Allergy

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Safety and Tolerability of a 3-h Build-Up Phase With Hymenoptera Venom Depot Extracts: Preliminary Results

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To the Editor,
Hymenoptera venom allergy may be responsible for systemic reactions ranging from urticaria to fatal anaphylaxis. Yellow jackets (*Vespula* spp.) and honeybees (*Apis mellifera*) are the most involved Hymenoptera [1]. Paper wasps (*Polistes* spp.) and hornets (*Vespa* spp.) are a frequent cause of systemic reactions in Southern Europe, with *Vespa velutina nigrithorax* being the commonest cause of anaphylaxis in Spain [2].

Venom immunotherapy (VIT) is the only treatment that can prevent or reduce the severity of new reactions, and it is effective in 77%–84% of patients receiving honeybee venom and in 91%–96% of patients treated with vespid venoms [1].

VIT can be performed with both aqueous and depot extracts. Aqueous extracts are used during the build-up phase, while depot extracts are preferred for the maintenance phase since they cause fewer local reactions [1].

Several regimens are available for the build-up phase, such as ultra-rush, rush, cluster, and conventional protocols. Conventional (12 weeks) and cluster protocols (7 weeks) are time consuming for both patients and physicians, while rush (2–4 days) and ultra-rush (1 day) can give protection in less time. However, rapid protocols may be at higher risk of systemic reaction during the buildup phase [1].

In our department we have used a 1-day, 3-h ultra-rush build-up phase with aqueous honey-bee or *Vespula* spp. venom extracts according to a previously published protocol [3]. Since aqueous extracts are no longer available, we decided to use depot extracts adsorbed with aluminum hydroxide (Alutard ALK Abelló, Hørsholm, Denmark) for honey-bee and *Vespula* spp. and with tyrosine (Anallergo, Scarperia e San Piero, Florence, Italy) for *Polistes dominula* and *Vespa crabro* for the ultra-rush build-up phase (Table 1). All subjects were strictly monitored (blood

TABLE 1 | Ultra-rush desensitizing protocol.

Time, minute	Dose, *USQ* (Alutard *Vespula* and Alutard *Apis mellifera*)	Dose, *mcg* (Anallergo thyrosine *Polistes dominula* and *Vespa crabro*)
0	100	0.1
30	1000	1
60	10,000	10
90	20,000	20
120	30,000	30
150	40,000	40

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pressure, heart rate) during the procedure and for 1 h after the last dose. Every patient received oral ebastine 10 mg 30 min before the procedure in order to prevent local and mild systemic reactions. The protocol was approved by our local ethics committee and informed consent was obtained by all patients.

Thirty-five (20 males) patients aged 29–74 years with a clinical history of a systemic reaction (grade 1–4 according to Mueller) to a Hymenoptera sting were included. Four patients underwent 2 VIT, 3 with *Vespula* and *Polistes dominula* venoms (the patient could not identify the culprit insect and both skin and laboratory tests were inconclusive) and 1 with *Vespula* and *Vespa crabro* venoms (he had a respiratory arrest after a hornet sting). Fourteen patients had a REMA score higher than 2 and two had a previous diagnosis of systemic indolent mastocytosis. All patients reached the maintenance dose with no systemic reactions

TABLE 2 | Clinical characteristics of investigated patients.

Culprit insect	
HB	12
YJ	10
PW	9
EH	1
Unknown vespid	3

Age						
Range	29–74					
Mean	53.6					
Sex (*n*)						
Male	20					
Female	15					
Venoms	Total ($n = 35$)	HB	YJ	PW	YJ + EH	YJ + PW
		12	10	9	1	3
Treatment (*n*)	Total ($n = 4$)					
Beta blockers	1	0	0	1	0	0
ACE-inhibitors	4	0	3	1	0	0
Grade of SR (Mueller classification)	Total ($n = 35$)					
I	6	1	3	2	0	0
II	4	4	0	0	0	0
III	9	5	2	2	0	0
IV	16	2	5	5	1	3
REMA (*n*)						
	≥ 2 ($n = 14$)	4	3	5	2	0
	< 2 ($n = 21$)	8	7	4	1	1
Reactions during ultra-rush (*n*)						
No side effects	Total ($n = 21$)	4	5	6	2[a]	4[a]
Large local reaction	Total ($n = 18$)	8	5	3	0	2[a]
Systemic reaction	Total ($n = 0$)	0	0	0	0	0
Reactions during maintenance dosing ($n = 200$)						
No side effects ($n = 190$)		84	40	47	3	16
Large local reaction ($n = 10$)		2	4	2	0	2[a]
Systemic reaction ($n = 0$)		0	0	0	0	0

Note: European hornet (*Vespa crabro*).
Abbreviations: HB, honey-bee (*Apis mellifera*); PW, paper wasp (Polistes dominula); YJ, yellow jacket (Vespula).
[a]With both venoms.

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while 8 out of 12 with honeybee venom, 6 out of 14 with *Vespula* venom, and 4 out of 12 with *Polistes dominula* venom had a late large local reaction (LLLR) (> 10 cm) which was treated with topical corticosteroids and/or oral antihistamines (Table 2). LLRs were more frequent in bee venom allergy subjects. On the contrary, in our previous work, bee venom was better tolerated than Vespula venom, and we also had four mild systemic reactions involving the skin during the procedure [3]. Skin systemic reactions may involve 8% of subjects treated with ultra-rush protocols when using aqueous extracts [4]. High venom specific IgE, a REMA score ≥ 2, high serum tryptase levels, and the severity of the index reaction did not seem to be risk factors for both local and systemic reactions [5]. However, the small number of patients treated does not consent to draw definitive conclusions.

Even if the number of subjects is low, our data suggests depot extracts can be used also for ultra-rush protocols with a good safety profile. The safety profile of depot extracts has been confirmed also by other studies with cluster (7 weeks) [6] and rush protocols (2 days for *Vespula* and 4 days for honeybee) [7], with a lower incidence of LLR.

However, ultra-rush protocols are less time-consuming and can provide protection in a few hours, reducing the risk of new field sting reactions when using conventional or cluster protocols.

As regards efficacy, only two patients were stung during the maintenance phase with no systemic reactions.

Larger studies are needed to assess the safety profile of this protocol and to put in evidence immunological changes after a rapid buildup phase.

Author Contributions

A.B. conceived the manuscript, designed the study, and edited and wrote the manuscript. A.A. and R.M. included patients and edited the manuscript. D.L. retrieved clinical data, performed data analysis, and edited the manuscript. E.N. designed the study and edited the manuscript. C.C. and A.G. retrieved clinical data and edited the manuscript. All authors contributed to the article and approved the submitted version.

Conflicts of Interest

The authors declare no conflicts of interest.

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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