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Disclosure of potential conflict of interest: M. Jutel has served as a clinical trial investigator for Allergopharma Joachim Ganzer KG and Schering-Plough. H. Mosbech has received research support from ALK-Abelló and has served as an expert witness on the topic of anaphylaxis. The rest of the authors have declared that they have no conflict of interest.

## REFERENCES

1. Severino MG, Cortellini G, Bonadonna P, Francescato E, Panzini I, Macchia D, et al. Sublingual immunotherapy for large local reactions caused by honeybee sting: a double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2008;122:44-8.
2. Golden DB, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Regimens of Hymenoptera venom immunotherapy. *Ann Intern Med* 1980;92:620-4.
3. Graft DF, Schuberth KC, Kagey-Sobotka A, Kwitrovich KA, Niv Y, Lichtenstein LM, et al. Assessment of prolonged venom immunotherapy in children. *J Allergy Clin Immunol* 1987;80:162-9.
4. Ruëff F, Wolf H, Schnitker J, Ring J, Przybilla B. Specific immunotherapy in honeybee venom allergy: a comparative study using aqueous and aluminium hydroxide adsorbed preparations. *Allergy* 2004;59:589-95.
5. Müller U, Helbling A, Bischof M. Predictive value of venom-specific IgE, IgG and IgG subclass antibodies in patients on immunotherapy with honey bee venom. *Allergy* 1989;44:412-8.
6. Golden DB, Lawrence ID, Hamilton RH, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Clinical correlation of the venom-specific IgG antibody level during maintenance venom immunotherapy. *J Allergy Clin Immunol* 1992;90:386-93.

doi:10.1016/j.jaci.2008.10.028

## Reply

### To the Editor:

We thank Ruëff et al<sup>1</sup> for their comments on our work on sublingual immunotherapy (SLIT) in large local reactions caused by Hymenoptera venom<sup>2</sup> and for giving us the opportunity to clarify some aspects of our study. Moreover, these comments testify to the interest raised by our article and, hopefully, will stimulate further scientific debates. Going to the specific points, our rebuttals are as follows.

It is true that some differences between the 2 groups seem to exist at baseline, but those differences were not statistically significant, and this is the reason why a *P* value was not explicitly reported. It is difficult to hypothesize, for instance, that a mean difference in tryptase of 1.3 µg/L (with the normal threshold value being 20 µg/L) would have represented an imbalance factor in favor of one of the 2 groups.

The dosage used was empirically chosen based on previous experiences with SLIT for aeroallergens, in which it has been shown that a dose-response relationship exists<sup>3,4</sup> and that higher amounts of allergen are needed than in subcutaneous immunotherapy. Indeed, as we mentioned in the discussion, dose-finding studies are needed to identify the optimal dose. Concerning the immunologic aspect, it is well known that the changes in circulating immunoglobulins are less pronounced with SLIT than with injections,<sup>5</sup> but this does not affect the efficacy of the treatment, as shown in numerous trials. In other words, we should be cautious in stating that SLIT does not work because it does not modify specific IgE levels. As acknowledged by Dr Ruëff herself, the immunoglobulin changes over time are weakly correlated with the clinical effect, and a judgment on the efficacy of an immunotherapy course is essentially clinical.

We acknowledge that in our article no mention was made of field stings, and this is an important point. We take this opportunity to clarify that none of the patients received field stings

during the 6-month period of the study. Thus the mentioned confounding factor can be reasonably excluded.

Concerning the efficacy, we could also state that there was a full success in 57% and a partial success in 43% of the patients, but we think that such sophisms are not helpful in interpreting the data and for research in general. There are thus far no standard criteria to define the “failure” or “success” of venom immunotherapy according to the reduction of large local reactions at the sting challenge.

Finally, Ruëff et al<sup>1</sup> express a “strong disagreement” about the use of SLIT in anaphylaxis after Hymenoptera sting. We do not understand their disagreement because such a scenario was not mentioned in our article. We simply envisaged the possibility of testing the efficacy of SLIT in systemic reactions, which might be, for instance, generalized urticaria.

To conclude, we would underline once more that our study was a proof-of-concept trial and did not imply recommendations or suggestions for the clinical use of SLIT in patients with Hymenoptera allergy but only the possibility of exploring a new clinical approach.

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Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

## REFERENCES

1. Ruëff F, Bilò MB, Jutel M, Mosbech H, Müller U, Przybilla R. Sublingual immunotherapy with venom is not recommended for patients with Hymenoptera venom allergy. *J Allergy Clin Immunol* 2009;123:272-3.
2. Severino MG, Cortellini G, Bonadonna P, Francescato E, Panzini I, Macchia D, et al. Sublingual immunotherapy for large local reactions caused by honeybee sting: a double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2008;122:44-8.
3. 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.
4. Didier A, Mallin HJ, Worm M, Horak F, Jäger 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.
5. Akdis CA, Barlan IB, Bahceciler N, Akdis M. Immunological mechanisms of sublingual immunotherapy. *Allergy* 2006;61(suppl 81):11-4.

doi:10.1016/j.jaci.2008.10.029

## Advances in allergic skin disease: Omalizumab is a promising therapy for urticaria and angioedema

### To the Editor:

The review by Drs Sicherer and Leung<sup>1</sup> entitled “Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2007” is a valuable update on the current literature for allergic skin disease.

The section on urticaria and angioedema mentions case reports on the use of omalizumab in idiopathic angioedema.<sup>2</sup> We published 3 earlier case reports on the efficacy of omalizumab in intractable chronic urticaria.<sup>3</sup> We reported on 3 patients with refractory chronic urticaria who had marked improvement with omalizumab. Two of the patients showed evidence of increased anti-FcεRI antibody levels, and 1 did not. We postulated that the possible mechanisms included the downregulation of IgE receptors, providing fewer targets for IgE or anti-FcεRI antibodies.

All our patients were started on injections every 2 weeks (based on weight and IgE level) but are currently still doing well with increasing the intervals between injections to every 4 weeks. We have also started 2 additional patients on omalizumab, with similar significant clearing of urticaria within 1 week.

Successful treatment of urticaria with anti-IgE therapy has also been reported by other authors.<sup>4,5</sup> Omalizumab appears to be a very promising therapeutic alternative for refractory urticaria and angioedema.

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Disclosure of potential conflict of interest: S. L. Spector has received honoraria, consulting fees, or both from Abbott, Amgen, AstraZeneca, Genentech, Novartis, Sanofi-Aventis, and Schering-Plough and has received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Novartis, Sanofi-Aventis, Schering-Plough, and Skypharma. R. A. Tan has declared that he has no conflict of interest.

**Editor's note:** There is no accompanying reply to this correspondence.

## REFERENCES

1. Sicherer SH, Leung DYM. Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2007. *J Allergy Clin Immunol* 2008;121:1351-8.
2. Sands MF, Blume JW, Schwartz SA. Successful treatment of 3 patients with recurrent idiopathic angioedema with omalizumab. *J Allergy Clin Immunol* 2007;120:979-81.
3. Spector SL, Tan RA. Effect of omalizumab in patients with chronic urticaria. *Ann Allergy Asthma Immunol* 2007;99:190-3.
4. Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. *J Allergy Clin Immunol* 2006;117:1415-8.
5. Metz M, Bergmann P, Zuberbier T, Maurer M. Successful treatment of cholinergic urticaria with anti-immunoglobulin E therapy. *Allergy* 2008;63:247-9.

Available online September 9, 2008.  
doi:10.1016/j.jaci.2008.07.033

## Vitamin C and exercise-induced bronchoconstriction in athletes

To the Editor:

Anderson and Kippelen<sup>1</sup> reviewed the mechanisms of and therapeutic approaches to exercise-induced bronchoconstriction (EIB) in athletes. In addition to the treatments they discussed, vitamin C can also affect EIB.

We carried out a systematic review of the effect of vitamin C supplementation on the common cold.<sup>2,3</sup> Vitamin C consistently reduced the duration of common cold symptoms, but the effect on common cold incidence was significantly heterogeneous. In the general population, vitamin C supplementation had no preventive effect; however, the supplements halved the incidence of colds in 6 placebo-controlled trials with participants under heavy acute physical stress: pooled relative risk, 0.50 (95% CI, 0.38-0.66; total, n = 642). Four of these trials were with marathon runners,

1 was with Canadian soldiers in a northern training exercise, and 1 was with schoolchildren in a skiing camp in the Swiss Alps.<sup>2,3</sup>

In the general community the acute symptoms of cough, sore throat, and runny nose usually have a viral cause. However, it is not obvious that similar symptoms occurring after a marathon run are caused by a viral infection because they can result from an injury to runners' airways caused by their hours of exceptional ventilatory exertion.<sup>1</sup> Thus the common cold studies of marathon runners might have been measuring, at least in part, the effects of vitamin C on the physical injury to their airways instead of viral infections.

In their trial with marathon runners, Peters et al<sup>4</sup> recorded the "self-reported symptoms including a running nose, sneezing, sore throat, cough, and fever" during a 2-week posttrace period. The incidence of posttrace cough was significantly reduced in the vitamin C group compared with the placebo group: relative risk, 0.29 (95% CI, 0.10-0.83; 4/43 vs 13/41). The incidence of sore throat was also reduced by vitamin C: relative risk, 0.33 (95% CI, 0.16-0.66; 8/43 vs 23/41). In contrast, vitamin C had no significant effect on the incidence of runny nose (*P* = .2). Peters did not carry out virologic or pulmonary function tests before or after the race, and thus the cause of the symptoms is uncertain, yet there is no strong basis to assume viruses caused the symptoms. Furthermore, a few studies have directly measured the effect of vitamin C supplementation on bronchial responsiveness.

Ogilvy et al<sup>5</sup> reported that vitamin C reduced the duration and intensity of bronchoconstriction induced by methacholine. The action of vitamin C was abolished by indomethacin, indicating that the effect was mediated through the prostaglandin metabolism. Direct evidence indicating that vitamin C affects EIB was found in 3 small (n ≤ 20) laboratory studies in which the decrease of FEV<sub>1</sub> after exercise was attenuated by vitamin C supplementation.<sup>6-8</sup> Tecklenburg et al<sup>8</sup> also reported that vitamin C decreased the levels of proinflammatory eicosanoids in urine. These 3 laboratory studies do not, however, define the clinical importance of vitamin C for athletes. On the other hand, the 6 trials with participants under heavy acute physical stress<sup>2,3</sup> indicate that vitamin C has clinically important effects on the respiratory symptoms of some athletes, although it is not clear to what degree that effect is directed at their viral infections and the physical injury to their airways. This means that more trials that examine the mechanisms and therapeutic effects of vitamin C on the respiratory symptoms of athletes are warranted.

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Disclosure of potential conflict of interest: The author has declared that he has no conflict of interest.

**Editor's note:** There is no accompanying reply to this correspondence.

## REFERENCES

1. Anderson SD, Kippelen P. Airway injury as a mechanism for exercise-induced bronchoconstriction in elite athletes. *J Allergy Clin Immunol* 2008;122:225-35.
2. Douglas RM, Hemilä H, Chalker EB, Treacy B. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev* 2007;3:CD000980.
3. Hemilä H. Do vitamins C and E affect respiratory infections? [thesis]. Helsinki, Finland: University of Helsinki; 2006. p. 46-51. Available at: <http://ethesis.helsinki.fi/julkaisut/laa/kansa/vk/hemila>. Accessed October 24, 2008.
4. Peters EM, Goetzsche JM, Grobbelaar B, Noakes TD. Vitamin C supplementation reduces the incidence of posttrace symptoms of upper-respiratory-tract infection in ultramarathon runners. *Am J Clin Nutr* 1993;57:170-4.