

Correspondence

Reply

To the Editor:

We were most interested to read the correspondence from Frank Kette and William Smith¹ concerning their analysis of the recently published large-scale clinical trials of sublingual immunotherapy in patients with grass-pollen-induced allergic rhinitis.²⁻⁶ All the cited studies reported a significant decrease in symptom intensity (evaluated on various scales) during the pollen season for participants receiving the active product (vs placebo). However, in some (but not all) studies, Kette and Smith¹ noted differences in symptom scores between the active treatment and placebo groups prior to the start of the pollen period evaluated by grass pollen counts, that is, when levels of exposure to the allergen are still considered low. It is well recognized that pollen counts imperfectly reflect the real pollen allergen content of the atmosphere. Nonetheless, Kette and Smith¹ suggest the possible presence of bias due to recognition of the allergen-containing formulation by patients in the active treatment group as a result of the greater frequency of local (ie, oropharyngeal) side effects, relative to patients receiving an inert placebo. Indeed, Kette and Smith¹ argue that the use of the term “double blind” to describe these trials is misleading.

The choice of a placebo for use in sublingual immunotherapy trials remains an issue. According to European Medicines Agency (EMA) Guideline CHMP/EWP/18504/2006 (<http://www.ema.europa.eu>), “superiority versus placebo or any other comparator has to be shown.” Although the use of histamine has been suggested, sublingual administration of histamine does not lead to pruritus; a substance that produces symptoms similar to those triggered by an allergen remains to be identified. However, we believe that 2 significant findings from these clinical studies will reassure Kette and Smith¹ as to the true efficacy of sublingual immunotherapy. First, the frequency of side effects in the studies’ placebo groups is far from negligible. In the study that we coordinated,⁵ 48.7% of the patients on placebo reported side effects at the start of the course of treatment. In the recently published US trials, about 25% of the patients on placebo reported local side effects.^{2,3} Second, in studies in which a dose-response effect was investigated, the occurrence and frequency of side effects were independent of the observed efficacy. Thus, in our study⁵ comparing the efficacy of 3 dose levels of an allergen (100 reactivity index [IR], 300 IR, and 500 IR) with that of a placebo, the proportion of patients reporting side effects was very similar in

the three active treatment arms (68.8%, 62.6%, and 64.4%, respectively). However, the mean symptom score of the group receiving 100 IR was similar to that of the placebo group and differed significantly from the scores of groups receiving 300 IR and 500 IR. Similar observations were made by Durham et al⁷ when comparing the efficacy of 3 allergen doses (2500, 25,000, and 75,000 standardized quality tablet [SQ-T]) with that of a placebo. In contrast to the lowest 2 doses, the 75,000 SQ-T dose differed significantly from placebo in terms of the recorded symptom and drug scores. However, there was no difference in the proportion of patients experiencing side effects when comparing the 75,000 SQ-T and 25,000 SQ-T groups. Thus, the hypothesis of positive bias due to the patients’ recognition of the active treatment is unlikely to hold true. Although this observation does not resolve the issue of finding an ideal placebo for sublingual immunotherapy studies, it does support the efficacy of tablet formulations in the treatment of grass-pollen-induced allergic rhinoconjunctivitis.

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REFERENCES

1. Kette F, Smith W. Sublingual immunotherapy: allergen specific or placebo effect? *J Allergy Clin Immunol* 2011;128: XXX-XXX.
2. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner D. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol* 2011;127:64-71.
3. Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol* 2011;127:72-80, e2.
4. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;118:434-40.
5. Didier A, Mallin HJ, Worm M, Horak F, Jager S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;120:1338-45.
6. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. Efficacy and safety of five grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009;123:160-6.
7. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:802-9.

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