Sublingual immunotherapy for allergic respiratory diseases: An evaluation of meta-analyses

Antonio Nieto, MD, PhD, Angel Mazon, MD, PhD, Rafael Pamies, MD, Laura Bruno, MD, Mariola Navarro, MD, and Ana Montanes, MD *Valencia, Spain*

Background: Five published meta-analyses (MAs) seem to prove the efficacy of sublingual immunotherapy in allergic asthma and rhinoconjunctivitis.
Objective: We aimed to assess the consistency, magnitude, and robustness of the results of these MAs.
Methods: The data reported in the MAs were checked with the data reported in the original studies. Funnel plots were performed to test for potential publication bias, and the trim-and-fill method was used to assess and correct the estimate of the effects if asymmetry was present.
Results: The 5 MAs included 43 studies; 17 were used in more than one MA. There were discrepancies among the MAs in the data reported from the same original studies: the MAs reported different estimates for the same outcome or the same estimates for different outcomes in 16 of those 17 studies. The MAs evaluated 15 main outcomes, 10 of which showed benefits that reached statistical significance. Funnel plots showed asymmetry in 7 outcomes, and correction by using the trim-and-fill method led to a decrease in their effect estimates and even to a loss of statistical significance in 4 of the previously significant outcomes. There was inconsistency among the MAs in the benefits when considering age, disease, allergen, or symptoms and medication use.
Conclusion: Because of discrepancies, inconsistencies, and lack of robustness, the MAs on sublingual immunotherapy do not provide enough evidence to support its current routine management in patients with allergic asthma or rhinoconjunctivitis. Sensitivity to potential publication bias should be tested and reported in all MAs. (J Allergy Clin Immunol 2009;124:157-61.)

Key words: *Allergy, asthma, bias, funnel plot, immunotherapy, meta-analysis, rhinoconjunctivitis, sublingual, trim and fill*

There has been a steady increase in the prevalence of allergic diseases in the last 20 years. The etiologic treatment of these diseases is based on avoidance measures and, when indicated, immunotherapy. Because of the high prevalence of allergy, the potential target population for immunotherapy is very large.

Abbreviations used
MA: Meta-analysis
SLIT: Sublingual immunotherapy

Subcutaneous injections of allergen have been used for almost 100 years. Although they have been proved efficacious, they can be time consuming and inconvenient.

Thus other routes for immunotherapy have been explored, and lately, the sublingual route is being increasingly used in European countries and is viewed with interest in the United States.[1] Its efficacy is a matter of discussion, and 5 meta-analyses (MAs) have been published that seem to prove its value in randomized studies.[2-7]

The aim of our study was to evaluate results published in MAs of sublingual immunotherapy (SLIT) and to assess their consistency, the magnitude of the effects, and the robustness of their conclusions.

METHODS

Five MAs on SLIT[2-7] were identified through a Medline search. They were all the MAs on SLIT published in the English language until June 2008. Systematic reviews not following the MA methodology were not included. The MAs analyzed original, randomized, mostly double-blind placebo-controlled studies in children, adults, or both with allergic asthma, rhinoconjunctivitis, or both. The original studies included in the MAs were scrutinized, and their data on the analyzed outcomes were compared with their reported correspondent data on the different MAs to check consistency in reports.

To assess potential publication bias in the MAs, their results on the different outcomes were used to generate funnel plot graphs by using the Review Manager 4.2 software (Cochrane Reviews). The methods of Begg and Mazumdar[8] and Egger et al[9] were performed, as was the trim-and-fill method,[10] which also allows correction of the effect estimate when potential bias is present, to test for significant asymmetry. Stata 9.1 software (StataCorp, College Station, Tex) was used.

Briefly, the funnel plot is a graph that plots the effect estimate of each original study in the x-axis and its precision in the y-axis. As a measure of precision, it might use the number of patients included in the study or, more commonly, the inverse of the SE of the effect estimate. The smaller the precision of the studies, the wider the variation of the effect estimates across the different studies, and conversely, the higher the precision, the narrower the amplitude in variation of effect estimates. Thus the plot will have the shape of an inverted funnel, which must have a roughly symmetric appearance. In case there is a publication bias (eg, studies with negative results are not published), the funnel plot will be truncated in one side and will show an asymmetric appearance. The trim-and-fill method assesses asymmetry and, through a nonparametric procedure, estimates the number of potentially missing studies, adjusts for them by using "mirrored" data of the most extreme present studies, and recalculates the effect estimate.

Finally, we calculated the estimates of the effects of SLIT on several major outcomes if the data of all the studies included in the 5 MAs were used to perform a new MA. The results were also tested with the Begg and

From the Section of Pediatric Allergy, Children's Hospital La Fe.

Disclosure of potential conflict of interest: A. Nieto and A. Mazon have received research support from ALK-Abelló and Leti. R. Pamies has received research support from ALK-Abelló. The rest of the authors have declared that they have no conflict of interest.

Received for publication December 18, 2008; revised March 31, 2009; accepted for publication April 6, 2009.
Available online June 1, 2009.

Reprint requests: Angel Mazon, MD, PhD, Section of Pediatric Allergy, Children's Hospital La Fe, Av. Campanar 21, 46009-Valencia, Spain. E-mail: amazon@comv.es.

0091-6749/$36.00

doi:10.1016/j.jaci.2009.04.015

TABLE I. Examples of discrepancies

Study	Source	SLIT			Placebo			SMD	CILL	CIUL	Outcome
		No.	Mean	SD	No.	Mean	SD				
Vourdas et al, 1998[E14]	Original	34 → 34	–	–	32 → 32	–	–				
		1R 33AR			3R 29AR						
	Wilson et al, 2003[4]	34	1.38	2.01	32	1.07	1.63	0.17	−0.32	0.65	Allergic rhinitis symptom score
	Penagos et al, 2006[5]	34	0.88	0.25	32	1.24	0.35	−1.18	−1.70	−0.65	Nasal score, rhinitis
	Olaguibel et al,2005[2]	34	0.98	1.31	32	1.34	1.78	−0.23	−0.71	0.26	Nasal symptom score
Rolinck-Werninghaus et al, 2004[E10]	Original	49 → 39	2.54	3.58	48 → 38	2.85	3.87				
		29RC 20ARC			29RC 19ARC						
	Calamita et al, 2006[6]	39	2.54	3.58	38	2.85	3.87	−0.08	−0.53	0.36	Reductions of medication use to allergies, general
	Penagos et al, 2006[5]	39	2.54	3.58	38	2.85	3.87	−0.08	−0.53	0.36	Medication score, rhinitis
	Penagos et al, 2008[7]	20	2.54	3.58	19	2.85	3.87	−0.08	−0.71	0.55	Medication score (asthma)

In the first study different data are reported by 3 MAs for the same outcome. In the second study 3 MAs report the same data for different outcomes.
SMD, Standardized mean difference; *CILL*, 5% to 95% CI lower limit; *CIUL*, 5% to 95% confidence interval upper limit. →, number of patients who initiate → finish treatment; *R*, rhinitis; *A*, asthma; *C*, conjunctivitis.

Mazumdar,[8] Egger et al,[9] and trim-and-fill[10] methods by using the Stata 9.1 software.

RESULTS

The 5 MAs cited 43 references (see the reference list in this article's Online Repository at www.jacionline.org): 2 studies were apparently included in some MAs, but their numeric data were not used for analysis. One study had 2 references, one as an abstract and the other as a journal publication; 26 studies were included in only one MA, and 17 (39.5%) studies were included in 2 to 5 MAs. The overlapping of studies is shown in Tables E1 and E2 in this article's Online Repository at www.jacionline.org. The MA by Wilson et al has been published in a journal[3] and in the Cochrane Library[4]; there were numerous differences between both sources in the figures provided, probably because of misprints in the editing process because the final result was the same, and therefore the results published in the Cochrane Library were used for evaluation.

There were discrepancies not caused by errata or rounding among the original studies, the MAs, or both in the reported data concerning the number of patients, mean effect, and SD in the active and placebo groups and hence in the standardized mean difference and its 5% to 95% CIs. Some discrepancies regarding the number of patients were due to the fact that 2 MAs[2,4] evaluated all initially included patients and included an intent-to-treat assessment, whereas the other 3 MAs[5-7] evaluated patients who actually finished the study. This pattern was not uniformly followed, and MAs 1[2] and 2[4] in some cases evaluated the number of patients who finished instead of those who initiated the treatment, and conversely, MAs 3[5] and 5[7] occasionally did the opposite. The MA by Calamita et al[6] evaluated patients who finished treatment for the outcomes of symptoms, medication, or their combination but evaluated patients who initiated treatment for a dichotomous outcome of "worse of asthma."

There were more important discrepancies in the effect estimates in the active and control groups, with reported values in one MA that were up to 8 times the reported values for the same outcome in another MA. In as many as 27 instances, the original study did not report all the values required for analysis: authors of MAs 3[5] and 5[7] occasionally calculated them through image analysis of the figures, but all 5 MAs included trials in which they had to obtain the values by asking the authors of the original study. The discrepancies in the effect estimates led to discrepancies among MAs in the standardized mean difference and its CIs, with differences that reached up to 1.35 standardized *z* units.

In some results in which no apparent numeric discrepancy was found, the outcome was different for one MA when compared with another MA and with the original study (eg, MA 2[4] used data for rhinitis symptoms, whereas the original study and MA 4[6] had the same results for a combined asthma plus rhinitis plus conjunctivitis symptom score). Table I shows 2 examples of discrepancies between the reported values in the original articles and their values as reported in the MAs. The results of all the studies are shown in Tables E3 to E6 in this article's Online Repository at www.jacionline.org.

In the 15 main outcomes of the MAs, as shown in Table II (left side), 10 significantly favored active treatment over placebo, whereas in 5 the 95% CI interval of the effect crossed the line of no effect. We found a negative correlation (Spearman rho = 0.54, $P = .037$), as shown in Fig E1 in this article's Online Repository at www.jacionline.org, of the benefit with the number of studies in each MA, and therefore the MAs with the highest number of evaluated studies showed the smallest benefits.

The MAs showed results of some subanalyses according to duration of SLIT, allergen, and age of patients. Regarding duration (Fig 1), MA 2[4] found a trend toward improvement of rhinitis symptoms with increasing duration, but at the same time, there was a decrease in the benefits in the rhinitis medication score. Likewise, MA 3[5] found a significant benefit in the symptom score, but not in the use of medication for rhinitis in children receiving more than 18 months of SLIT, although the number of studies included in these subanalyses was low.

For allergens, MA 2[4] found no benefit with perennial (mainly mites) allergens, and small benefits were found with pollens in children and adults with rhinitis. MA 3[5] found benefits for pollen but not for mites in children with rhinitis, but the same authors, in MA 5,[7] found benefit for mites but not for pollen in children with asthma.