

CORRESPONDENCE

Response by authors: The safety of sublingual-swallow immunotherapy: an analysis of published studies. **Gidaro GB, Marcucci F, Sensi L, Incorvaia C, Frati F and Ciprandi G**

We are particularly grateful to Dr Burastero for the interest shown in our article. Thus, we have the opportunity for arguing about some issues:

- (1) The cut-off of the sublingual immunotherapy (SLIT)/subcutaneous immunotherapy (SCIT) ratio (at least 50) is the only one available and was introduced in the document allergic rhinitis and its impact on asthma (ARIA) prepared by 37 of the most renowned experts in allergy [1]. Therefore, it appears rather surprising that Dr Burastero defines that statement as "incorrect". Regarding the Torres-Lima trial, in which the treatment had an SLIT/SCIT ratio of 40–50, who can reasonably argue that such a ratio is over the cut-off we used? Thus, the hypothesis that attributing this study to the high allergen dose would subvert the results does not make sense.
- (2) Tables 2 and 3 report integers and do perfectly fit with the χ^2 test. The significance, as anyone can easily verify by repeating the test, is referred to the overall numbers (i.e. 209/445 vs. 423/417 of the local reactions, and 67/445 vs. 60/302 of the systemic reactions). The proportions showed in Tables 4 and 5 refer to an analysis (the number of adverse events (AEs) per number of administered doses) stated as correct by Dr Burastero himself. Regarding gastrointestinal AEs, Dr Burastero should know that low numbers do not allow for sound conclusions to be stated. Thus, establishing that an event concerning only 56 reactions in 747 actively treated patients is "far more clinically relevant" than buccolingual reactions, which were 576 in the same patients, is at least questionable. The weakness of low numbers, well known to those who are involved in statistical analysis, is further demonstrated by the fact that using the Fisher's test, recommended by Dr Burastero, wrong conclusions may be drawn. For example, analysis by Fisher's test shows that the placebo-treated patients of the high allergen dose group have significantly

higher reaction rate than the placebo-treated patients of the low allergen dose group (10/405 vs. 1/285, $P < 0.03$). Notably, using the χ^2 test, no significant difference can be detected in such groups. This finding does clearly provide evidence how inappropriate statistical testing can distort data. In fact, according to reference textbooks on biomedical statistics [2], the Fisher's exact test is indicated only when the population numbers to analyse are too small to be normalized. This is not the case in our analysis, conducted on a large number of patients, in which the χ^2 test is the correct one. As regards the ratio (Table 4) between the number of patients with AE and the number of doses, stated as "meaningless" by Dr Burastero, we introduced it following the reviewer's suggestion, which was precious in recovering data otherwise not obtainable from some studies.

- (3) Regarding the final presumptions of Dr Burastero, they are not pertinent to our analysis and do not need to be commented on.

Indeed, we are convinced that the major outcome of the analysis is the demonstration that SLIT, differently from SCIT, has no dose-dependent tolerability profile, at least with the doses administered thus far.

References

- 1 Bousquet J, van Cauwenberge P, Khaltaev N, eds. ARIA workshop report. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108:S1–S315.
- 2 Stanton A, Glanz Primer of Biostatistics, 5th edn. C.H.I.P.S Books, Weimar, TX, USA 2001.

Giorgio Ciprandi
San Martino Hospital
16132 Genoa
Italy
E-mail: gio.cip@libero.it