

A Clustered Schedule for Venom Immunotherapy With a Depot Extract: Reaching the Target in 7 Days

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Hymenoptera insect stings are relatively common in the general population and can cause life-threatening anaphylactic reactions in patients with hypersensitivity to Hymenoptera venom [1]. Currently, venom immunotherapy (VIT) is the only etiological treatment for Hymenoptera venom allergy that is capable of changing its course and preventing the occurrence of new severe systemic reactions [2]. VIT is effective in 77%-84% of patients treated with honeybee venom and in 91%-96% of patients treated with vespid venoms [3,4].

VIT can be performed with aqueous or depot extracts, the former being the most common in Spain [5,6]. In 2021, the Spanish authorities approved 2 registered alum-based depot products (Alutard SQ *Apis mellifera* and Alutard SQ *Vespula spp* [ALK-Abello A/S]) for administration in hospital settings. The lack of experience with depot extracts for clustered VIT schedules led us to investigate their safety and tolerance.

We prospectively studied 62 consecutive patients with allergy to Hymenoptera venom who initiated VIT between September 2021 and October 2022. All patients experienced a systemic reaction shortly after being stung by *Apis mellifera* (n=19), *Vespula* species (n=14), or *Vespa velutina* (n=27). Two patients could not clearly identify the culprit insect responsible for the reaction, and the VIT composition was selected based on specific IgE (sIgE) detected using component-resolved diagnosis. The severity of the systemic reaction was graded following the Brown classification into mild, moderate, or severe [7]. Serum sIgE was measured in serum samples obtained 1-2 months after the reaction. Serum tryptase was measured using the ImmunoCAP 250 tryptase assay (Thermo Fisher Scientific). The REMA score was calculated as previously suggested [8]. Patients received *Apis mellifera* venom (n=18) if they had been stung by a honeybee and sIgE was positive. One of the patients who could not identify the insect was treated with *Apis mellifera* venom because of the allergology work-up results. Patients received *Vespula* species venom (n=40) if they had been stung by *Vespula* species or *Vespa velutina* and sIgE was positive. We used *Vespula*

species venom for *Vespa velutina*-allergic patients because no registered product is available for the latter and previous results supported its use in *Vespa velutina*-allergic patients [9]. The other patient who could not identify the insect was treated with *Vespula* species venom because of the immunological results. All participants gave their written informed consent to be included in the study, which was approved by our Institutional Ethics Committee (code 2022-011).

We used a 2-day, 5-dose cluster-based induction schedule. On day 0, patients received subcutaneous injections (10 µg, 20 µg, and 20 µg) of the venom extract on alternate arms at 30-minute intervals for the first 2 doses and waited 60 minutes after the third dose. On day 7, each patient received 2 subcutaneous injections with 50 µg on alternate arms with a 60-minute interval and waited 60 additional minutes before leaving the allergy department. This was followed by the administration of 100 µg of the venom extract 1 month later. In the case of local or systemic reaction to VIT, pretreatment with antihistamines was recommended for subsequent doses.

The Table shows the demographic, clinical, and analytical data of the patients included in the study according to the composition of VIT. More detailed information can be found in the Supplementary file. Most patients were adults (except for a 16-year-old boy), with a median age of 58 years (range, 16-84 years) and a predominance of males (70.3%).

All patients reached the expected maintenance dose at day 7 with a good tolerability profile. Of the 360 doses administered (310 in the clustered schedule and 50 in the first maintenance dose 1 month later), only 6 patients developed immediate mild local reactions (2/20 in the *Apis mellifera* venom group [10.0%] and 4/42 in the *Vespula* species venom group [9.5%]). Regarding systemic reactions, 3 patients experienced mild systemic reactions. Patient #13, who was treated with *Apis mellifera* venom, presented mild pruritus and erythema on the neck following the second dose of the first cluster. After an additional 30 minutes, the patient received the third dose, with no reaction. Patients #31 and #60 were allergic to *Vespa velutina* and experienced a mild reaction comprising facial erythema and itchy throat after the second dose of the first cluster and the first dose of the first cluster, respectively. The third dose of the first cluster was subsequently administered without incident. All reactions resolved within a few minutes after treatment with oral cetirizine 10 mg. One week later, patients tolerated the second cluster and reached the maintenance dose as expected, after receiving premedication with antihistamines. No delayed reactions were recorded. A search for markers to identify patients at risk of local or systemic reactions showed that they tended not to significantly diminish with age and were more frequent in women.

The selection of the build-up protocol to treat Hymenoptera venom allergy is a matter of debate [4,11-13]. Standard protocols lasting up to 15 weeks or more seem to be safer, although patients remain unprotected until the maintenance dose is reached [3]. A multicenter, observational study comparing 3 build-up protocols performed in Spain has suggested a similar safety profile for 3-, 4-, or 9-week schedules, although these alum-based depot products were not analyzed [13]. The shortest published schedule with alum-based Hymenoptera venom extracts lasts 2 and 4 days

Table. Clinical and Laboratory Data of Study Patients Stratified by the Venom Used for Allergen Immunotherapy.^a

	Allergen immunotherapy	
	<i>Apis mellifera</i> (n=20)	<i>Vespula</i> species (n=42)
Age, y	52 (44-66)	59 (49-72)
Male sex	14 (70.0%)	30 (71.4%)
β-Blocker/ACE-inhibitors	1 (5.0%)	7 (16.7%)
Severity of reaction (Brown)		
Grade I	9 (45.0%)	11 (26.2%)
Grade II	8 (40.0%)	20 (47.6%)
Grade III	3 (15.0%)	11 (26.2%)
Total serum IgE, kU/L	50 (23-98)	141 (52-278)
Serum tryptase, ng/mL	5.3 (3.7-9.1) ^b	6.0 (4.6-8.0)
Serum specific IgE, kU _A /L		
<i>Apis mellifera</i>	9.02 (3.67-24.7)	ND
rApi m 1	4.25 (2.15-11.3)	ND
rApi m 10	0.16 (0.01-0.84)	ND
<i>Vespula vulgaris</i>	ND	9.81 (4.00-17.8)
rVes v 1	ND	1.23 (0.10-5.63)
rVes v 5	ND	5.30 (1.48-16.1)

Abbreviation: ACE, angiotensin-converting enzyme; ND, not done.

^aAge and laboratory data are presented as median (IQR). The remainder are presented as No. (%).

^bSerum tryptase values were not available for 2 patients in the group who received *Apis mellifera* venom immunotherapy.

for *Vespula* species and *Apis mellifera*, respectively. The initial dose was 0.1 µg for *Vespula* species and 0.01 µg for *Apis mellifera*, although in both cases they repeated the cluster with the higher doses (30, 35, and 35 µg) 7 days later and an additional cluster of 40 and 60 µg 14 days after the previous one [14]. In another study, the maintenance dose was reached after 7 weeks, although patients were pretreated with antihistamines [15]. Even though guidelines recommend the use of lower doses to start VIT [3], shorter schedules with higher doses, such as that used in this study, could be useful when administering alum-based depot products. The good tolerability profile of this schedule makes it appropriate for outpatient clinics. It saves time and is cost-efficient for both patients and professionals, thus potentially leading to better acceptance of and adherence to VIT by patients.

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Conflicts of Interest

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