and negative trials are reported, as this may reduce the risk of publication bias.^{39,46} Studies with so-called negative results are more often not submitted for publication or for report to regulatory authorities, and take longer to be published.⁴⁶ The lack of this information may be reflected in the data included for meta-analyses that might lead to an overestimation of beneficial effects of SIT. Trials need to be reported in accordance with CONSORT guidelines.⁴⁷

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