



The current overuse and misuse of meta-analyses on sublingual immunotherapy: the case of grass pollen allergy

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Purpose of review

Meta-analysis provides the highest level of evidence-based efficacy of a medical treatment or intervention. Allergen immunotherapy in its two forms of subcutaneous immunotherapy and sublingual immunotherapy (SLIT) is an effective treatment of respiratory allergy as shown by meta-analyses, but in recent years there has been an overflow of meta-analyses on SLIT, with contrasting results that may generate confusion among physicians.

Recent findings

It can be observed that flaws are often present in meta-analyses including: incorrect selection of trials, inappropriate use of evaluation parameters for the analysis, and unsuitable analyses. For instance, it is clear that a meta-analysis of several small studies does not predict the results of a single large study that remains the gold standard to assess the efficacy and safety of a treatment. To assess the interest of the matter, we calculated the number of citations of meta-analyses on SLIT efficacy in the 10 years after the first publication in 2005 and detected a continuous decrease in citations.

Summary

Today, the appropriateness of a meta-analysis should be carefully evaluated, taking into account that a meta-analysis uses a statistical approach to combine the results from multiple small studies to increase power, to improve estimates of the size of the effect, and/or to resolve uncertainty when reports disagree. Editors and reviewers of medical journals should consider that to judge a meta-analysis requires a high level of expertise that is obvious in reviewers belonging to the Cochrane organization.

Keywords

cochrane database systematic revisions, large trials, meta-analysis, sublingual immunotherapy

INTRODUCTION

For a large part of its long history, allergen immunotherapy for respiratory allergy remained essentially an empirical treatment of allergic rhinitis and asthma. Only after more than 50 years of clinical use, subcutaneous immunotherapy (SCIT) began to be evaluated by rigorous experimental trials and after the 1970s the number of double-blind, randomized, placebo-controlled trials (DBRPC) rapidly increased [1]. The overall data from these trials, consistently showing the efficacy of the treatment, resulted in the first consensus document [2]. Sublingual immunotherapy (SLIT) was firstly proposed in the 1980s [3], but its application in clinical practice started in the 1990s [1]. For both SCIT and SLIT, many of the early trials included small populations of patients, and were therefore

unable to provide a sufficient statistical robustness. Meta-analysis involves a special statistical approach that combines the results of multiple studies to increase the power over individual studies, improving estimates of the size of the effect and clarifying uncertainty when the reports disagree [4].

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KEY POINTS

- Allergen immunotherapy in its two forms of SCIT and SLIT is an effective treatment of respiratory allergy as shown by Cochrane meta-analyses.
- Recent meta-analyses, especially those on SLIT with grass pollen extracts, have produced contrasting results that may generate confusion.
- Often such meta-analyses are concerned by defects in selection of trials, use of assessment parameters, and performance of unsuitable analysis.
- The overflow of meta-analyses on SLIT is associated with a significant decrease in scientific interest, as measured by a steady decline in the number of citations.

A meta-analysis produces a weighted average, commonly expressed by the main parameter of the standardized mean difference (SMD), of the included study results, and is currently considered the method giving the highest level of evidence [4].

META-ANALYSIS ON SUBCUTANEOUS IMMUNOTHERAPY AND SUBLINGUAL IMMUNOTHERAPY

Distinct meta-analyses on the efficacy of SCIT and SLIT in allergic rhinitis and asthma have been performed in the context of the Cochrane Collaboration. The meta-analysis on the effects of SCIT in asthma (88 trials) [5] and rhinitis (51 trials) [6] provided clearly positive results, with a SMD of -0.59 for asthma and -0.73 for rhinitis, respectively. Also, the efficacy of SLIT in rhinitis was supported by two positive meta-analyses; the first was performed in 2005 and included 22 trials [7], whereas in the 2010 update the trials analyzed were 60 [8]. The SMS was comparable, with a value of -0.42 in the first and -0.49 in the second meta-analysis. About the efficacy in asthma, a meta-analysis was published in the Cochrane Database Systematic Reviews on August 2015, including 52 studies, but the results were inconclusive [9]. Concerning asthma symptoms, 42 studies reported them as main outcome, but various scoring systems (often not validated) were used, and numerical data were sometimes lacking. Thus, the authors judged that a meta-analysis with a SMD would not be a sound methodological approach. In addition, they stated that 'Lack of data for important outcomes such as exacerbations and quality of life and use of different nonvalidated symptom and medication scores have limited our ability to draw a clinically useful conclusion. Further research, using better validated systems, relevant for patients and decision

makers is needed so that SLIT can be properly assessed as clinical treatment for asthma' [9]. All the results reported above were obtained by using the rigorous methods of the Cochrane Steering Group and Subgroups that include 14 Centres (with 19 regional Branches) worldwide, 11 Fields, 16 Methods Groups, and 53 Review Groups [10]. In 2009, a meta-analysis by a Global Allergy and Asthma European Network (GA2LEN) group, based on the observation that the previous sub-analyses for single allergens had provided uncertain results, investigated the efficacy of SLIT with house dust mite extracts in rhinitis and asthma. A significant reduction in symptoms in patients receiving SLIT compared with those receiving placebo was found for rhinitis and asthma (SMD -0.95 in both cases). The reduction in rescue medication gave a SMD of -1.88 for rhinitis and -1.48 for asthma. The authors concluded for a promising evidence of efficacy for SLIT in mite-allergic patients but claimed for more data derived from large population-based high-quality studies [11]. This became possible with the 'big trials' on grass pollen tablets and mite tablets that were performed to obtain the authorization from Regulatory Agencies (the European Medicines Agency and the Food and Drug Administration in the United States) as pharmaceutical quality products [12–15]. Based on the results of the trials on the five-grass pollen tablet and the one-grass (*Phleum pratense*) tablet, the two products were authorized and listed as drugs to treat grass pollen allergy in Europe, the United States, and Canada, and were approved in Italy for full reimbursement (A class) with the same indication [16]. Indeed, in the latest years an increasing number of 'home-made' meta-analyses on the efficacy of SLIT in rhinitis and asthma were published, also including the grass pollen tablets registered by European Medicines Agency and Food and Drug Administration. In such meta-analyses serious flaws are apparent. The first meta-analysis on SLIT for grass pollen allergy mixed together trials carried out with extremely different dosages: in some studies the doses were hundreds of times greater than in others. The authors concluded for a clinically modest benefit, and suggested that criteria were needed to identify patients most likely to benefit from SLIT [17]. Indeed, a reanalysis performed by other authors showed that the SMS was -0.16 in patients treated with low doses and -0.47 in patients treated with high doses [18], fully confirming the reported dose dependence of SLIT efficacy [19]. The same authors of the mentioned meta-analysis [17] performed a further analysis on the efficacy and safety of grass pollen tablets, again concluding for 'a small benefit of the grass pollen sublingual tablets in reducing symptoms and

in decreasing the use of symptomatic medication in patients with seasonal allergic rhinitis'. They also added that 'Considering the low magnitude of the benefit, the convenience and easy administration do not seem to be sufficient reasons for the choice of SLIT' [20]. These conclusions claim to wipe out all the long process leading to the acknowledgement of the quality and to registration of grass pollen tablets, but are substantially unfounded because the meta-analysis is significantly flawed, as highlighted by Cox *et al.* [21]. In particular, Di Bona *et al.* [20] included two trials that used the five-grass pollen extract in tablets, but containing a dose of 100 index of reactivity and not the 300 index of reactivity dose of the registered tablets, they analyzed separately symptoms scores and medication scores whereas a combined symptom-medication score is recommended as the primary outcome [22], and stated that a single-point change in the rhinoconjunctivitis total symptom score (RTSS) is not clinically relevant, whereas it was consistently estimated that the minimally important difference in the RTSS is 1.1–1.3 [23]. In addition, according to an updated vision, meta-analyses on allergen immunotherapy should not mix different products [24], and tablets based on five grass pollens or a single grass pollen (*Phleum pratense*) are clearly different, as admitted by Di Bona *et al.* [20]. Another relevant conceptual error is the inappropriateness of performing a meta-analysis on large randomized controlled trials, including high number of patients, that are generally considered the gold standard in evaluation of medical interventions. Instead, meta-analyses are appropriate when large trials are not available and the results of multiple small trials have to be pooled [25]. Villar *et al.* [26] recalculated the relative risks (and 95% confidence intervals) for 30 meta-analyses of different interventions in perinatal medicine after removing the largest trials and compared the results with those of the largest trials (total sample size more than 1000) done on that intervention. Only 18 meta-analyses were the same both in direction of treatment effect and in statistical significance as the largest trial. LeLorier *et al.* [25] compared the results of large randomized, controlled trials with the results of meta-analyses published earlier on the same topics; 12 large randomized, controlled trials, and 19 meta-analyses addressing the same issues were identified. The positive and negative predictive values of the meta-analyses were 68% and 67%, respectively, and the difference in point estimates between the randomized trials and the meta-analyses was statistically significant for only five of the 40 comparisons. Overall, the outcomes of the 12 large trials were not predicted accurately in 35% of meta-analyses published previously on the

same topics [25]. This makes clear that performing a meta-analysis of large trials is an inconsistent action and actually no such analysis is available in the Cochrane Database Systematic reviews site.

Indeed, a decreasing interest for meta-analysis on SLIT emerged from the number of citations. We calculated, on 14 April 2016, the number of meta-analyses on SLIT from 2005 (first meta-analysis published) to 2015 [7,8,11,17,20,27–38] and the number of citations they received. A continuous decline in citations in spite of the increase in publications, especially in the latest 3 years (meta-analyses of trials on patients with grass pollen allergy amounting to 40% of total), is apparent (Fig. 1).

POSSIBLE SOLUTION OF THE OVERUSE AND MISUSE OF META-ANALYSES

Meta-analysis is a powerful tool, but it can suffer from a number of biases, the major ones being the selection criteria for including the trials and the heterogeneity of the materials and methods used in the trials themselves. In 2009, Milgrom and Tran [39] in a balanced Editorial reviewed the value and limits of meta-analysis on SLIT. They wrote that 'The practitioner of meta-analysis, as any other scientist, must use correct methods and sound judgment, and the readers, reviewers, and editors of journal that publish the results must be aware of potential pitfalls'. It is apparent that such wise suggestion was poorly followed. It is time for reviewers and editors of medical journals to reconsider it. The fascination with meta-analysis as a statistical alchemy [40]

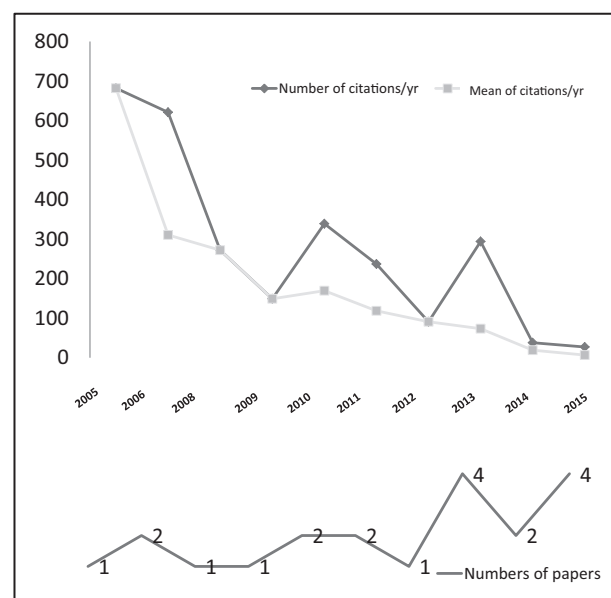


FIGURE 1. Number of meta-analyses on SLIT and citations from 2005 to 2015.

should be no more averse to scrutiny for its appropriateness and accuracy. Conceptually, a meta-analysis uses a statistical approach to combine the results from multiple small studies to increase power over individual studies and to improve estimates of the size of the effect. Its application in different issues such as large randomized trials is unwarranted. To suitably address the problem of appropriateness and accuracy, any meta-analysis submitted to a medical journal should be entrusted to reviewers with high level of expertise, preferably belonging to the Cochrane organization that has a universally acknowledged reliability in the field.

CONCLUSION

Cochrane meta-analyses on SCIT and SLIT defined the evidence of efficacy of these treatments in respiratory allergy. In recent years, there was an overflow of further meta-analyses, particularly concerning SLIT for grass pollen allergy, with contrasting results. However, the growing number of meta-analyses is in contrast with the decreasing number of citations, which mirrors a lowering scientific interest. Indeed, the recent meta-analyses are often flawed by incorrect selection of trials, inappropriate use of evaluation parameters for the analysis, and unsuitable analyses. Editors of medical journals should consider, when receiving meta-analyses, entrusting them to reviewers with a high level of expertise on the matter.

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Conflicts of interest

C.I. is a scientific consultant for Stallergenes Italy. The other authors have no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Incorvaia C, Frati F. One century of allergen-specific immunotherapy for respiratory allergy. *Immunotherapy* 2011; 3:629–635.
 2. 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.
 3. Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. *Clin Allergy* 1986; 6:483–491.
 4. O'Rourke K. An historical perspective on meta-analysis: dealing quantitatively with varying study results. *J R Soc Med* 2007; 100:579–582.
 5. Abramson MJ, Puy RM, Weiner JM. Injection immunotherapy for asthma. *Cochrane Database Syst Rev* 2010; 8:CD001186.
 6. Calderon MA, Alves B, Jacobson M, *et al.* Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 2007; 1:CD001936.
 7. Wilson DR, Lima MT, Durham S. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005; 60:4–12.
 8. Radulovic S, Calderon MA, Wilson D, *et al.* Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2010; 12:CD002893.
 9. Normansell R, Kew KM, Bridgman AL. Sublingual immunotherapy for asthma. *Cochrane Database System Rev* 2015; 8:CD11293.
 10. The Cochrane Steering Group & Subgroups. Available from: www.cochrane.org/about-us/cochrane-groups. [Accessed 13 February 2016].
 11. Compalati E, Passalacqua G, Bonini M, *et al.* The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. *Allergy* 2009; 64:1570–1579.
 12. Durham SR, Yang WH, Pedersen MR, *et al.* Sublingual immunotherapy with once daily grass allergen tablet: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; 117:802–809.
 13. Didier A, Malling 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; 120:1338–1345.
 14. Wahn U, Tabar A, Kuna P, *et al.*, SLIT Study Group. Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009; 123:160–166.
 15. Maloney J, Bernstein DI, Nelson H, *et al.* Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. *Ann Allergy Asthma Immunol* 2014; 112:146–153.
 16. Ciprandi G. A major step forward for sublingual immunotherapy: the quality of 5-grass pollen tablet is recognized also in Italy. *J Asthma Allergy* 2015; 8:25–27.
 17. Di Bona D, Plaia A, Scafidi V, *et al.* Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2010; 126:558–566.
 18. Frati F, Incorvaia C, Scurati S, *et al.* Dose-dependence of sublingual immunotherapy shown by meta-analysis. *J Allergy Clin Immunol* 2011; 127:1076–1077.
 19. Canonica GW, Bousquet J, Casale T, *et al.* Sublingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 2009; 64 (suppl 91):1–59.
 20. Di Bona D, Plaia A, Leto-Barone MS, *et al.* Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinoconjunctivitis: a systematic review and meta-analysis. *JAMA Intern Med* 2015; 175:1301–1309.
 21. Cox LS, Didier A, Demoly P, *et al.* Methodological aspects of a meta-analysis of grass pollen allergen sublingual immunotherapy tablets. *J Allergy Clin Immunol* 2016; 138:314–315.
 22. Pfaar O, Demoly P, van Wijk RG, *et al.* Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis; an EAACI Position Paper. *Allergy* 2014; 69:854–867.
- The international document on the recommendations on how to perform and analyze the trials on allergen immunotherapy in patients with allergic rhinoconjunctivitis.
23. Devillier P, Chassany O, Vicaut E, *et al.* The minimally important difference in the Rhinoconjunctivitis Total Symptom Score in grass-pollen-induced allergic rhinoconjunctivitis. *Allergy* 2014; 69:1689–1695.
 24. Canonica GW, Bagnasco D, Ferrantino G, *et al.* Update on immunotherapy for the treatment of asthma. *Curr Opin Pulm Med* 2016; 22:18–24.
 25. LeLorier J, Grégoire G, Benhaddad A, *et al.* Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med* 1997; 337:536–542.
 26. Villar J, Carroli G, Belizan JM. Predictive ability of meta-analysis of randomised controlled trials. *Lancet* 1995; 345:772–776.
 27. 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.
 28. Calamita Z, Saconato H, Pelà 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.
 29. Penagos M, Passalacqua G, Compalati E, *et al.* Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest* 2008; 133:599–609.
 30. Calderon MA, Penagos M, Sheikh A, *et al.* Sublingual immunotherapy for allergic conjunctivitis: cochrane systematic review and meta-analysis. *Clin Exp Allergy* 2013; 41:1263–1272.
 31. Kim JM, Lin SY, Suarez-Cuervo C, *et al.* Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. *Pediatrics* 2013; 131:1155–1167.
 32. Lin SY, Ereksomima N, Kim JM, *et al.* Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA* 2013; 309:1278–1288.
 33. Dretzke J, Meadows A, Novielli N, *et al.* Subcutaneous and sublingual immunotherapy for seasonal allergic rhinitis: a systematic review and indirect comparison. *J Allergy Clin Immunol* 2013; 131:1361–1366.

34. Chelladurai Y, Suarez-Cuervo C, Ereksom N, *et al.* Effectiveness of subcutaneous versus sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *J Allergy Clin Immunol Pract* 2013; 1:361–369.
35. Tao L, Shi B, Shi G, Wan H. Efficacy of sublingual immunotherapy for allergic asthma: retrospective meta-analysis of randomized, double-blind and placebo-controlled trials. *Clin Respir J* 2014; 8:192–205.
36. Devillier P, Dreyfus JF, Demoly P, Calderon MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. *BMC Med* 2014; 12:71.
37. Nelson H, Cartier S, Allen-Ramey F, *et al.* Network meta-analysis shows commercialized subcutaneous and sublingual grass products have comparable efficacy. *J Allergy Clin Immunol Pract* 2015; 3:256–266.
38. Liao W, Hu Q, Shen LL, *et al.* Sublingual immunotherapy for asthmatic children sensitized to house dust mite: a meta-analysis. *Medicine (Baltimore)* 2015; 94:e701.
39. Milgrom H, Tran ZV. Sublingual immunotherapy, meta-analysis, and knowledge in the age of information. *J Allergy Clin Immunol* 2009; 124:162–163.
40. Feinstein AR. Meta-analysis: statistical alchemy for the 21st century. *J Clin Epidemiol* 1995; 48:71–79.