Received: 17 August 2021 | Revised: 11 October 2021 | Accepted: 28 October 2021

DOI: 10.1111/cea.14039

RESEARCH LETTER

WILEY

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.[4,6,7] 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 orientalis*[9] or *Vespa crabro*[10] 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

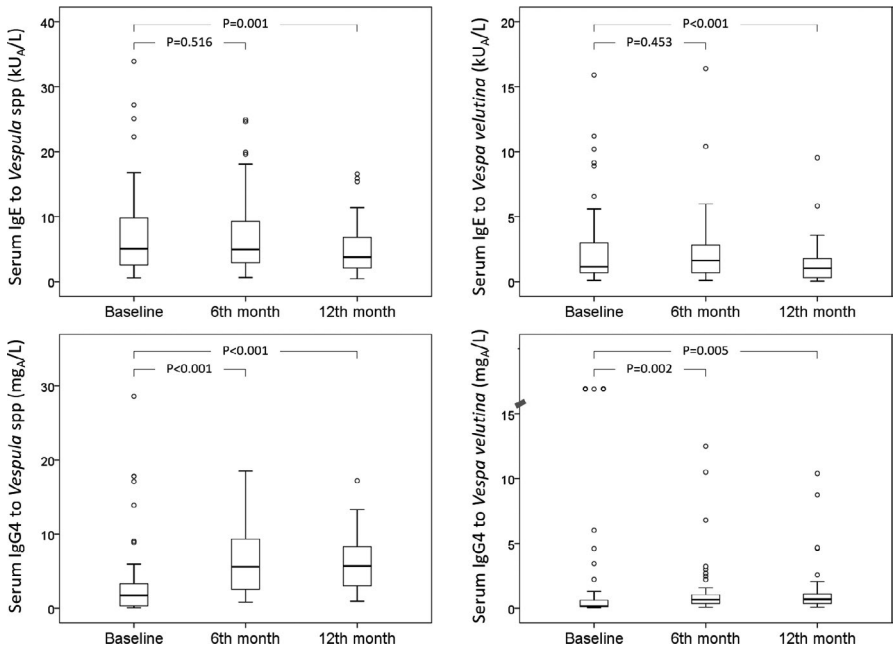

FIGURE 1 Boxplot of time-course changes of sIgE and sIgG4 against *Vespula* spp venom and *Vespa velutina* venom after immunotherapy with *Vespula* venom in *Vespa velutina nigrithorax* allergic patients ($n = 46$ in each case). Horizontal lines represent the median, boxes represent the interquartile (25–75th percentile), whiskers represent the extremes and dots represent the outliers (values outside 1.5 times the interquartile range above the upper quartile and below the lower quartile). *p*-values were obtained with the Wilcoxon test for paired data

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 sIgG4 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 sIgE and sIgG4. A significant reduction in sIgE 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 sIgG4 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 sIgE, changes in sIgG4 were significant at 6 months. The decrease in sIgE at 12 months was observed in 35 patients (76.1%) while the increase in sIgG4 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 sIgE 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 sIgG4 or a decrease in sIgE 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 [11] 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 sIgE and sIgG4 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. [6] 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 [1,2] so that studies could be easily reproducible. In a subsample of 36 patients, a significant correlation was found between sIgE to U1223 and sIgE 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 [12], 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 [1,2] 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 sIgE and sIgG4 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

ACKNOWLEDGEMENTS

The authors thank Prof. González-Quintela for his critical review and technical support.

The study was supported by the Instituto de Salud Carlos III (Fondo de Investigaciones Sanitarias, Spanish Ministry of Health, PI19/01023) (Co-funded by the European Regional Development Fund 'A way to make Europe'), and Fundación de la Sociedad Española de Alergología e Inmunología Clínica (SEAIC).

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 Rodriguez 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.

FUNDING INFORMATION

The study was supported by the Instituto de Salud Carlos III (Fondo de Investigaciones Sanitarias, Spanish Ministry of Health, PI19/01023) (Co-funded by the European Regional Development Fund 'A way to make Europe'), and Fundación de la Sociedad Española de Alergología e Inmunología Clínica (SEAIC).

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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