

**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 the venom of these insects [1]. Currently, the only etiological treatment for Hymenoptera venom allergy, capable of changing its course and preventing the occurrence of new severe systemic reactions, is venom immunotherapy (VIT) [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, being the first most commonly used in Spain [5,6]. In 2021 two registered alum-based depot products, Alutard SQ® *Apis mellifera* and Alutard SQ® *Vespula spp* (ALK-Abello A/S, Hørsholm, Denmark), were approved by the Spanish authorities to be administered at hospital settings. The lack of experience with depot extracts for clustered schedules of VIT led us to investigate their safety and tolerance.

We prospectively studied sixty-two consecutive patients with allergy to Hymenoptera venoms who initiated VIT from September 2021 to October 2022. All patients presented a systemic reaction shortly after being stung by *Apis mellifera* (n=19), *Vespula spp* (n=14) or *Vespa velutina* (n=27). Two patients did not identify with certainty the culprit insect responsible for the reaction and the VIT composition was selected based on specific IgE (sIgE) in component resolved diagnosis. The severity of the systemic reaction was graded following Brown's 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 with the ImmunoCAP 250 tryptase assay (Thermo Fisher Scientific). REMA

score was calculated as previously suggested [8]. Patients received *Apis mellifera* venom (n=18) if they had been stung by a honey bee and sIgE was positive. One patient who did not recognise the insect was treated with *Apis mellifera* venom because of the allergological work-up results. Patients received *Vespula spp* venom (n=40) if they had been stung by *Vespula spp* or *Vespa velutina* and sIgE was positive. We have used *Vespula spp* venom for *Vespa velutina* allergic patients because no registered product is available for the latter and previous results in *Vespa velutina* allergic patients supported its use in these patients [9]. One additional patient who did not recognise the insect was treated with *Vespula spp* venom because of the immunological results. All participants gave written informed consent for the study which was approved by the Institutional Ethics Committee (code 2022-011).

We used a 2-day, 5-dose induction cluster 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 two doses, and waited 60 minutes after the third dose. On day 7, each patient received two subcutaneous injections with 50 µg on alternate arms at 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 one month later. In case of local or systemic reaction with VIT, pretreatment with antihistamines was recommended for the subsequent doses.

Table 1 shows the demographic, clinical and analytical data of the patients included in the study according to the composition of the venom immunotherapy. A more detailed information can be found in the Supplementary file. Most of the patients were adults (except for a 16-year-old male) with a median age of 58 years (range, 16–84 years), and with 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 (310 in the clustered schedule and 50 in the first maintenance dose one 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 spp* venom group, 9.5%). Regarding systemic reactions, three patients experienced mild systemic

reactions: #13, treated with *Apis mellifera* venom presented mild skin pruritus and erythema on the neck after the second dose of the first cluster. After 30 additional minutes, the patient received the third dose with no reaction; #31 and #60 were patients allergic to *Vespa velutina* who suffered from a mild reaction of 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 with no problems. All reactions resolved within a few minutes after being treated with 10 mg oral cetirizine, and one week later, patients tolerated the second cluster and reached the maintenance dose as expected with premedication with antihistamines. No delayed reactions were seen. When searching for markers to identify patients at risk for suffering local or systemic reactions, they tended to not 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 or more weeks seem to be safer but patients remain unprotected until the maintenance dose is reached [3]. A multicentre, observational study comparing 3 build-up protocols performed in Spain has suggested a similar safety profile for 3-, 4- or 9-week schedules but these alum-based depot products were not analysed [13]. The shortest published schedule with alum-based Hymenoptera venom extracts lasts 2 and 4 days for *Vespula* spp and *Apis mellifera*, respectively. The initial dose was 0.1 µg for *Vespula* spp and 0.01 µg for *Apis mellifera*, but 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 but patients were pretreated with antihistamines [15]. Even though guidelines recommend the use of lower doses to start venom immunotherapy [3], shorter schedules and with higher doses as the one presented in this study could be useful when using alum-based depot products. The good tolerability profile of this schedule seems convenient for outpatient clinics, saving time and being cost efficient for patients and professionals, which could result in better acceptance and adherence of VIT by patients.

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**Conflicts of interest**

The following author declare no conflict of interest regarding this manuscript

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## References

1. Bilò MB, Pravettoni V, Bignardi D, Bonadonna P, Mauro M, Novembre E et al. Hymenoptera Venom Allergy: Management of Children and Adults in Clinical Practice. *J Investig Allergol Clin Immunol*. 2019;29:180-205.
2. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med*. 1978;27:157-61.
3. Sturm GJ, Varga EM, Roberts G, Mosbech H, Bilò MB, Akdis CA et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. *Allergy*. 2018;73:744-64.
4. Ruëff F, Przybilla B, Biló MB, Müller U, Scheipl F, Aberer W et al. European Academy of Allergy and Clinical Immunology Interest Group. Predictors of side effects during the buildup phase of venom immunotherapy for Hymenoptera venom allergy: the importance of baseline serum tryptase. *J Allergy Clin Immunol*. 2010;126:105-11.
5. Sánchez-Machín I, Moreno C, González R, Iglesias-Souto J, Pérez E, Matheu V. Safety of a 2-visit cluster schedule of venom immunotherapy in outpatients at risk of life-threatening anaphylaxis. *J Investig Allergol Clin Immunol*. 2010;20:91-2.
6. Sánchez-Morillas L, Reaño Martos M, Rodríguez Mosquera M, Iglesias Cadarso A, Domínguez Lázaro AR. Seguridad de la inmunoterapia con una pauta rápida con veneno de himenópteros [Safety of rush immunotherapy with Hymenoptera venom]. *Allergol Immunopathol*. 2005;33:224-7.
7. Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;114:371-6.
8. Alvarez-Twose I, González-de-Olano D, Sánchez-Muñoz L, Matito A, Jara-Acevedo M, Teodosio C et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. *Int Arch Allergy Immunol*. 2012;157:275-80.
9. Rodríguez-Vázquez V, Armisen M, Gómez-Rial J, Lamas-Vázquez B, Vidal C. Immunotherapy with *Vespula* venom for *Vespa velutina nigrithorax* anaphylaxis: Preliminary clinical and immunological results. *Clin Exp Allergy*. 2022;52:345-7.
10. Mosbech H, Müller U. Side-effects of insect venom immunotherapy: results from an EAACI multicenter study. *European Academy of Allergology and Clinical Immunology*. *Allergy*. 2000;55:1005-10.
11. Müller U, Helbling A, Berchtold E. Immunotherapy with honeybee venom and yellow jacket venom is different regarding efficacy and safety. *J Allergy Clin Immunol*. 1992;89:529-35.
12. Youlten LJ, Atkinson BA, Lee TH. The incidence and nature of adverse reactions to injection immunotherapy in bee and wasp venom allergy. *Clin Exp Allergy*. 1995;25:159-65.
13. Gutiérrez Fernández D, Moreno-Ancillo A, Fernández Meléndez S, Domínguez-Noche C, Gálvez Ruiz P, Alfaya Arias T et al. Insect Venom Immunotherapy: Analysis of the Safety and Tolerance of 3 Buildup Protocols Frequently Used in Spain. *J Investig Allergol Clin Immunol*. 2016;26:366-73.

14. Pucci S, Ciccarelli F, De Pasquale T, Illuminati I, D'Alò S. Depot extracts for rush venom immunotherapy: A new therapeutic opportunity for Hymenoptera sting allergy. *Ann Allergy Asthma Immunol.* 2018;121:376-77.
15. Schrautzer C, Arzt-Gradwohl L, Bokanovic D, Schwarz I, Čerpes U, Koch L, et al. A safe and efficient 7-week immunotherapy protocol with aluminum hydroxide adsorbed vespil venom. *Allergy.* 2020;75:678-80.

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Table 1. Clinical and laboratory data in patients of the study, stratified by the venom used for allergen immunotherapy

	Allergen immunotherapy	
	<i>Apis mellifera</i> (n=20)	<i>Vespula spp</i> (n=42)
<b>Age</b> (years)	52 (44-66)	59 (49-72)
<b>Gender</b> (male)	14 (70.0%)	30 (71.4%)
<b>Beta-blocker/ACE-inhibitors</b>	1 (5.0%)	7 (16.7%)
<b>Severity of reaction (Brown)</b>		
Grade I	9 (45.0%)	11 (26.2%)
Grade II	8 (40.0%)	20 (47.6%)
Grade III	3 (15.0%)	11 (26,2%)
<b>Total serum IgE</b> (kU/L)	50 (23-98)	141 (52-278)
<b>Serum tryptase</b> (ng/mL)	5.3 (3.7-9.1)*	6.0 (4.6-8.0)
<b>Serum specific IgE</b> (kU <sub>A</sub> /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)

Age and laboratory data are presented as median and interquartile range (within parenthesis). The remainder are absolute numbers and percentages (within parenthesis).

(\*) Serum tryptase values were not available in two patients in the group who received *Apis mellifera* venom immunotherapy.

ND: not done.