Immunotherapy with Vespula venom for Vespa velutina nigrithorax anaphylaxis: Preliminary clinical and immunological results

To the Editor,

The Asian wasp, Vespa velutina nigrithorax, has become the most prevalent Hymenoptera species involved in anaphylactic reactions in NW Spain.1,2 In previous studies, we have proven a strong correlation between serum-specific IgE (sIgE) to Vespula spp. venom and Vespa velutina nigrithorax venom.2 Besides, inhibition experiments suggested that Vespula spp. venom is the genuine sensitizer in these cases, supporting the idea that sensitization could have occurred after Vespula spp stings.2 These results were not surprising since cross-reactivity among allergens from different Vespidae is well known.3

Venom immunotherapy is the only effective treatment in patients with a history of anaphylaxis and has proven to be effective for up to 95% of patients with Vespula venom allergy.4,5 During the course of venom immunotherapy, gradual decreases in sIgE and gradual increases in specific IgG4 (sIgG4) have been reported, even though these time course changes do not always correlate with clinical improvements.6,7 Clinical tolerance to re-sting either spontaneous or after a controlled sting challenge is considered the gold standard for clinical efficacy in venom immunotherapy.6,8

Well-standardized commercial venom extracts are only available for Vespula spp, Apis mellifera and Polistes dominula. In cases of allergy to different Hymenoptera species, when the venom of the allergy-eliciting insect is not accessible for immunotherapy, the proper therapeutic selection should be based on the knowledge of the sIgE patient sensitization profile, trying to find which composition best represents shared allergens recognized by patients.6,8 For example, Vespula spp extracts have proven to be efficacious in patients with anaphylaxis to Vespa orientalis9 or Vespa crabro10 to prevent from happening additional systemic reactions with the culprit insect.

In this scenario of increasing frequency of Vespa velutina nigrithorax anaphylaxis and lack of available specific venom for immunotherapy, we have used a Vespula spp venom extract (Pharmalgen, ALK Lab.) to treat patients with anaphylaxis due to Vespa velutina nigrithorax. The present study was aimed to evaluate the usefulness of this Vespula spp venom in terms of clinical and immunological (sIgE and sIgG4) evolution in 46 of these patients during the first year of treatment. Patients had been studied at the Allergy Department of the University Hospital of Santiago de Compostela because of an...
anaphylactic reaction after being stung by Vespa velutina nigrithorax. The median age was 61 years (range, 20–78 years) and 39 (84.8%) were men. Most of the patients (93.5%) reported previous stings by Vespula spp and/or Apis mellifera (31, 67.4%) and only 10 (21.7%) reported previous stings by Vespa velutina nigrithorax. Patients who started allergen immunotherapy with Vespula spp venom from November 2019 to May 2020 were included. Vespula spp venom was administered in a 2 days, five-dose induction cluster schedule. On day 0, patients received subcutaneous injections (10 µg, 20 µg, and 30 µg) of the venom extract on alternate arms at 30 minutes intervals for the first two doses, and 60 minutes after the third dose. On day 7, each patient received two subcutaneous injections with 50 µg on alternate arms at 60 minutes intervals. This was followed by monthly administration of 100 µg of venom extract. All participants gave written informed consent for the study, which was approved by the Institutional Ethics Committee (code 2018/622). Specific IgE and slgG4 against Vespa velutina (commercially available as ‘research allergen U1223’, Thermo Fisher Scientific™) and Vespula spp were measured by using the ImmunoCAP-250™ system (Thermo Fisher Scientific™) before starting allergen immunotherapy, and 6 and 12 months later. Figure 1 represents the changes in slgE and slgG4. A significant reduction in slgE was seen against both Vespa velutina and Vespula spp (median reduction, 10.4% and 25.0% respectively) after 12 months. No significant changes were detected at 6 months. Regarding slgG4 a significant increase was detected against both Vespa velutina and Vespula spp (median increase, 25.3% and 30.8% respectively) after 12 months. Contrary to what had happened with slgE, changes in slgG4 were significant at 6 months. The decrease in slgE at 12 months was observed in 35 patients (76.1%) while the increase in slgG4 was observed in 37 patients (80.4%). We could not find any baseline difference among patients who presented changes with respect to those who did not regarding age, severity of the reaction or baseline slgE levels to Vespa velutina or Vespula spp (data not shown). We did not perform sting challenges with Vespa velutina nigrithorax, but 13 patients (28.2%) suffered in field stings with no systemic reactions after a median of 9 months (range, 4–12 months) after starting immunotherapy. Twelve of these patients presented either an increase in slgG4 or a decrease in slgE or both.

The development of venom extracts for immunotherapy is a complex process and ideally should require experimental randomized controlled trials with well-standardized venom extracts that are not still available for Vespa velutina nigrithorax. Our results from a quasi-experimental study suggest a possible role of Vespula spp venom immunotherapy in patients with systemic reactions to Vespa velutina nigrithorax. Time-course changes in both slgE and slgG4 against Vespa velutina venom might support a positive immune modulation by using Vespula spp venom extract in these patients. The IgG4 induction per se is not a marker for therapeutic success, but the lack of IgG4 induction might be a marker for unresponsiveness. For that purpose, we used the newly commercially available ImmunoCAP Vespa velutina instead of a customized CAP coupled to streptavidin (o212, Thermo Fisher Scientific) that we had used in previous experiments so that studies could be easily reproducible. In a subsample of 36 patients, a significant correlation was found between slgE to U1223 and slgE to the customized Vespa velutina coupled to o212 (Spearman’s Rho 0.832, p < .001). More importantly, our preliminary results suggest that immunotherapy with Vespula spp venom extract may be clinically useful in patients with Vespa velutina nigrithorax anaphylaxis. Sting challenges were not performed because of the previously reported toxicity of Vespa velutina venom, but real-life observations confirmed that no anaphylaxis episode developed after spontaneous stings by the culprit insect in more than a quarter of treated patients.

Taken together, both the prior evidence for Vespula venom as a genuine sensitizer and the preliminary results suggesting clinical and immunological efficacy of immunotherapy with Vespula spp venom in patients with Vespa velutina nigrithorax anaphylaxis, we propose the use of Vespula spp venom products approved to treat this emerging problem until a specific extract has been standardized.

**KEY MESSAGES**

- **Vespula** venom immunotherapy induces changes in slgE and slgG4 against Vespa velutina in allergic patients.
- Spontaneous stings provoked no reaction in Vespa velutina allergic patients treated with Vespula venom immunotherapy.
- Vespula venom may be used to treat patients with Vespa velutina anaphylaxis.

**KEYWORDS**

basic mechanisms, IgE, immunologic tests, immunotherapy and tolerance induction, venom and insect allergy

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**CONFLICTS OF INTEREST**

The authors have no conflicts of interest regarding this manuscript.

**AUTHOR CONTRIBUTION**

Carmen Vidal is the principal investigator of the study. I have received the grants and I have designed the study, collected data, analysed results, wrote the manuscript and created the Figure. Margarita Armisén and Virginia Rodríguez. They are coordinators of the study in Santiago where they have collected data and classified them. Besides, Virginia Rodríguez is working on her Doctoral Thesis on Vespa velutina allergy. Jose Gómez-Rial and Beatriz Lamas-Vázquez. They have performed specific IgE and IgG4 determinations.
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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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