

Correspondence

Sublingual immunotherapy: Allergen specific or placebo effect?

To the Editor:

We read with interest the 2 sublingual immunotherapy (SLIT) trials^{1,2} published in the January 2011 issue of the *Journal* and several other large, evaluable grass pollen SLIT studies³⁻⁵ published in the *Journal* since 2005. Effective allergen immunotherapy is undertaken on the premise that it is allergen specific. The corollary is that the active and placebo groups will be symptomatically indistinguishable in the absence of allergen.

These articles report symptom data for variable periods before, during, and after the pollen season. None have statistically analyzed the percentage “improvement” over the entire pre-seasonal period or compared this with the pollen season. From the graphs presented in the respective articles, we have graphed (ruler and calculator, Fig 1) mean active treatment scores as a percentage of placebo by using the authors’ formula:

$$(\text{Active} - \text{Placebo})/\text{Placebo}.$$

Disturbingly, there is a marked yet similar mean improvement (10% to 32%) in symptoms in the actively treated group pre-seasonally and, from Blaiss et al¹ and Dahl et al,³ before any detection of grass pollens. If improvement in symptom scores can occur independently of pollen exposure, the logical deduction is that the improvement observed during the pollen season might not be allergen specific.

How might this be explained? Conceivably, there could be a problem with the grass pollen collection data. A second more likely explanation is that blinding of subjects has been compromised, perhaps as early as the first treatment day. The various authors¹⁻⁶ report rates of oral pruritis of up to 5% in the placebo group compared with rates of up to 46% in the active treatment group, with similar large-magnitude differences in the incidence of oral edema, ear pruritis, and throat irritation. The median onset of most of these symptoms is on day 1, and treatment-emergent side effects occur in 75% of subjects receiving active treatment compared with 25% receiving placebo. Furthermore, Bufe et al⁶ (in their Online Repository) report that it takes a mean of 48.4 and 59.5 days for resolution of oral pruritis and throat irritation, respectively, in the active treatment group and less than 1 day in the placebo group. We argue that subjects experiencing “allergy-like” symptoms on the first days of treatment when the alternative was an inert placebo would reasonably come to the conclusion that they were receiving the active treatment, carrying this expectation of benefit/reward throughout the study period and hence that the improvement seen might be simply an unblinding/placebo effect.

We realize that there must be some difficulty in manufacturing suitable placebos, but in their absence, it can be argued that the use of the term *double-blind* is misleading. An unblinding/

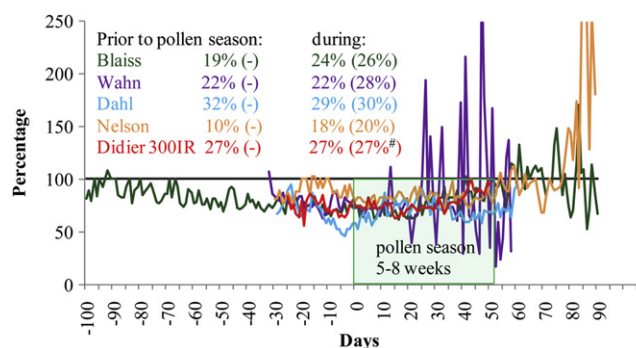


FIG 1. Mean SLIT score as percentage compared with placebo (100%). Figures shown refer to the calculated mean percentage change during the preseasonal period and pollen season. Figures in brackets are mean percentage improvements reported by the respective authors. [#]Derived from Table II.⁴

expectation-of-outcome survey would seem to be crucial in these studies, and a *post hoc* analysis of symptom scores taking this into account might be revealing.

In conclusion, because the percentage improvement in symptom scores was no greater during the pollen season than during the preseasonal period, these trials do not demonstrate that symptom benefit with SLIT is allergen specific. We suggest that the improvement reported might reasonably be explained by an unblinding/placebo effect in the active treatment groups.

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