

Correspondence

Reply

To the Editor:

We read with interest the letter from Calderon et al¹ regarding our meta-analysis comparing subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) in patients with monosensitization to grass.² However, we found their comments unsurprising because they support the use of SLIT.³

Calderon et al¹ suggest that the Pradalier et al⁴ and Smith et al⁵ studies should not have been included in our analysis because they used a subtherapeutic dose of allergen. However, excluding these 2 studies does not make any difference in the overall results (standardized mean difference [SMD] without the Pradalier et al and Smith et al studies, -0.37 ; SMD with the Pradalier et al and Smith et al studies, -0.38) and only leads to a loss of sample size. However, in a recent meta-analysis published by Radulovic et al,⁶ which included Dr Calderon as an author, to evaluate the efficacy of SLIT, both the Pradalier et al⁴ and Smith et al⁵ studies were included. It is curious that Dr Calderon himself did not exclude the studies that he suggests we should have excluded because, in his opinion, they are not suitable for the efficacy analysis.

Regarding the clinical prerequisites for an ideal meta-analysis, of course we all agree with Calderon et al¹ on the importance of including studies with similar characteristics. Unfortunately, studies are very different from each other, and we can only use the available evidence to perform meta-analyses, which, on the other hand, would be practically unnecessary if the results of the studies were indeed similar and heterogeneity was not present. Concerning the specific criticisms of Calderon et al¹ on the importance of taking into account allergen dose, treatment duration, end point, assessment period, and pollen exposure, we wish to emphasize that all these points were considered in the subgroup analyses in our study. The allergen dose was analyzed only for SLIT because data for SCIT were insufficient for a reliable analysis. This issue was discussed in the current meta-analysis² and had already been discussed in our previous meta-analysis.⁷ The treatment duration and assessment period were analyzed in the subgroup analyses (see comparisons 3 and 4 in Figs 2 and 4 and the Results and Discussion sections²). We discussed the subject of pollen exposure in the Additional results and comment section, where it was moved due to lack of space. Thus a more careful reading of our study might have prevented the misunderstanding.

The criticisms Calderon et al¹ make on our statistical methodology are based on incorrect assumptions. We showed a difference between SCIT and SLIT when analyzing data using the random-effects model. Calderon et al¹ assert that if we had used the fixed-effects model, there would have been no difference between these 2 treatments, and they state that the difference in the results between these 2 models are to be considered mandatory information for drawing firm conclusions. However, this is only true when both models can be applied, whereas in the current case the fixed-effects model was unacceptable for the following reasons. The fixed-effects model starts from the assumption that the true effect is the same in all studies: this assumption is implausible in many systematic reviews. When incorporating a group of studies in a meta-analysis, we assume that the studies have

enough in common that it makes sense to synthesize the information, but there is no reason to assume that they are “identical” in the sense that the true effect size is exactly the same in all the studies. Using the random effects model, we allow that the true effect could vary from study to study, depending on the value of a number of covariates, as shown in the descriptive subgroup analyses in Figs 2 and 4. For this reason, the studies included in the meta-analysis are assumed to be a random sample of the relevant distribution of effects, whereas the combined effect estimates the mean effect in this distribution.

The fixed-effects model is appropriate if 2 conditions are met. First, we have to believe that all the studies included in the analysis are functionally identical. Second, our goal must be to compute the common effect size for the identified population and not to generalize to other populations. In contrast, when a researcher is accumulating data from a series of studies performed by researchers operating independently, it would be unlikely for all the studies to be functionally equivalent. Typically, the subjects or interventions in these studies would differ in ways that would affect the results, and therefore we should not assume a common effect size. Therefore the random-effects model is more appropriate than the fixed-effects model in such cases.

Furthermore, the goal of this analysis is to generalize to a range of scenarios. Therefore if one were to argue that all the studies used an identical and narrowly defined population, then it would not be possible to extrapolate from this population to others, and the utility of the analysis would be severely limited.⁸

This criticism by Calderon et al¹ seems to stem from a misunderstanding in their reading of our Methods section, in which we stated that data were analyzed with both the fixed- and random-effects models. Of course, in that sentence it was implied “when possible,” as in the case of data from SLIT, where a low between-study variance was shown ($\tau^2 = 0.03$ for SLIT tablets), but not those from SCIT, where the between-study variance was 1 order of magnitude higher ($\tau^2 = 0.299$). However, for the above-reported reasons, we also chose the random-effects model for SLIT, which is more conservative than the fixed-effects model, because CIs will always be wider under the random-effects model.

When using the fixed-effects model, an excessive and disproportionate weight is given to a single study, the study by DuBuske et al⁹ in our case, which had the biggest sample size and, consequently, a weight of 52.5% (ie, greater than the remaining 13 studies combined). Moreover, with the fixed-effects model, all the small studies were practically ignored in the analysis, together with the information they provided, without a clinical reason.

Removing the study by DuBuske et al⁹ (robust analysis), the results with the fixed-effects model dramatically changed from -0.38 to -0.62 (SMD), whereas removing each of the other studies in turn did not change the overall results, showing that the overall result is strictly dependent on the single study by DuBuske et al when using the fixed-effects model. No change in the overall result was shown when we removed each SLIT study in turn, once again demonstrating that even with the clearly inappropriate fixed-effects model (proposed by Calderon et al¹), SCIT still remains more effective than SLIT after the exclusion of the study by DuBuske et al,⁹ according to the results of the robust analysis.

The described situation, unacceptable both from a clinical and statistical point of view, shows how an inappropriate model leads to misleading results (see the incorrect figure in Calderon et al¹) because with the inappropriate fixed-effects model, all the conclusions are dependent on only 1 of a total of 36 randomized controlled trials.

Finally, it must be noted that the fixed-effects model is practically never used to analyze data from immunotherapy, curiously not even in the meta-analyses by Radulovic et al⁶ and Calderon et al,¹⁰ in which data were analyzed with the random-effects model. A single standard should be used to judge both one's own research and that of others.

On the question of the strength of a recommendation when there is a high degree of heterogeneity, we did not make any treatment recommendation. However, we did point out the need for a comparative randomized controlled trial, for which the available evidence is sufficient. In contrast, Dr Calderon himself, in the study by Radulovic et al,⁶ made a treatment recommendation on the basis of the results of his meta-analyses, with heterogeneity reaching 90% in several comparisons.

Regarding the problems in estimating the magnitude of efficacy with the random-effects model in the presence of high heterogeneity, it must be emphasized that the same magnitude but with a very different variability means that a comparison cannot be made only on magnitude. The way to account for this difference in variability is to adjust magnitudes by means of SDs.

The robust and influential analyses were excluded from the original version of the article for lack of space. They are available for SLIT in our previous meta-analysis.⁷ In any case the exclusion of the study by Dolz et al¹¹ showed an irrelevant difference in the overall results from a clinical point of view (SMD of -0.75 without the study and an SMD of -0.92 with the study). We analyzed the study by DuBuske et al⁹ because it is "the guideline-compliant, multinational, multisite trial used in the modern development of specific immunotherapy." Calderon et al¹ seem to have misunderstood that this randomized controlled trial was not excluded by us in either the general analysis or in subgroup analyses. The study by DuBuske et al⁹ is a multicenter study involving 75 North American centers and only 9 European centers. One of the most striking results of that study was the clinically significant difference in the treatment benefit between European and North American populations. We asked the researchers to provide separate data for European and North American subjects, but they only provided data for the entire population. Dr DuBuske himself, in the first paragraph of his Discussion section, underlined the significant difference between European and North American centers, speculating that this might result from differences in lifestyle and environmental conditions, such as air conditioning. Future studies, especially on American populations (the DuBuske et al study is the only one to date for SCIT), could help to clarify this issue, but it is plausible that studying a population under more homogeneous conditions might be critical for correctly assessing immunotherapy with inhaled allergens.

The suggestion of Calderon et al¹ that we should have added the results of the subgroup analyses in our conclusions is difficult to understand because we discussed the subgroup analyses in detail throughout the Discussion section.

According to Calderon et al,¹ our study did not "provide solid evidence that SCIT is more effective than SLIT in reducing symptoms and medication use in patients with seasonal allergic rhinoconjunctivitis to grass pollen." However, it must be emphasized

that our conclusions are solid and correct in that they are not only based on the comparisons of the general meta-analyses but also on the results of descriptive subgroup analyses, which we used to explain the heterogeneity of the results, analyzing groups of studies sharing common characteristics. In every subgroup comparison (except duration of treatment, see the text for details), SCIT showed better efficacy than SLIT, demonstrating that even when groups of more homogeneous studies were compared, the general results did not change.

Calderon et al¹ claim that our meta-analysis does not live up to scientific standards; we are perplexed by this criticism because in 2007, Dr Calderon himself published a meta-analysis on SCIT for seasonal allergic rhinitis, analyzing all the inhaled allergens, including grass.¹⁰ Calderon et al¹⁰ included in their analysis all the studies that we included in our analysis for grass, except for the studies by DuBuske et al⁹ and Pfaar et al,¹² which were published after their meta-analysis. Therefore it is very difficult to understand this criticism because our meta-analysis includes the same studies as his meta-analysis, analyzes data using the same model (ie, the random-effects model, which was the only possible model), and expresses the results using the same measure (ie, SMD).

Journal readers should carefully consider criticisms that attempt to discredit our conclusion that the results of our meta-analysis are solid and that there is a need for randomized controlled trials comparing SCIT and SLIT to justify a treatment (SLIT) that is more profitable for its producers but is not more effective for patients.

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