Venom immunotherapy in clinical practice: comparison of two ultra-rush protocols

Ricardo Moço Coutinho[1], Ana Margarida Mesquita[2], José Luís Plácido[1], Alice Coimbra[1]

1. Allergy and Clinical Immunology Department, São João Local Health Unit, Porto, Portugal
2. Allergy and Clinical Immunology Department, Braga Local Health Unit, Braga, Portugal

Abstract

Background: Ultra-rush venom immunotherapy protocols have shown to be a safe and effective approach to prevent the occurrence of systemic reactions after hymenoptera stings. The aim was to describe our experience with two ultra-rush protocols – a five-step with 1 µg starting dose and a six-step with 0.1 µg starting dose, as well as to compare their safety profile.

Methods: This is a retrospective study of all the patients who underwent VIT with honey bee or wasp venom between January 2008 and December 2021, in our department.

Results: A total of 110 patients was included, with 109 patients (99%) completing the protocol. A total of 63 (57%) patients had no local or systemic reactions. Most systemic reactions occurred with 20 µg or higher doses (24, 83%). There were no documented grade IV systemic reactions (Mueller grading). No differences were found in local or systemic reactions regarding sex, atopy, β-blocker medication, the severity of the index reaction, ID test positivity, levels of total IgE, specific IgE and tryptase (all $p>0.05$). Younger age, treatment with bee VIT or being a beekeeper were associated with more systemic reactions ($p=0.035$, 0.006 and 0.047, respectively). No statistical differences in the number of local and systemic reactions were found when comparing both protocols ($p=1.000$).

Conclusions: Ultra-rush protocols are safe and effective, but systemic reactions are to be expected, especially with honeybee. Our data supports that ACE inhibitors do not compromise safety. Beginning with 1 µg is safe and can save time and resources.

Keywords: 1 µg; hymenoptera; immunotherapy; ultra-rush.

Impact Statement: To our knowledge, this is the first study reporting the safety of ultra-rush protocols starting with 1 µg of venom, shortened to 180 minutes, exclusively in outpatient setting.

Introduction

Hymenoptera venom allergy (HVA) is an important cause of morbidity worldwide, and systemic reactions are potentially life-threatening (1). Venom immunotherapy (VIT) is the most effective and the only disease modifying treatment that can prevent the occurrence of systemic reactions. In Europe, including Portugal, non-purified aqueous extracts are used for skin tests and VIT (2). The EAACI guidelines state that VIT should be recommended to adults and children with a history of systemic sting reactions exceeding generalized skin symptoms, with confirmed sensitization (3). There are different build-up protocols in which the maintenance dose can be achieved in a time-span of several weeks or in mere hours (4). Ultra-rush protocols represent the latter, and these have been shown to be safe and effective (5-9). In our department, these protocols are used for starting VIT since 2008. The protocol was adapted from the one reported by Birnbaum (10), that has 210 minutes of duration and starts with a 0.1 µg dose. One study has already shown that a starting dose of 1 µg can be safe (11). Our aim was to characterize the safety profile of ultra-rush protocols in our patients, as well as, to compare the safety of a faster, five-step, 180 minutes long ultra-rush regimen, with a starting dose of 1 µg, versus the standard six-step, 210 minutes long protocol, with a starting dose of 0.1 µg.

Materials and Methods

A retrospective study of all the patients who underwent VIT with ultra-rush protocols with honey bee or wasp venom between January 2008 and December 2021, in the Allergy and Clinical Immunology department of the Unidade Local de Saúde de São João, was performed.

Patient work-up included a detailed clinical history, intradermal tests, measurement of total and venom specific immunoglobulin E (IgE) (whole extract and molecular components), as well as serum tryptase. Intradermal tests were performed using *Apis*, *Vespula* and/or *Polistes* venom extracts from LETIPharma®, Stallergenes Greer®, Bial-Aristegui/Roxall®, ALK-Abelló® or Inmunotek®, in concentrations ranging from 0.01 to 1 µg/mL.

Diagnostic approach and proposal for treatment with VIT were all performed according to the European Academy of Allergy and Clinical Immunology (EAACI) guidelines (3).

All patients who initiated VIT using a six (starting dose of 0.1 µg) or five-step (starting dose of 1 µg) ultra-rush protocol (Table I) were included. Patients who initiated VIT using other protocols were excluded.

VIT was started in a Day Hospital setting using aqueous extracts from LETIPharma®, Stallergenes Greer®, Bial-Aristegui/Roxall®, ALK-Abelló® or Inmunotek®. All patients were prescribed pre-treatment with oral H1 anti-histamines during the five days prior to VIT induction. Patients on anti-hypertensive medication (angiotensin-converting enzyme inhibitors (ACE inhibitors) and β-blockers) were not advised to discontinue it.

Data regarding age, sex, clinical history, sting reaction severity, diagnostic workup (skin tests, immunoglobulin E (IgE) and serum tryptase measurement), VIT protocol used and adverse reactions during VIT was collected.

The severity of systemic reactions to the stings and to VIT was graded according to the Mueller grading system (12).

During this medical records review of the clinical practice in our department, only the authors had access to patients' data, in order to maximize confidentiality. All patients signed an informed consent form before starting VIT.

Statistical analysis was performed with IBM SPSS Statistics®, version 29.0 for Windows®, and the Mann-Whitney U, chi-square and Fisher exact tests were used. Results were considered statistically significant for p values below 0.05.

Results

A total of 110 patients was included, 84 (76%) men with a median age 41 (IQR 29-54) years, 12 younger than 18 years old. All patients had a history of at least one systemic reaction after a hymenoptera sting. The characterization of the sample is in Table II. None of the patients had a diagnosis of any mast cell disorder.

The dose of 101.1 µg (six-step) or 101 µg (five-step) was achieved in 109 patients (99%). One patient was not able to finish a six-step ultra-rush protocol due to having multiple systemic reactions. In this patient VIT was later restarted using a semi-rush protocol. A total of 63 (57%) patients did not have any local or systemic reactions.

The number of local and systemic reactions, severity grading, VIT administered and protocol used were organized in three tables: Table III includes data about patients on anti-hypertensive medication; Table IV includes details about the manufacturer used for VIT and at which dose the systemic reactions occurred; Table V organizes the patients in two age groups – less than 18 years old and 18 years old or more.

Most systemic reactions occurred with a cumulative dose of at least 31 µg (24, 83%) in both protocols.

No statistical differences were found in local or systemic reactions regarding sex (p=0.113 and p=0.312), atopy (p=0.428 and p=0.802), β-blocker medication (p=0.681 and p=0.441), the severity of the index reaction (p=0.231 and p=0.671), ID test positivity (p=1.000 and p=0.421), levels of total IgE (p=1.000 and p=0.090), specific IgE (p=0.806 and p=0.618) and tryptase (p=0.515 and p=0.776). Age at the start of VIT did not have any influence in local reactions (p=0.818), but being younger was associated with more systemic reactions (p=0.035). However, no differences were found when comparing patients below and above the age of 18 years. In ACE inhibitors medicated patients, no difference was found regarding local reactions (p=0.289), but these had less systemic reactions (p=0.018).

There were no differences in local reactions with bee VIT (p=0.808) when compared to wasp, but there was an association with more systemic reactions (p=0.006). From the patients that were treated with bee VIT, no differences were found regarding local reactions (p=0.773), but beekeepers had more systemic reactions (p=0.047).

When comparing manufacturers, LETIPharma® was associated with less local reactions than Bial-Aristegui/Roxall® (p=0.035). There were no other statistically significant differences found in regard to local or systemic reactions.

When comparing both protocols, no statistical differences in the number of local and systemic reactions were found (six and five-steps, both p=1.000) and the same can be said for the severity of systemic reactions.

Discussion

This study details the experience of our department with VIT using ultra-rush protocols.

We documented more systemic reactions than in most studies that evaluate the safety of ultra-rush protocols (5-8). In these studies, the majority of patients included were allergic to wasp. This contrasts with our sample, that is more similar to the one included in another Portuguese study (9). The difference most likely reflects the prevalence of apiculture in our country, and this alone could explain the higher percentage of systemic reactions.

Bee VIT is the most recognized risk factor for systemic reactions (13, 14) and our results also support this. It is also noteworthy that beekeepers were, from all the patients that initiated bee VIT, the ones with more systemic reactions. Some studies report bee VIT in beekeepers to be safer but these did not use ultra-rush protocols (15, 16). One study, also from Portugal, did not find any association with systemic reactions (9). It is unknown whether beekeepers have other risk factors for systemic reactions besides treatment with bee VIT.

Regarding the severity of systemic reactions during VIT, it is important to note that there were no grade IV reactions, regardless of the protocol used, even though this was the severity grade reported in 24% of the index reactions. No differences were found when comparing the severity of systemic reaction between both protocols, which reinforces the safety of the faster protocol.

In this sample, the age distribution of patients with and without systemic reactions was different. No differences were observed when comparing patients below and above the age of 18 years old. However, the median age of patients that had systemic reactions was significantly lower. These findings are not supported in other studies, in which older age is usually mentioned as a risk factor for systemic reactions (17).

There has been some controversy concerning the effects of anti-hypertensive medications in the security of VIT. However, current evidence is leaning more towards the idea that these medications do not play a role in augmenting the number or severity of systemic reactions (3, 17, 18). Our results also support this. In fact, patients on ACE inhibitors had no systemic reactions and only one patient on β-blockers had a systemic reaction (grade 1). We believe that, during

VIT, it is safe not to stop antihypertensive medication, but we do not think that these drugs play a role in protecting against systemic reactions. We attribute this result to the fact that patients on ACE inhibitors were older, and, in this sample, older patients had less systemic reactions.

None of the manufacturers used for VIT were associated with a better safety profile regarding systemic reactions. Even though LETIPharma® was associated with less local reactions when compared to Bial-Aristegui/Roxall®, we do not have any evidence to prefer any manufacturer over another. Further studies with data on tolerability and efficacy, as well as the exact allergen composition of each VIT are needed.

One of the stronger points of this study is the comparison of two different schedules of ultra-rush VIT. There are many factors contributing to patient adherence to treatment (19). Reducing the time of hospital stay necessary for administering VIT, is more convenient for patients and potentially reduces costs associated with longer stays. Our results support that initiating VIT with a 1 µg dose using ultra-rush protocols exclusively in an outpatient setting does not compromise safety. To our knowledge, there is only one other study (11) reporting this finding. However, in this research, the ultra-rush protocols were used after hospitalizing patients, and a modified rush protocol was used for the outpatient setting.

Some limitations of this study are that the retrospective review of medical records can result in loss of information that was not recorded, and not taking into account other potential confounders. This was evident when evaluating local reactions, in that most records did not mention dimensions. We decided to include all of these, assuming they were large local reactions, in order to not underestimate their numbers, and this could explain the high number of documented local reactions. The higher prevalence of honeybee allergy than what is described in most studies about the safety of ultra-rush regimens, also makes it harder to extrapolate results.

In conclusion, ultra-rush protocols are successful in reaching the VIT maintenance dose faster. Our data supports that being medicated with anti-hypertensive medication during VIT does not compromise safety. Systemic reactions are to be expected, especially with honeybee. However, the shorter protocol that began with 1 µg was not associated with any change in the number or severity of systemic reactions, saving time and resources. Further studies are still needed to consolidate these findings.

No fundings were received for this research.

Conflict of interest statement: The authors have no conflicts of interest to declare.

Contributions of each author:

RMC: conceptualization, data curation, formal analysis, investigation, writing - original draft

AMM: data curation, investigation, writing - original draft

JLP: project administration, writing – review

AC: conceptualization, investigation, methodology, project administration, supervision, writing – review

References

1. Bilo 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(3):180-205.
2. Floyd ML, Adams KE, Golden DBK. Updates and Recent Advances on Venom Immunotherapy. Curr Treat Options Allergy. 2023:1-19.
3. Sturm GJ, Varga EM, Roberts G, Mosbech H, Bilo MB, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. Allergy. 2018;73(4):744-64.

4. Demsar Luzar A, Korosec P, Kosnik M, Zidarn M, Rijavec M. Hymenoptera Venom Immunotherapy: Immune Mechanisms of Induced Protection and Tolerance. Cells. 2021;10(7).
5. Selcuk A, Baysan A, Yesillik S, Demirel F, Kartal O, Gulec M, et al. Adverse reactions in venom immunotherapy protocols: conventional versus ultra-rush. Ann Med. 2022;54(1):2321-5.
6. Stock R, Fischer T, Aßmus K, Zoeller N, Ackermann H, Kaufmann R, et al. Safety and tolerability of venom immunotherapy: Evaluation of 581 rush- and ultra-rush induction protocols (safety of rush and ultra-rush venom immunotherapy). World Allergy Organ J. 2021;14(1):100496.
7. Bozek A, Kolodziejczyk K. Safety of specific immunotherapy using an ultra-rush induction regimen in bee and wasp allergy. Hum Vaccin Immunother. 2018;14(2):288-91.
8. Nittner-Marszalska M, Cichocka-Jarosz E, Malaczynska T, Kraluk B, Rosiek-Biegus M, Kosinska M, et al. Safety of Ultrarush Venom Immunotherapy: Comparison Between Children and Adults. J Investig Allergol Clin Immunol. 2016;26(1):40-7.
9. Cosme J, Spinola-Santos A, Pereira-Santos MC, Pereira-Barbosa M. Venom Immunotherapy: a 20-year experience with an ultra-rush protocol (210-min). Eur Ann Allergy Clin Immunol. 2019;51(3):122-8.
10. Birnbaum J, Ramadour M, Magnan A, Vervloet D. Hymenoptera ultra-rush venom immunotherapy (210 min): a safety study and risk factors. Clin Exp Allergy. 2003;33(1):58-64.
11. Roumana A, Pitsios C, Vartholomaios S, Kompoti E, Kontou-Fili K. The safety of initiating Hymenoptera immunotherapy at 1 microg of venom extract. J Allergy Clin Immunol. 2009;124(2):379-81.
12. Mueller UR. Insect Sting Allergy: Clinical Picture, Diagnosis, and Treatment: Gustav Fischer; 1990.
13. Sahiner UM, Durham SR. Hymenoptera Venom Allergy: How Does Venom Immunotherapy Prevent Anaphylaxis From Bee and Wasp Stings? Front Immunol. 2019;10:1959.
14. Rueff F, Przybilla B, Bilo MB, Muller U, Scheipl F, Aberer W, et al. 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(1):105-11 e5.
15. Muller UR. Bee venom allergy in beekeepers and their family members. Curr Opin Allergy Clin Immunol. 2005;5(4):343-7.
16. Eich-Wanger C, Muller UR. Bee sting allergy in beekeepers. Clin Exp Allergy. 1998;28(10):1292-8.
17. Stoevesandt J, Sturm GJ, Bonadonna P, Oude Elberink JNG, Trautmann A. Risk factors and indicators of severe systemic insect sting reactions. Allergy. 2020;75(3):535-45.
18. Sturm GJ, Herzog SA, Aberer W, Alfaya Arias T, Antolin-Amerigo D, Bonadonna P, et al. beta-blockers and ACE inhibitors are not a risk factor for severe systemic sting reactions and adverse events during venom immunotherapy. Allergy. 2021;76(7):2166-76.
19. Kvarnstrom K, Westerholm A, Airaksinen M, Liira H. Factors Contributing to Medication Adherence in Patients with a Chronic Condition: A Scoping Review of Qualitative Research. Pharmaceutics. 2021;13(7).

Table I. Ultra-rush protocols used for venom immunotherapy

	6-step protocol	Time interval before next administration	5-step protocol
	0.1 µg	30 minutes	-
	1 µg	30 minutes	1 µg
	10 µg	30 minutes	10 µg
	20 µg	60 minutes	20 µg
	30 µg	60 minutes	30 µg
	40 µg	-	40 µg
Total time	210 minutes		180 minutes

Table II. Characterization of the patients

Severity of index reaction	
Grade 1	5 (4%)
Grade 2	20 (18%)
Grade 3	59 (54%)
Grade 4	26 (24%)
Atopy	25 (23%)
Beekeepers	36 (33%)
Positive ID	86 (78%)
Median total IgE	148 (IQR 67-309)
Median specific IgE	12 (IQR 4-34)
Median tryptase	4.4 (IQR 3.3-5.5)
Honeybee (*Apis*) VIT	68 (62%)
Wasp (*Vespula*) VIT	36 (33%)
Paper wasp (*Polistes*) VIT	6 (6%)
6-step	36 (33%)
5-step	74 (67%)

ID – intradermal; IgE – immunoglobulin E; VIT – venom immunotherapy.

Table III. Characterization of local and systemic reactions, severity grading, as well as anti-hypertensive medication, by protocol used and VIT administered

	6-step n=36	5-step n=74		Honeybee n=68	Wasp n=36	Paper wasp n=6		Total n=110
β-blockers	2 (6%)	7 (10%)		2 (3%)	5 (14%)	2 (33%)		9 (8%)
ACE inhibitors	1 (3%)	12 (16%)		5 (7%)	7 (19%)	1 (17%)		13 (12%)
No anti-hypertensives	33 (92%)	55 (74%)		61 (90%)	24 (67%)	3 (50%)		88 (80%)
Local reactions	8 (22%)	17 (23%)		15 (22%)	9 (25%)	1 (17%)		25 (23%)
β-blockers	0	1 (6%)		1 (7%)	0	0		1 (4%)
ACE inhibitors	0	1 (6%)		0	1 (11%)	0		1 (4%)
No anti-hypertensives	8 (100%)	15 (88%)		14 (93%)	8 (89%)	1 (100%)		23 (92%)
Systemic reactions	9 (25%)	20 (27%)		25 (37%)	4 (11%)	0		29 (26%)
β-blockers	0	1 (5%)		1 (4%)	0	0		1 (3%)
ACE inhibitors	0	0		0	0	0		0
No anti-hypertensives	9 (100%)	19 (95%)		24 (96%)	4 (100%)	0		28 (97%)
Severity grading								
Grade 1	3 (33%)	7 (35%)		6 (24%)	4 (100%)	0		10 (35%)
β-blockers	0	1 (14%)		1 (17%)	0	0		1 (10%)
Grade 2	3 (33%)	11 (55%)		14 (56%)	0	0		14 (48%)
Grade 3	3 (33%)	2 (10%)		5 (20%)	0	0		5 (17%)

ACE – angiotensin-converting enzyme

Table IV. Characterization of local and systemic reactions, as well as manufacturer used, by protocol used for VIT

	6-step, n=36	5-step, n=74	Total 110
LETIPharma®	0	36 (49%)	36 (33%)
Bial-Aristegui/Roxall®	1 (3%)	35 (47%)	36 (33%)
Stallergenes Greer®	33 (92%)	1 (1%)	34 (31%)
ALK-Abelló®	2 (6%)	1 (1%)	3 (3%)
Inmunotek®	0	1 (1%)	1 (<1%)
Local reactions	8 (22%)	17 (23%)	25 (23%)
LETIPharma®	0	3 (18%)	3 (12%)
Bial-Aristegui/Roxall®	0	11 (65%)	11 (44%)
Stallergenes Greer®	8 (100%)	1 (6%)	9 (36%)
ALK-Abelló®	0	1 (6%)	1 (4%)
Inmunotek®	0	1 (6%)	1 (4%)
Systemic reactions	9 (25%)	20 (27%)	29 (26%)
LETIPharma®	0	7 (35%)	7 (24%)
Bial-Aristegui/Roxall®	1 (11%)	13 (65%)	14 (48%)
Stallergenes Greer®	7 (78%)	0	7 (24%)
ALK-Abelló®	1 (11%)	0	1 (3%)
Inmunotek®	0	0	0
Dose administered			
0.1 µg	1 (11%)	-	1 (3%)
Stallergenes Greer®	1 (100%)	0	1 (100%)
1 µg	0	0	0
10 µg	1 (11%)	3 (15%)	4 (14%)
LETIPharma®	0	1 (33%)	1 (25%)
Bial-Aristegui/Roxall®	0	2 (67%)	2 (50%)
Stallergenes Greer®	1 (100%)	0	1 (25%)
20 µg	4 (44%)	9 (45%)	13 (45%)
LETIPharma®	0	3 (33%)	3 (23%)
Bial-Aristegui/Roxall®	0	6 (67%)	6 (46%)
Stallergenes Greer®	3 (75%)	0	3 (23%)
ALK-Abelló®	1 (25%)	0	1 (8%)
30 µg	2 (22%)	3 (15%)	5 (17%)
LETIPharma®	0	1 (33%)	1 (20%)
Bial-Aristegui/Roxall®	0	2 (67%)	2 (20%)
Stallergenes Greer®	2 (100%)	0	2 (20%)
40 µg	1 (11%)	5 (25%)	6 (21%)
LETIPharma®	0	2 (40%)	2 (33%)
Bial-Aristegui/Roxall®	0	3 (60%)	3 (50%)
Stallergenes Greer®	1 (100%)	0	1 (17%)

Table V. Characterization of local, systemic reactions and severity grading in each age group (<18 years old and ≥18 years), by protocol used and VIT administered

	6-step n=36	5-step n=74		Honeybee n=68	Wasp n=36	Paper wasp n=6		Total n=110
Age <18 years	6 (17%)	6 (8%)		10 (15%)	2 (6%)	0		12 (11%)
Local reactions	2 (33%)	1 (17%)		3 (30%)	0	0		3 (25%)
Systemic reactions	1 (17%)	3 (50%)		4 (40%)	0	0		4 (33%)
Severity grading								
Grade 1	0	1 (33%)		1 (25%)	0	0		1 (25%)
Grade 2	1 (100%)	2 (67%)		3 (75%)	0	0		3 (75%)
Honeybee	5 (83%)	5 (83%)						10 (83%)
Wasp	1 (17%)	1 (17%)						2 (17%)
Age ≥18 years	30 (83%)	68 (92%)		58 (85%)	34 (94%)	6 (100%)		98 (89%)
Local reactions	6 (20%)	16 (24%)		12 (21%)	9 (26%)	1 (17%)		22 (22%)
Systemic reactions	8 (27%)	17 (25%)		21 (36%)	4 (12%)	0		25 (26%)
Severity grading								
Grade 1	3 (38%)	6 (35%)		5 (34%)	4 (100%)	0		9 (36%)
Grade 2	2 (25%)	9 (53%)		11 (52%)	0	0		11 (44%)
Grade 3	3 (38%)	2 (12%)		5 (34%)	0	0		5 (20%)
Honeybee	16 (53%)	42 (62%)						58 (59%)
Wasp	13 (43%)	21 (31%)						34 (35%)
Paper wasp	1 (3%)	5 (7%)						6 (6%)