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Venom Immunotherapy: a 20-year experience with an ultra-rush protocol (210-min)

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Keyword
adverse reactions; honey-bee; paper wasp; ultra-rush; wasp

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Doi
10.23822/EurAnnACI.1764-1489.85

Summary
Background. *Ultra-rush (UR) are induction protocols used in venom immunotherapy (VIT).* **Objectives.** *To evaluate the adverse reactions during a 210-minutes UR and determine possible risk factors.* **Methods.** *Retrospective study of 129 patients submitted to UR with VIT in the last 20 years.* **Results.** *In 114 (88.4%) patients, the 101.1 µg maintenance dose was reached in 210 minutes. Systemic reactions (SR) occurred in 22% of patients (71% mild). There were no severe SR, late reactions or fatalities. Adrenaline was administered in 10% of all UR. The SR were more frequent with honey bee VIT and had greater severity in the patients with a previous severe systemic sting reaction. No significant difference in the risk of SR was found with other demographic, clinical or laboratory factors. There were 5% of large local reactions (LLR), these being more frequent in females.* **Conclusion.** *Most SR during UR were mild with no need for adrenaline treatment. The honey bee venom and the severity of the anaphylaxis during the field sting were the only SR's risk factors for systemic adverse reactions during the UR.*

Introduction

It is estimated that between 56.6% to 94.5% of the general population has been stung, at least once in life, by a Hymenoptera (1,2). In Portugal, the most common Hymenoptera are the honey bee (Apis mellifera), the wasp (Vespula species) and the paper wasp (Polistes dominula).

Hymenoptera stings can be associated with local or systemic reactions (2,3). Local reactions that have a diameter greater than 10 cm and are maintained for a period of more than 24 hours, are called large local reactions (LLR) (1,2). The systemic reactions include anaphylactic, toxic and uncommon reactions (1,2). The most common reactions after Hymenoptera stings are LLR and systemic anaphylactic reactions (1,4,5).

Venom immunotherapy (VIT) is well recognized as the most efficient treatment to prevent further Hymenoptera systemic allergic reactions (1), being associated with a long-term protection in 85-90% of cases (1,6,7).

VIT is usually administered by subcutaneous injections with aqueous extracts and comprises an induction phase and a maintenance phase necessary to ensure a sustained effect over time (1). Since its development, several induction protocols have been proposed for VIT. These protocols differ from one another in the time required to reach the maintenance dose and in the interval between the injections (8,9,10). The risk of a new systemic sting reaction implies the need for the patient to reach the protection dose as quickly as possible. Thus, slow, conventional protocols with an induction period of 4 to 6 months and intervals between doses of 3 to 7 days have been progressively replaced by faster protocols (11,12). The latest include cluster or *rush*-modified protocols in which induction lasts generally 6 weeks (administration of 2 injections separated for 30 minutes every 3 to 7 days), *rush* protocols in which the induction lasts less than a week and the *ultra-rush* (UR) protocols in which the induction may last from 120 minutes to 2 days with doses being administered at intervals ranging from 20 minutes to 2 hours (11,12,13).

UR protocols allow a complete and rapid desensitization with a smaller number of injections and hospital visits. In these protocols the protective dose of 100 µg venom is reached in a quicker way, decreasing the potential risk of an anaphylactic sting reaction (1,8,14). Over the years, several studies have shown that this induction protocol is safe and effective (15,16,17,18). Nevertheless, there are still some concerns related to the occurrence of severe systemic reactions during the UR protocols.
The objective of the present study is to evaluate the frequency of local and systemic reactions associated with a 210-minute UR protocol with VIT and to identify possible risk factors for these reactions.

Materials and methods

Population

Retrospective study of 129 patients submitted to VIT using a 210-minutes UR protocol, from June 1998 to June 2018, in an Immunoallergology Department. Demographic, clinical and laboratory data were collected from the patients' file. VIT was prescribed to patients with a previous history of immediate systemic reaction after a Hymenoptera sting and sensitization to at least one of these venoms demonstrated by skin tests and/or specific IgE measurement, according to the criteria established by EAACI (1). The severity of the sting reactions was classified according to Mueller (19).
A written informed consent was obtained from all patients and/or their legal representatives before their diagnostic and therapeutic evaluation. Data were anonymized, and their confidentiality guaranteed, and this study protocol was approved by the Ethical Board of Centro Hospitalar Universitário de Lisboa Norte.

Skin tests

The skin tests with Apis mellifera, Vespula spp. and Polistes spp. venoms were performed with Stallergenes® or Bial-Aristegui / Roxall® extracts, at least three weeks after the last sting reaction (1). The skin prick tests were performed using a 100 µg/mL concentration and with 0.9% NaCl as negative control and 10 mg/ml histamine as a positive control. The intradermal tests were performed with increasing concentrations from 0.001 to 1 µg/ml and with a negative control (20).

Lab results

Specific IgE for Apis mellifera, Vespula spp. and Polistes spp. were determined in the sera of the patients by ImmunoCAP, Thermo Fisher Scientific (Uppsala, Sweden). All results > 0.35 kUL were considered positive. Basal serum tryptase was also determined and a tryptase value of < 11.4 ng/mL was considered normal.

Venom immunotherapy ultra-rush protocol

The induction protocol used was the 210-minute UR proposed by Birnbaum (21). In this, a cumulative dose of 101.1 µg, divided by 6 injections, is given as follows: an initial dose of 0.1 µg, followed by 1, 10 and 20 µg at 30-minute intervals. Then 30 and 40 µg were given every 60 minutes. The maintenance dose of 100 µg was repeated 15 days after the UR and administered at 4-6-week intervals over a period of 3 to 5 years, as established in the EAACI guidelines (1).
All injections were given by trained medical personnel in an Immunoallergology Day Hospital, equipped with material for the treatment of anaphylactic reactions. All patients had a venous access with saline during the procedure. Heart rate, blood pressure and peripheral oxygen saturation were continuously monitored. Patients received pretreatment with oral H1 antihistamine (cetirizine 10 mg, ebastine 10 mg or other equivalent 2nd generation H1 antihistamine) in the 2 days prior to UR and in the morning of the UR.
Therapy with ACE inhibitors or with cardio-selective beta blockers in patients with stable cardiovascular disease is continued during UR and VIT.

Classification of adverse reactions

Systemic reactions in UR were stratified according to the Mueller classification (19) and treated with intravenous corticosteroids, antihistamines and, if necessary, with intramuscular adrenaline. The UR was not finished in patients with systemic grade III or IV adverse reactions and in patients with grade I or II systemic reactions that had an unsuccessful response to its treatment. Regarding local adverse reactions, only LLR (mean diameter > 10 cm) were considered. All local reactions were treated with ice, topical corticosteroids and oral antihistamine.

Statistical analysis

Statistical analysis was performed using version 24 of SPSS® software for Windows (SPSS Inc., Chicago, Ill). The median value and the first and third quartiles [Q1, Q3] are presented for the results. The Chi-square test or the Mann-Whitney U test were used to calculate differences between variables and p values < 0.05 were considered statistically significant.

Results

Characteristics of the population

In the last 20 years, 129 patients (73% men, median age 42 years, minimum age 10 years, maximum age 74 years) were submitted to VIT with a 210-minutes UR protocol in our Immu-

noallergology Department. Nine of these were under 18 years of age (90% boys, minimum age 10, median age 16 years).
All patients had a previous history of anaphylaxis after insect sting (29% grade III and 34% grade IV). Demographic and clinical data and the results of in vivo and in vitro diagnostic tests are summarized in **table I**. None of the patients from our population had mastocytosis or any mast cell disorder. A total of 96 patients (74.4%) received VIT with honey bee, 19 (14.7%) with wasp and 14 (10.9%) with paper wasp. UR was performed with aqueous extracts purified from Hymenoptera venom (97% produced by Stallergenes® or Bial-Aristegui / Roxall®).

Adverse reactions during the ultra-rush protocol

From a total of 129 patients who underwent UR, 114 (88.4%) achieved a dose of 101.1 µg and 94 (72.9%) did not present any systemic reaction or large local reaction during the protocol (**table II**). There were no fatalities or late reactions.

Table I *– Demographic and clinical characterization of the studied population*

	Honey bee	**Wasp**	**Paper wasp**	**Total**
Patients - n (%)	96 (74.4)	19 (14.7)	14 (10.9)	129 (100)
Age - $\tilde{x}$ [Q1;Q3]	41 [30.3; 55.5]	52 [35; 57]	43.5 [31.8; 57.3]	42 [31; 56.5]
Age group (≤45/>45) – n (%)	56 (58.3)/ 40 (41.7)	7 (35.8)/ 12 (63.2)	7 (50)/ 7 (50)	70 (54.3)/ 59 (45.4)
Gender				
Male - n (%)	72 (75)	10 (52.6)	12 (85.7)	94 (72.9)
Female - n (%)	24 (25)	9(47.4)	2 (14.3)	35 (27.1)
Atopy - n (%)	37 (38.5)	6 (31.6)	5 (35.7)	48 (37.2)
Asthma - n (%)	11 (11.5)	1 (5.3)	1 (7.1)	13 (10.1)
Cardiovascular disease- n (%)	14 (14.6)	4 (21.1)	3 (21.4)	21 (16.3)
Beekeeper - n (%)	66 (68.8)	-	-	66 (68.8)
Beekeeper direct family member - n (%)	16 (16.7)	-	-	16 (16.7)
Severity of anaphylactic reaction after Hymenoptera sting – n (%)				
Grade I	9 (9.4)	3 (15.8)	1 (7.1)	13 (10.1)
Grade II	32 (33.3)	1 (5.3)	2 (14.3)	35 (27.1)
Grade III	27 (28.1)	5 (26.3)	5 (35.7)	37 (28,7)
Grade IV	28 (29.2)	10 (52.6)	6 (42.9)	44 (34.1)
Use of adrenaline after Hymenoptera sting				
Yes - n (%)	31 (39.7)	6 (46.2)	1 (10)	38 (37.6)
Basal tryptase (ng/mL) - $\tilde{x}$ [Q1;Q3]	3,6 [2.3; 5.7]	5.4 [2; 9.5]	3.3 [1.8; 5.6]	3.6 [2; 5.8]
Apis mellifera sIgE (kU/L) - $\tilde{x}$ [Q1;Q3]	11.5 [3.9; 31.2]	-	-	-
V*espula spp*. sIgE (kU/L) - $\tilde{x}$ [Q1;Q3]	-	8.1 [1.2; 21.4]	-	-
Polistes spp. sIgE (kU/L) - $\tilde{x}$ [Q1;Q3]	-	-	8.7 [1.7; 21.7]	-
Positivity of Hymenoptera venom skin tests - n (%)				
Skin prick tests	12 (9.3)	0	1 (0,8)	13 (10)
ID 0.001 µg/mL	12 (9.3)	2 (1.6)	0	14 (10.9)
ID 0.01 µg/mL	35 (27.1)	9 (7)	8 (6.2)	52 (40.3)
ID 0.1 µg/mL	25 (19.4)	5 (3.9)	3 (2.3)	33 (25.5)
ID 1 µg/mL	10 (7.9)	2 (1.6)	1 (0.8)	13 (10)

Abbreviations: ID – Intradermal tests, $\tilde{x}$ – Median; sIgE – specific IgE

Table II shows that during the UR, 28 patients (27 with honey bee venom and 1 with paper wasp venom) had a systemic reaction. Considering the percentage of systemic reactions according the type of venom that was administered, 28% of patients submitted to honey bee venom UR protocol had a systemic reaction, 7% of those who received an UR protocol with paper wasp had a systemic reaction and there were no systemic reactions among the patients with wasp venom UR protocol.
Although most of the 28 systemic reactions were mild (71% grade I or II), 13 patients received adrenaline and one patient was admitted for surveillance. Systemic reactions were more frequent with 20 µg or higher venom doses ($p < 0.05$) (**table II**). Systemic reactions were more frequent in patients submitted to VIT with honey bee venom ($p = 0.003$).
There were no significant differences between the occurrence of systemic reactions and the patient's gender ($p = 0.85$), personal history of atopy ($p = 0.8$), asthma ($p = 0.10$) or cardiovascular disease ($p = 0.7$). Regarding age, we stratified patients in two age groups (≤ 45 years or > 45 years) and we did not find any difference between the age group and the development of systemic reactions during VIT ($p = 0.44$). Being a beekeeper ($p = 0.15$) or a direct family member of a beekeeper ($p = 0.8$) did not increase the frequency of systemic reactions. Different vaccine manufacturer also did not influence the frequency of systemic reactions ($p = 0.6$).
However, we found that severity of the reactions during the UR protocol was worse in patients who had a previous history of a severe anaphylactic reaction after insect sting ($p < 0.05$) (**table III**).
No statistically significant relationship was found between the existence of systemic reaction during UR and patients' baseline tryptase values ($p = 0.8$) or the venom concentration that elicited a positive response in the skin tests ($p = 0.6$).
Fifteen patients did not reach the cumulative dose of 101.1 µg on the UR protocol day (8 with grade III systemic reactions and 7 with grade II systemic reaction and unsuccessful response to the treatment). In all, UR was repeated 15 days after a reinforcement in premedication (30 minutes before starting the UR: clemastine 2 mg i.v. and hydrocortisone 100 mg i.v.). In the second UR, 10 of the 15 patients successfully completed the protocol without systemic reaction. The remaining 5 patients were included in other induction protocols.

Table II *- Systemic and local adverse reactions.*

	Honey bee	**Wasp**	**Paper wasp**	**Total**	**p-value**
Patients - n	96	19	14	129	-
Adverse reactions (locals and systemic) - n (%)	31 (32.3)	2 (10.5)	2 (14.2)	35 (27.1)	-
Systemic reactions - n (%)	27 (28.1)	0 (0)	1 (7.1)	28 (21.7)	0.003
Grade I	4 (14.8)	0 (0)	0 (0)	4 (14.2)	
Grade II	15 (55.6)	0 (0)	1 (100)	16 (57.1)	
Grade III	8 (29.6)	0 (0)	0 (0)	8 (28.6)	
Grade IV	0 (0)	0 (0)	0 (0)	0 (0)	
Reactions that required adrenaline - n (%)	12 (12.5)	0 (0)	1 (7.1)	13 (10)	-
Rate of systemic reactions per injection - %	6	0	1.2	5.4	-
Dose administered when the systemic reaction occurred - n (%)					
0.1 µg	0 (0)	0 (0)	0 (0)	0 (0)	-
1 µg	0 (0)	0 (0)	0 (0)	0 (0)	
10 µg	4 (14.8)	0 (0)	0 (0)	4 (14.2) **[4 GI]**	
20 µg	14 (51.9)	0 (0)	0 (0)	14 (50) **[7 GII; 7 GIII]**	
30 µg	4 (14.8)	0 (0)	0 (0)	4 (14.2) **[4 GII]**	
40 µg	5 (18.5)	0 (0)	1 (100)	6 (21.4) **[5 GII; 1 GIII]**	
Large local reactions (LLR) - n (%)	4 (4.2)	2 (10.5)	1 (7.1)	7 (5.4)	0.4

Abbreviations: GI-Grade I systemic reaction, GII – Grade II systemic reaction, GIII- Grade III systemic reaction – according to Muller et al.19

There were 7 LLR (**table II**): 4 with honey bee venom, 2 with wasp and one with paper wasp. From these, one reaction was identified after the administration of the 30-µg and the remaining after the 40-µg injection. All patients with LLR finished the 210-minutes UR in the first attempt. These reactions were more frequent in females (p = 0.02). We did not find any other factor that had a significant association with the occurrence of LLR.

Discussion

This study is a retrospective survey of the last 20 years of all patients undergoing VIT using a 210-minutes UR protocol. From a total of 129 patients included, 114 (88%) achieved the dose of 101.1 µg in the planned period of time, while 15 (12%) patients did not complete the UR in the first attempt. Of these, two thirds (n = 10) reached the cumulative dose of 101.1 µg in a further UR, 15 days later, with a premedication reinforcement and using the same UR protocol.

In contrast to other studies published to date (16,17,21,22) our study has much more patients submitted honey bee VIT, and also 13 patients that underwent an UR protocol with paper wasp venom. These are particular aspects related to the environmental exposure to insects' stings in our country.

The UR protocols allow a rapid desensitization and are associated with fewer injections and hospital visits. Additionally, they are associated with a reduced risk of anaphylaxis in case the patient is re-stung before reaching the protective dose (1,10,14). Despite being safe, these fast protocols are not totally risk free, as they can be associated with systemic and/or local adverse reactions.

Regarding the systemic reactions, we documented a frequency of systemic reactions of 22%, most of them being mild. We also found that only 10% of all our patients were treated with adrenaline during the protocol, and no fatalities were reported. The frequency of systemic reactions during VIT UR protocols (≤ 210 minutes) reported in previously published studies ranges from 0% to 30% (14,21,22,23).

Our results are similar to the ones reported by Birnbaum et al (21), who documented a frequency of systemic reactions of 30% in a subset of patients treated with honey bee venom and of 6.1% in patients treated with wasp venom, using a 210-minutes UR protocol. Roll et al (22), on the other hand, reported a lower frequency of systemic reactions. These authors analyzed 67 patients (total of 80 UR procedures) that received VIT with honey bee or wasp venoms and found a total of 12.5% of systemic adverse reactions (bee 5% and wasp 7.5%). Although, in this study (22), the overall percentage of adverse reactions is inferior to ours, the number of reactions in patients treated with wasp VIT is higher than the number of reactions that occurred in patients treated with honey bee VIT. This data is not in agreement to what is published in most studies where bee venom alone is a risk factor for systemic reactions (1,24,25,26). An explanation for this difference in systemic reactions between honey bee and wasp VIT could be the degree of purity of the Hymenoptera venom vaccines. It has been demonstrated through laboratory studies that honey bee vaccines have a lower concentration of non-allergenic proteins, whereas in the wasp vaccines the allergenic proteins are diluted with non-allergenic proteins from the venom bag (11). Several studies have been developed in order to identify possible clinical or laboratory risk factors for the occurrence of systemic adverse reactions (24,26).

In our study, in addition to the venom administered, we verified that there is a relationship between the severity of anaphylaxis after honey bee sting and the severity of the systemic reaction during UR with honey bee venom (p = 0.04). Birnbaum et al. (24) also demonstrated that patients who had grade III or IV anaphylaxis after Hymenoptera sting more frequently devel-

Table III - *Relation between the severity of the reaction after Hymenoptera sting and the severity of anaphylactic reaction during VIT-UR.*

Severity of the reaction@ after insect sting/ Severity of the reaction @during VIT-UR*		**Severity of the reaction after insect sting**			
		Grade I (n=13)	Grade II (n=35)	Grade III (n=37)	Grade IV (n=44)
Severity of the reaction during the VIT-UR	**Without reaction (n=101)**	13/11	35/25	37/30	44/35
	Grade I	13/1	35/3	37/0	44/0
	Grade II	13/1	35/7	37/2	44/6
	Grade III	13/0	35/0	37/5	44/3
	Grade IV	13/0	35/0	37/0	44/0

*p-value <0.05

oped a grade III or IV systemic reaction during the UR. This data may point out to the need of a reinforcement in premedication before UR in the subset of patients with a previous history of more severe systemic reaction after insect sting.

We did not find any relationship between the occurrence of systemic reactions and the patients' age (p = 0.44), gender (p = 0.85), personal history of atopy (p = 0.8), asthma (p = 0.1) or of cardiovascular disease (p = 0.7). Besides this, no statistically significant relationship was found between the existence of systemic reactions during the UR protocol and the results of the skin tests (p = 0.6) or the level of the baseline tryptase (p = 0.8). These data are in line with previous reports (5,24,25,27,28).

Regarding LLR, we also did not find any significant association between their occurrence and the patients' age, previous history of atopy, asthma or cardiovascular disease or, also, with the type of venom administered to the patient. However, as previously reported (20,29), we found that LLR were more frequent in females (p = 0.02). However, there were only 7 LLR reactions which limits interpretation of these results.

Another aspect that deserves mention is the fact that 10 of the 15 patients who did not complete the UR in a first attempt, achieved the 101.1 µg dose in a second UR session, which increased our success rate to 96%. It was not possible to identify any risk factors that led to the failure of the first UR in these patients.

Conclusion

In conclusion, over the past 20 years, in our Immunoallergology Department, 129 patients underwent a 210-minutes VIT UR protocol, with an overall completion rate of 96%, considering the 114 patients that completed VIT UR at a first attempt and the 10 patients that completed it at a second attempt with premedication reinforcement. This protocol was carried out in the Day Hospital and was performed by trained medical staff with quick access to the necessary equipment for the treatment of an anaphylactic reaction. UR protocols allow a quicker achievement of the protective dose; however, it is not a risk-free procedure. In our study, we documented a frequency of 22% of systemic reactions, most of them being mild and without need for adrenaline. The only predictive factors for a systemic reaction that we found in our study were the use of honey bee venom and the severity of systemic insect sting reaction.

Acknowledgements

The authors would like to thank to Elisa Pedro, Insect Allergy Clinic coordinator in CHULN, for letting us have access to all patients' data and also for the scientific revision of the paper. We also like to thank Manuel Branco Ferreira for the scientific revision of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest

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