

Correspondence

Reply

To the Editor:

In reply to Patriarca et al.,¹ we acknowledge the fact that we did not refer to their publication² in our recent comment on the study by Severino et al.³ However, we omitted the study by Patriarca et al.² deliberately, because this study also does not present data that show effectiveness of sublingual venom immunotherapy (SL-VIT).

In the study by Patriarca et al.,² SL-VIT was performed in 21 patients with a history of a systemic anaphylactic sting reaction. The intended maintenance dose was 100 µg vespid venom per week. Seventeen patients were re-examined after a period of 6 to 24 months. Twenty patients who were treated with subcutaneous venom immunotherapy (SC-VIT) served as controls.

Our major criticism of this study refers to the number of resting patients (n = 4). Three of 4 patients on SL-VIT tolerated the sting without systemic reaction; 1 patient reported throat constriction. In the SC-VIT, 1 of 9 resting patients reported a subjective systemic reaction (dizziness). In both study arms, this number was too small to allow any valid conclusion regarding treatment efficacy. Taking the well documented 5.6% chance for therapeutic failure after a SC-VIT in vespid venom allergy⁴⁻⁶ (unpublished data, B. Przybilla, 2004) and assuming an (at the most) acceptable minimum failure rate of 10% after SL-VIT, more than 300 patients would be required in each study arm to prove noninferiority at an α error of 0.05 (1-sided test) and a β error of 0.2. Altogether, more than 600 patients will have to undergo a standardized procedure to evaluate the efficacy of the mode of treatment chosen. In this context, it is important to know that field stings are no reliable method to evaluate such an efficacy.⁴ Sting challenge tests with entomologically characterized insects are recommended to identify unprotected patients.

Another concern results from the reported immunologic findings in the study by Patriarca et al.² In contrast with what is known from patients after SC-VIT, neither venom-specific IgE nor IgG changed significantly during the observation period after SL-VIT. Thus, there was no immunologic evidence of a SL-VIT effect.

Some other aspects of the study by Patriarca et al.² must be addressed if the issue is the equal efficacy or even superior tolerance of an experimental treatment, as claimed by the authors. First, the selection process of patients in the study by Patriarca et al.² was poorly defined. It is unclear whether the 21 patients who had originally refused SC-VIT and who were then treated with SL-VIT were recruited from the same consecutive patient series as the patients in the control group. It must be excluded that patients in the SL-VIT group had been diagnosed much earlier than patients in the control group and were now reinvited for SL-VIT. Such a time delay in the SL-VIT group may be an important confounding variable because clinical and also immunologic reactivity may change spontaneously over time in patients who had had sustained their last systemic reaction to a sting years or decades before. There is a strong suspicion for such a time delay in the

SL-VIT patients of the study by Patriarca et al.² Thus, venom-specific IgE appeared to be much lower in patients in the SL-VIT group (3.66 ± 7.4 kU/L) than in those in the SC-VIT group (14.27 ± 23.65 kU/L). Unfortunately, no statistical comparison was made. Furthermore, patients in the SC-VIT group had severe reactions (grade III and IV) after a field sting more often than patients in the SL-VIT group (50% vs. 34%). Although the difference was not significant, one would prefer a much better match of potentially important risk factors in a small case-control study. The observation that SL-VIT was associated with few side effects is irrelevant in that context.

In summary, SL-VIT should not be offered to patients with a potentially life-threatening disease before sound experimental data on the pharmacokinetics of sublingually administered venom (influence of saliva on the venom, data on absorption, change of immunologic parameters) are available. Patients who refuse regular treatment may qualify for alternative therapies. Nevertheless, this refusal cannot be taken as a justification to use therapies such as SL-VIT, which still lacks sufficient experimental evidence regarding its efficacy.

Franziska Ruëff, MD^a

M. Beatrice Bilo, MD^c

Marek Jutel, MD^d

Holger Mosbech, MD, DMSc^e

Ulrich Müller, MD^f

Helmut Küchenhoff, PhD^b

Bernhard Przybilla, MD^a

From ^aAllergieZentrum, Klinik und Poliklinik für Dermatologie und Allergologie, and ^bthe Statistical Consulting Unit, Department of Statistics, Ludwig-Maximilians-Universität, Munich, Germany; ^cthe Allergy Unit, Department of Internal Medicine, Allergy, Immunology and Respiratory Diseases, Ospedali Riuniti di Ancona, Azienda Ospedaliero-Universitaria, Ancona, Italy; ^dthe Department of Clinical Immunology, Silesian Piasts University of Medicine in Wrocław, Poland; ^ethe Allergy Unit, National University Hospital, Rigshospitalet, Copenhagen, Denmark; and ^fAllergiestation Medizinische Klinik, Zieglerspital, Spitalnetz Bern, Switzerland. E-mail: Franziska.Rueff@med.uni-muenchen.de.

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