

CORRESPONDENCE

Regarding Gidaro GB, Marcucci F, Sensi L, Incorvaia C, Frati F, Ciprandi G. The safety of sublingual-swallow immunotherapy: an analysis of published studies. Clin Exp Allergy 2005; 35:565–71

I read the interesting meta-analysis by Gidaro et al. in the May issue of Clinical and Experimental Allergy [1] with great interest. Over the past years, I have been working on the clinical problems related to sublingual immunotherapy (SLIT) and I think that this critical overview of literature will contribute to extend and improve the usage of this efficacious therapeutic approach, totally devoid of severe systemic side-effects, in a growing number of allergic patients.

However, I found several problems in the analysis that brought the Authors to conclude that the occurrence of adverse events (AEs) in SLIT controlled trials is not dose-dependent. The authors compared the frequency of AE in published placebo-controlled SLIT-swallow trials and subdivided them in two groups, namely those with a low allergen dose (LAD) and those with a high allergen dose (HAD) according to the value of the ratio of the dose commonly administered in SLIT, as compared with that used for subcutaneous immunotherapy (SCIT).

I would like to underline the following critical points:

The cut-off of the sublingual immunotherapy/subcutaneous immunotherapy ratio

This SLIT/SCIT ratio is used in the allergic rhinitis and its impact on asthma (ARIA) consensus document [2] to highlight the fact that higher dosages, as compared with SCIT, appear efficacious in SLIT. In particular, ratio 50 is indicated as the lowest dose necessary to achieve a significant efficacy. However, the statement of the consensus document: *Efficacy of high allergen dose sublingual-swallow specific immunotherapy (at least 50 to 100 times the cumulative dose of subcutaneous immunotherapy) has been documented in double-blind, placebo-controlled studies* (p. S242) [2] quite notoriously is incorrect. In fact, among studies that are quoted to sustain this specific assumption, 7/13 fall under ratio 50 [3–9] and 2/13 are SLIT-spit studies [4, 6], which were supposed to be excluded. Also Gidaro et al. were aware of these discrepancies, and correctly assigned to the low-dose group those studies, which were mistakenly quoted in the ARIA statement as high-dose swallow SLIT. However, they maintained the critical value of 50 as a cut-off between LAD and HAD.

I think we all agree that the SLIT/SCIT ratio of 50 is not scientifically based and does not set up any critical standard value for differentiating the amounts of allergen administered in different immunotherapy protocols, in particular on the basis of the fact that only those above this amount of administered allergen would be efficacious. The SLIT/SCIT parameter should be considered as a mere operational tool to compare different immunotherapy trials until the amount of

major allergen expressed in micrograms will be used by all investigators.

An example of the problems raised by this cut-off value is the Torres-Lima trial, which the authors identify in the Discussion as critically involved in determining a remarkable number of AE in the meta-analysis (Table 1). The treatment used in this study has a SLIT/SCIT ratio indicated as '40–50'. Thus, a re-attribution of this trial to HAD studies is at least as legitimate as the present attribution to a LAD study. This choice would increase the observed AE/10 000 doses in HAD from 226.9 to 547.7, whereas values of AE/10 000 doses among LAD would decrease from 711 to 390.2. These figures would totally subvert the results of all comparisons in favour of a lower incidence of AE in the LAD group. As the authors themselves remark, the levels of accuracy in reporting AE may be very different in different trials, which can explain the observed discrepancies in their average frequency in the course of SLIT. In particular, in single studies a proportion of buccolingual AE may be considered irrelevant from patients and/or from investigators.

Usage of the χ^2 test and other statistical issues

The χ^2 test can be used on a contingency table only with integers, not with proportions. Proportions can be compared by the χ -test only when an observed vs. an expected ratio is to be evaluated. It is not appropriate to use either LAD or HAD or placebo as an expected value. Thus, proportions of reactions per patient in Tables 2–5 cannot be compared with the χ^2 test. This test can be properly applied, instead, to the number of AE per number of administered doses. Indeed, numbers from Tables 1 and 2 indicate a higher frequency of AE in LAD (423 doses with AE out of 98 604 administered doses) vs. HAD (209 doses with AE out of 99 949 administered doses) ($\chi^2_1 = 74.943$, 2×2 contingency table, two-tailed χ^2 with Yate's correction, $P < 0.0001$), confirming Authors' conclusions. However, gastrointestinal (GI) effects are by far more clinically relevant and annoying to patients than buccolingual AEs. The number of GI AE per dose (numbers from Tables 1 and 2) is significantly lower in LAD (six out of 98 604 doses) than HAD (50 out of 99 949 doses) ($\chi^2_1 = 32.492$, 2×2 contingency table, two-tailed χ^2 with Yate's correction, $P < 0.0001$).

By applying the χ^2 test to the numbers of 'patients with AE' in HAD vs. LAD, no significant difference is reported (Table 4). However, this is not the case, and HAD patients with AE (114 out of 445) are significantly more numerous than LAD patients with AE (34 out of 191) (2×2 contingency table, two-tailed Fisher's exact test, $P = 0.0322$). This result is simply the opposite to the authors' conclusion on the lower frequency of AE in HAD trials and can be obtained by

considering a parameter which is at least as clinically relevant as the number of AEs per dose. Notably, the prevalence of patients with AE in the HAD group as opposed to the prevalent occurrence of AE in the LAD group, indicate that a few LAD individuals suffered a high number of AE. In this respect, the rate of AEs per patient (Table 1) does not allow distinguish the case when single patients suffer several AEs vs. the case where most patients have one or few AEs.

The ratio reported at the bottom of Table 4 between the numbers of patients with AE vs. the number of doses is meaningless. The only possibility to consider a rational use of this ratio would be the case when each patient in the different trials received the same number of doses (which obviously is not the case).

Conclusion, I think that this meta-analysis suffers major limitations derived from the choice of the cut-off value of the SLIT/SCIT ratio and from the non-homogenous rules for monitoring AE in different studies. However, I would like to point out that also with these caveats in mind, by applying a correct statistical analysis, the reviewed papers allow to conclude that LAD SLIT is better tolerated than HAD SLIT because of the lower occurrence of GI AE in particular and to the lower proportion of patients suffering AE in general. Thus, the sentences: 'There is evidence that AE occurrence is substantially not dose-dependent' and 'It is difficult to explain why low doses are associated with more frequent local reactions' are unsupported. On the contrary, reported data indicate the existence of a reasonable dose-response relationship between numbers of clinically relevant AE and the amount of administered allergen. This is in agreement with the opinion expressed by Canonica and Passalacqua [10] in a comprehensive review where they concluded that GI AE increase when the dosage rises.

Dedicated studies comparing directly the number of homogeneously recorded AE following administration of allergen doses close to the lowest vs. allergen doses close to the highest value of the active range would be necessary to reach meaningful results. Available dose-dependence studies focussed on the efficacy of SLIT [11] do not allow reach any conclusion, because of the relatively narrow dose-range of compared treatments. I think that this issue is reminiscent of the well-established ethical and scientific problem of placebo-controlled vs. active-control trials [12–14] where the crucial point is the drive pushing companies to highlight the activity of their respective products vs. placebo. In contrast, in specific circumstances, the interest of the patients and of public health would be better served by directly comparing one active product against another one, from the same or from a different company. This approach is obviously hampered by the risk of finding the lack of any advantage in the direct comparison.

References

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