

Considerations about the evaluation of the SLIT meta-analyses

To the Editor:

We have read with great interest the article by Nieto et al,¹ which claims insufficient evidence for the use of SLIT on the basis of discrepancies and inconsistencies found in the published meta-analyses (MAs). In this regard, we would like to discuss some of the points specifically raised by the authors.

From a general point of view, MAs represent the highest level of evidence, but it is important to remember that randomized controlled trials generate an evidence Ia and a grade A recommendation.² According to the assumptions of Nieto et al,¹ most medical interventions, lacking MAs, should not be recommended for clinical use.

The so-called "author's reporting bias" is responsible for the discrepancies between different MAs that include data from the same studies. This bias can be limited by requiring authors to provide the exact data, but those data are sometimes different from what was published in the original articles. Mistakes or imprecisions in data extraction are normally expected in MAs, but they are considered a random error, unable to affect the extent of estimations achieved by robust statistical methods, especially when differences are small.³ This seems to be the case in the majority of the MAs considered.

Discrepancies between MAs published in different years and including different numbers of studies are not surprising. On the contrary, when the number of studies increases, inconsistencies tend to resolve. Expecting a correlation between the clinical benefit and the number of studies as suggested by Nieto et al¹ is at least questionable, because smaller effects from numerous studies can be more robust than larger effects from a few imprecise studies. In addition, the existence of a real significant inter-MA difference in effect size cannot be evaluated without comparing the CIs. Nieto et al¹ seemed to ignore this fact in all their evaluations. Moreover, the authors outlined only some selected *post hoc* discrepancies and ignored that MAs represent a continuum in the research. Arbitrarily adopting selected *post hoc* and subgroups analyses to downgrade evidence is not a balanced approach.

Funnel plot asymmetry is intended as a measure of small study effects, but it does not automatically imply publication biases.⁴ For instance, asymmetry can be a result of the wide interstudy and intrastudy heterogeneity that is actually a relevant characteristic of the mentioned MAs.⁵ In addition, funnel plot and asymmetry tests perform poorly and are not reliable when fewer than 10 studies are analyzed.⁴ Considering the large number of unchanged estimations after the arbitrary adjustments and the absence of asymmetry for some outcomes, the evaluation by Nieto et al¹ must be interpreted with caution and without inappropriate generalizations. Finally, Nieto et al¹ claim an overall superiority of injection immunotherapy but do not provide a critical revision of the MAs as done for SLIT. Thus, their claim remains, in this context, a simple speculation.

Despite the limitations and possible mistakes common to all MAs, we warn against a totally pessimistic interpretation, because the suggestive results of SLIT-MAs are corroborated by large randomized controlled trials performed following a rigorous methodology.⁶ We believe that the inappropriate judgments on publication bias, the unbalanced way of evaluating consistency, the unjustified generalizations, and the speculative

conclusions strongly weaken the criticisms by Nieto et al.¹ This implies the concrete risk of a misleading impact on lay-readers, who quickly come to conclusions because they do not have adequate tools to interpret a very difficult article.

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Reply

To the Editor:

Regarding our article¹ about meta-analyses (MAs) on sublingual immunotherapy, we have read with much interest the letters by Calamita² and Compalati et al.³

The letter by Calamita² clarifies the source of some discrepancies we found in his meta-analysis and the reasons for the apparent incongruence of analyzing patients who finished treatment for some outcomes and patients who started treatment for others. This further stresses the importance of adhering to guidelines for communicating results of medical interventions⁴ and that of accurately describing the methods used in all scientific articles. Overall, his conclusions on the robustness of current evidence are much like ours.

The comments by Compalati et al³ are quite different, but not surprising, because they strongly supported the use of sublingual immunotherapy in 2 of the MAs we evaluated and recently in an article published in another journal.⁵ Randomized clinical trials are able to generate evidence Ia, we agree, but not only when they favor the active treatment. They also generate negative evidence when they show no benefit. This is the case of some randomized clinical trials accessible at clinical trials registers.⁶ Two of the authors of the letter (G.W.C. and G.P.) are well aware of some of them, because they explicitly acknowledge it in a very recent coauthored article in the Journal.⁷ To state that we suggest that medical interventions lacking MAs cannot be recommended is an unacceptable proposition, because nothing in our article supports this erroneous assumption made by Compalati et al.³

We cannot really think of a good reason to justify that authors of any study provide different data from those published in their original article, or provide different data when requested by different investigators. Authors of MAs are not to be blamed for the “author’s reporting bias,”³ and although this may be expected, it does not mean that it is acceptable. Measures to minimize this have been proposed in a constructive article⁴ coauthored by 3 of the authors of the letter, as cited in our article. Meanwhile, the number and the size (up to 8 times) of discrepancies across MAs that we have found are not to be considered small. Although robust statistical methods are used, the reliability of the results will be severely flawed when the analyzed data themselves are not reliable.

We do not expect a correlation between the clinical benefit and the number of studies. We expect that, in principle, the results of an MA with a higher number of studies will approach the real effect of a treatment more accurately than an MA with few studies. What Fig E1 in our article shows is that the beneficial effects decrease with the increase in the number of studies, and what it suggests is that, if more studies were included, especially those correcting for potential publication bias, the benefit will probably fade away. This is, certainly, a suggestion to be demonstrated. Regarding our supposed arbitrary selection of subgroup analyses, we must state that the selection was not decided by us, but by the authors of the MAs. We just evaluated the results they decided to show. This was the case in the 2 MAs coauthored by Compalati et al.³

If asymmetry was a result of heterogeneity or the small size of the included studies, we should expect a random asymmetry in both sides. Nevertheless, as shown in Figs E2 to E16 in our article, with the exception of Figures E2, E3, and E14, the patent visual asymmetry that is clearly perceived always favors the active treatment. Of the 5 more reliable funnel plots including ≥ 10 studies (Table II), 4 showed a significant asymmetry and, after trim and fill adjustment (not arbitrary, but systematic), 3 lost their statistical significance. “Publication is not the only reason for asymmetry,” and “Some outcomes included too few studies to have reliable results,” as quoted from our article (pages 160 and 159 respectively), mean that we do recognize some limitations of our evaluation. That is why we have interpreted our findings with extreme caution, and we refer to just potential publication bias. We would not have been so strict if we had acknowledged the unpublished studies that G.W.C. and G.P. acknowledge, as referenced.⁷ Subcutaneous immunotherapy was not the point of our article, so we just could compare it to sublingual immunotherapy

in terms of compliance and rapid treatment of potential severe reactions. An overall comparison is needed, because the paucity of direct comparative studies is striking.

The generalization that mistakes are common to all MAs is astonishing. This is speculative and hazardous, and we cannot accept that medical decisions may be based on “evidence” built from mistaken data. We warn against the use of only favorable randomized clinical trials and the omission of unfavorable ones to evaluate a medical intervention. Compalati et al.³ question our interpretation but not the data we have disclosed. Critical readers can judge the number and size of discrepancies across MAs, their discordant results, and the impact of potential publication bias, to reach their own conclusions. We reaffirm ours, as stated in our article, and sincerely consider them cautious and judicious. We are also worried about lay-readers, but because of the impact of the numerous articles uncritically extolling the virtues of sublingual immunotherapy based on incomplete evaluations.

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