Safety and Efficacy of the First Venom Immunotherapy for Allergy to *Vespa velutina nigrithorax*: Interim Analysis of the W-STING Study

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J Investig Allergol Clin Immunol 2025; Vol. 35(3)
doi: 10.18176/jiaci.1058

Key words: *Vespa velutina nigrithorax*. Venom immunotherapy. Hymenoptera venom. Asian hornet.

Palabras clave: *Vespa velutina nigrithorax*. Inmunoterapia con veneno de himenópteros. Veneno de himenópteros. Avispa asiática.

Hymenoptera venom allergy is a potentially life-threatening allergic disease triggered by a bee, wasp, hornet, or ant sting [1]. *Vespa velutina*, commonly known as the Asian hornet, has been one of western Europe's most significant invasive species since 2010. Its European subspecies, *Vespa velutina nigrithorax* (VVN), is currently one of the main triggers of anaphylactic reactions due to Hymenoptera sting in northwest Spain [2], with fatal outcomes in some cases [3]. The first case of anaphylaxis due to VVN in Spain was reported in 2014 [4]. The main allergen components identified in VVN venom are Vesp v 1 (phospholipase A1), Vesp v 2 (hyaluronidase), and Vesp v 5 (antigen 5), although only Vesp v 5 can be considered a major allergen [5]. In addition, the recently identified protein dipeptidyl peptidase IV has been considered a potential major allergen [4-5]. All these allergens share a high level of cross-reactivity with their homologs in *Vespula* species.

The only treatment that can potentially prevent further systemic sting reactions and improve patients' quality of life is venom immunotherapy (VIT) [6], which is effective in 91%-96% of vespid venom stings [2]. Until a specific VIT treatment with VVN venom became available, VVN-allergic patients were treated with *Vespula* VIT [3,7], which could, presumably, leave some patients unprotected against a new VVN sting.

Since 2021, a specific VIT with VVN venom has been available in some European countries and has proven both safe and effective [8,9].

W-STING is an ongoing prospective, multicenter, and noninterventional study that evaluates the safety, tolerability, and efficacy of the first VVN venom–based VIT. Here, we present the results of an interim analysis. The study includes patients who have previously experienced a systemic reaction (SR) to VVN sting, with positive skin test results and specific IgE for VVN venom. Subcutaneous VIT (HYMNOX *Vespa velutina*, ROXALL Medicina España S.A.) is administered following a cluster schedule with a 3-week initiation phase. The study records all adverse reactions (ARs) and assesses the improvement in patients' quality of life using the HiCaVi questionnaire of the Spanish Society of Allergy and Clinical Immunology 1 year after initiation of treatment and the effectiveness of treatment in the case of a field sting. The study was approved by the Institutional Review Board *Comité de ética de la investigación con medicamentos de Galicia* (CEIm-G), with registration number 2021/440.

The initial study population comprised 101 patients, of whom 93 were eligible for this interim analysis (80 men [86%] and 13 women [14%]; mean [range] age, 57.2 [24-87] years). One-third (33.3%) had associated cardiovascular conditions. Most patients (80.6%) were from a rural environment, and most (88.2%) had experienced an initial SR of grade II or above (Mueller scale). Mean (SD) serum tryptase level was 10.6 (12.4) µg/L before initiation of treatment (Supplementary material: Patients' baseline characteristics). At the time of the interim analysis, 71 patients (76.3%) had attended the 6-month follow-up visit, and 45 patients had already completed the study.

Eleven patients (10 men and 1 woman) experienced 15 field stings during follow-up. Six involved VVN, and the remaining 9 other vespids. The mean duration of treatment at the time of the field sting was 6.1 months. In 2 of the 6 cases of field stings with VVN, the patients only had a local reaction (100% protective efficacy). In 5 out of 9 stings with other vespids, the patients only experienced a local reaction and, in 1 case, a grade I SR (generalized erythema). Two of the 15 field stings occurred before the patient started maintenance treatment, with one of them being the patient who experienced an SR (Table).

No severe ARs associated with VIT have been reported to date. Only 14 out of 93 patients (15.1%) experienced an AR (41 ARs in total), including 3 grade I SRs in 3 patients (3.2%). SRs consisted of bilateral palpebral edema, with itching

Table. Data on Field Stings and Patient Characteristics.

Patient ID	Sex (age in y)	Müller grade	REMA score	Serum tryptase, µg/L	Dose,µg	Treatment duration at field sting	Culprit insect	LR[b]	SR
01-002	Male (28)	I	- 2	3.50	100 100 100	5 mo 6 mo 9 mo	*V germanica* *V germanica* *V velutina*	Normal LR No Normal LR	No No No
01-003	Male (64)	I	- 2	5.12	100 100 100	5 mo 7 mo 7 mo	*V germanica* *Vespid* *V velutina*	Normal LR Extensive LR Extensive LR	No No No
02-004	Female (69)	I	- 4	4.10	100	6 mo	Unknown	Local edema	No
03-010	Male (31)	II	- 2	3.60	100	6 mo	*V velutina*	No	No
05-006	Male (24)	IV	3	2.52	50+50	1 mo	*V velutina*	No	No
01-001	Male (44)	II	- 2	2.50	100	10 mo	*Vespid*	No	No
04-002	Male (68)	II	NA	4.2	100	6 mo	*V germanica*	No	No
05-002	Male (45)	III	- 2	3.80	100	15 mo	*V velutina*	No	No
03-017	Male (63)	III	1	10.60	50+50	1 mo	Unknown[a]	No	Erythema
01-009	Male (55)	II	- 2	5.46	100	1 mo	*P dominula*	Normal LR	No
02-016	Male (51)	III	- 2	6.65	100	7 mo	*V velutina*	No	No

Abbreviations: LR, local reaction; REMA, Red Española de Mastocitosis (Spanish Mastocytosis Network); SR, systemic reaction.
[a]The patient indicated that the insect came out from a nest in the ground
[b]Normal LR <10 cm; extensive LR ≥10 cm

and eyelid oppression, lip edema sensation, and urticaria on the chest, all of which resolved without intervention after a few hours. The remaining ARs were local reactions (38). Of these, 13 were clinically relevant (ie, >10 cm), occurring in 5 patients (5.4 %). More than half of the ARs occurred during initiation of VIT.

In patients who had already completed the study, the mean specific IgE levels against VVN decreased from 7.96 (17.5) kU/L to 2.86 (5.7) kU/L. The difference was statistically significant (32 patients; $P<.05$, Wilcoxon test). The HiCaVi questionnaire score also improved significantly for these patients, with the mean baseline value increasing from 4.1 to 4.5 at the final assessment (44 patients; $P<.05$).

Anaphylactic reactions to VVN venom are becoming an emerging health and economic problem in Europe, with Spain, Portugal, and Italy being the most affected countries [3,9]. Accordingly, the need to incorporate a specific VIT treatment into the therapeutic arsenal has been highlighted by physicians [3]. To date, treatment with *Vespula* venom has proven to be effective (see above), although some doctors are reporting cases of therapeutic failures with this approach, indicating that by not including prevalent allergens such as Ves v 3, some patients may not be protected from the potential risk of an SR [5]. A similar situation was observed in patients sensitized to *Polistes dominula* treated with *Polistes* species venom. Despite the high homology between the allergens of the different species, therapeutic failures were reported, leading to the introduction of the specific venom to the market [10].

Our preliminary results suggest that specific VIT with VVN venom has an adequate safety profile, with no serious ARs to date and a low percentage of patients with systemic or clinically relevant local reactions.

Moreover, changes in sIgE to VVN venom over time might support the positive immunomodulatory effect of this treatment, and the absence of SRs in patients stung by VVN in the field also suggests that the treatment is effective in protecting VVN-allergic patients.

In conclusion, pending the results of W-STING, this newly developed VIT with VVN venom seems to be both safe and effective for protecting allergic patients.

Funding

This study was funded by ROXALL Medicina España S.A.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Manuscript received September 13, 2024; accepted for publication December 19, 2024.

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