ORIGINAL ARTICLE

Safety of Ultrarush Venom Immunotherapy: Comparison Between Children and Adults

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Abstract

Background: The ultrarush protocol is an attractive approach in the buildup phase of venom immunotherapy (VIT-UR). However, the degree of risk of VIT-UR in children remains unknown. The objective of this study was to compare the safety of VIT-UR in children and adults.
Methods: We performed a study based on prospectively gathered medical records of children and adults with hymenoptera venom allergy treated with VIT-UR in 3 allergy centers in Poland.
Results: The study population comprised 134 children (mean [SD] age, 12.6 [3.7] years; males, 70.1%) and 207 adults (mean age, 42.4 [14.0] years; males, 47.8%). The number of children in the subgroups of bee venom (BV) allergy and wasp venom (WV) allergy were comparable, although sensitization to WV was more predominant in the adult group (70.1%). Skin reactivity to both venoms was more common in children than in adults (*P*<.001); however, children had higher concentrations of total IgE and specific IgE to BV (both *P*<.001). Systemic allergic reactions (VIT-SARs) occurred in 6.2% of the patients (3.7% in children and 7.7% in adults; nonsignificant). In adults, SARs occurred more frequently in patients treated with BV than WV extracts (21.4% vs 2.6%; *P*<.001). The same pattern was observed in children (7.2% vs 0%; *P*=.058). However, VIT-SARs to BV were less frequent in children than in adults (*P*=.034). Similarly, no significant relationship was noted between children and adults receiving WV VIT (2.6% vs 0%; nonsignificant). The severity of VIT-SAR did not differ between children and adults.
Conclusions: VIT-UR is safer in children. Age below 18 is not a risk factor for VIT-SARs.

Key words: Adults. Children. Insect venom immunotherapy. Systemic adverse reaction.

Resumen

Introducción: Los protocolos ultra rápidos son considerados de utilidad para realizar la fase de inicio de la inmunoterapia con venenos de himenópteros (VIT-UR). La seguridad de estos protocolos VIT-UR en los niños sigue siendo una cuestión debatida. El objetivo de este estudio fue comparar la seguridad de VIT-UR en niños y adultos.
Métodos: Estudio prospectivo de seguimiento de la seguridad de la inmunoterapia en niños y adultos regularmente tratados con VIT-UR seguidos en tres unidades de alergia en Polonia.
Resultados: En el estudio fueron incluidos un total de 134 niños (edad media de 12,6 años, SD 3,7; varones 70,1%) y 207 adultos (edad media 42,4 años, SD 14,0; 47,8% varones). El número de niños sensibilizados a veneno de abeja (BV) era comparable al de los sensibilizados a veneno de avista (WV), mientras que la sensibilidad al veneno de avispa prevaleció en el grupo de adultos (70,1%). Los niños con hipersensibilidad a venenos (HVA) mostraron menor reactividad cutánea a ambos venenos que los adultos con HVA (p <0,001) pero, por el contrario, en comparación con los adultos presentan concentraciones de IgE sérica total e IgE específica frente a BV (ambas p <0,001). Un 6,2% de todos los pacientes (3,7% de los niños y 7.7% de los adultos, NS) presentaron reacciones alérgicas sistémicas frente a la inmunoterapia con venenos (VIT-SAR). En los adultos, el SARS fueron más frecuentes en los pacientes tratados con BV que los tratados con WV (21,4% frente a 2,6% p <0,001). El mismo patrón se produjo en niños (7,2% vs 0%; p = 0,058). Sin embargo, las VIT-SAR frente a inmunoterapia con BV fueron menos frecuentes en los niños que en adultos (p = 0,034). Del mismo modo la frecuencia de reacciones frente a WV VIT fue menor en niños que en adultos pero sin diferencias significativas (0% vs 2,6%, NS). La gravedad de las VIT-SAR fue similar para niños y adultos.
Conclusiones: Los protocolos VIT-UR son más seguros en los niños. Edad menor de 18 años no es un factor de riesgo de VIT-SAR.

Palabras clave: Adultos. Niños. Inmunoterapia con veneno de insectos. Reacción adversa sistémica.

Introduction

Hymenoptera venom allergy (HVA) is a crucial health issue in both children and adults. Depending on the geographical region and climate, the frequency of systemic reactions to HVA ranges from 0.9% to 3.4% in children and from 5.0% to 8.9% in adults [1,2,3]. HVA is one of the most frequent causes of anaphylaxis in adults and children [4] and is seriously detrimental to the quality of life of the persons affected [5,6].

The only treatment that addresses the cause of HVA is specific venom immunotherapy (VIT). According to EAACI guidelines [7], VIT is recommended regardless of age for severe reactors (grade III-IV in the Mueller classification) with a confirmed venom-specific IgE-positive reaction, although it is also allowed in milder reactors (grade I-II), who are at an increased risk of severe systemic reactions to insect stings (eg, asthmatics, bee keepers and their family members).

VIT provides fast, effective, and long-lasting protection against the risk of a repeated allergic reaction, thus improving the quality of life of persons who receive VIT [8].

However, VIT also involves the risk of systemic allergic reactions (VIT-SARs), especially during the buildup phase. Studies conducted in large patient populations report that up to 20% experience a VIT-SAR during VIT and that 8.4% of reactions are moderate to severe, requiring medical treatment [9-11]. The factors identified as being predictive of VIT-SARs include VIT with bee venom, higher baseline tryptase concentration in patients receiving vespid venoms, and mastocytosis [7,9,12-13]. Age and therapy with angiotensin-converting enzyme inhibitors (ACEIs), and ß-blockers are also considered to be predictive of VIT-SARs [9,14].

The degree of risk of VIT in children remains unknown and has not been investigated in published prospective multicenter projects assessing the safety of VIT [9,10]. The few studies that have estimated the risk of VIT in children were performed in a single center [15-17] and evaluated the safety of slow, conventional protocols involving a large number of weekly visits (15 visits), fast protocols conducted over 8 weeks (modified or semirush), and only sporadically fast and very fast protocols in which the maintenance dose was reached within 3 days (rush) and 1 day (ultrarush [VIT-UR]).

The safety of VIT-UR warrants special attention. The protocol has been broadly used in the treatment of HVA for its many merits: (*1*) venom tolerance can be achieved within 1 day (especially important if a patient starts treatment just before or during the Hymenoptera insect flight season); (*2*) optimal compliance; (*3*) very few injections (reduced fear and stress associated with pain); and (*4*) time saving in the case of working adults and schoolchildren and their working parents. However, while the protocol has obvious advantages, its safety is not clear. Some researchers have found VIT-UR to be safe [18], although most find it less safe than slower induction protocols [9,19]. As the latter opinion predominates, VIT-UR is rarely used in children, although it is very common in adult patients.

Given the merits of VIT-UR and the lack of data on safety, we assessed the safety of VIT-UR in children. Our comparison was based on a parallel evaluation in a group of adult patients treated with the same protocol, thus enabling us to investigate the association between safety of VIT-UR and age.

Methods

We performed a prospective, observational study to assess the safety of VIT-UR in 3 allergy treatment centers specializing in the diagnosis and treatment of HVA in children and adults. The children were recruited between 2008 and 2014, the adults between 2010 and 2012. The recruitment time frame was selected based on the assumption that within a set period potentially more VIT-treated adults than children are recruited. Thus, in order to ensure a similar power of analysis, the recruitment time frame for adults was reduced, limiting the number of recruited adults to roughly twice the number of children.

The inclusion criteria were a history of SAR to wasp or bee venoms, positive specific IgE results to wasp or bee venoms (positive cutoff, 0.35 kU_A/L), and/or positive intradermal skin test results obtained at a maximum concentration of 1.0 µg/mL. The previous systemic sting reactions were graded according to the Mueller scale. The exclusion criteria were acute infection, pregnancy, breastfeeding, badly controlled cardiovascular or respiratory diseases, use of ACEIs and ß-blockers, mastocytosis, neoplastic diseases, and psychiatric diseases. Also excluded were patients sensitive to both wasp and bee venom in whom the insect responsible for the previous SAR was not identified. All the participants signed a written informed consent document and were enrolled by trained medical personnel.

The Bioethics Committee of Jagiellonian University approved the study protocol. VIT-UR treatments were given at 3 hospital sites (Gdansk, Krakow, and Wroclaw), and we collected data on all doses and reactions for the induction-phase of VIT.

Diagnostic Procedures

Diagnoses were made and VIT-UR treatments performed as inpatient procedures according to EAACI guidelines [7]. The same standardized venom extract (lyophilized wasp and bee venom [Pharmalgen, Alk-Abelló]) was used for skin testing and immunotherapy. Specific IgE for wasp venom and/or bee venom allergens, total IgE, and baseline serum tryptase were determined using a UniCAP 100 analyzer (CAP System, Phadia). Intradermal tests with venom extract were performed at concentrations ranging from 0.0001 µg/mL to 1.0 µg/mL. The longer diameter of the wheal (mm) was recorded.

VIT-UR Protocol

VIT-UR was performed following the standard approach in all study patients. To prevent recruitment of patients with comorbidities, we took a detailed clinical history and performed biochemistry tests, complete blood count, and baseline spirometry. In addition, a 12-lead electrocardiogram was recorded for the adults. We screened for mastocytosis by measuring the baseline mast cell tryptase level (Phadia CAP; normal, <11.4 mg/L).

VIT procedures were conducted according to the Birnbaum ultrarush protocol, in which treatment begins with an initial dose of 0.1 µg and the total dose of 101.1 µg is reached within 3.5 hours [16]. An infusion of 0.9% saline solution was administered before the first injection. During VIT-UR, blood pressure and pulse were taken, and an electrocardiogram recorded. Neither children nor adults were pretreated with antihistamines.

Evaluation of SARs

Safety of treatment was evaluated based on both the frequency of systemic adverse events and their severity. Systemic reactions were defined by the presence of objective, generalized cutaneous symptoms (flush, urticaria, erythema, and angioedema), gastrointestinal syndromes (abdominal cramps, vomiting, and diarrhea), respiratory symptoms (dyspnea and wheezing), and cardiovascular symptoms (tachycardia, arrhythmia, hypotension, collapse, and unconsciousness). Hypotension was defined as systolic blood pressure of less than 90 mmHg for patients aged 11 years and older, <70 mmHg + (2 × age in years) for patients aged 1 to 10 years, or as a decrease of >30% from baseline. The severity of VIT-SARs was based on the Mueller classification. All VIT doses and symptoms of VIT-SAR were recorded simultaneously in the treatment database.

Statistical Analysis

The statistical tests applied were the chi-square, with a Yates correction when appropriate, and the Mann-Whitney and Kolmogorov-Smirnov tests. The receiver operating characteristic (ROC) method was applied to determine the properties of immunological parameters as predictors of SARs in VIT. The analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp).

Results

Demographical and Clinical Parameters

The study groups comprised 207 adults aged 18-76 years and 134 children aged 4-17 years. In adults, the male:female ratio was comparable for the whole group and in the wasp venom allergic (WV-HVA) and bee venom allergic (BV-HVA) subgroups (males accounted for 47.8% in the whole adult group, 45.7% in WV-HVA, and 53.6% in BV-HVA). Among HVA children, males predominated both in the whole group (70.1%) and in the WV-HVA and BV-HVA subgroups (66.2% and 73.9%, respectively). Most adults lived in the city, whereas most children lived in the country.

In the adult group, more patients presented allergic symptoms to wasp venom than to bee venom, whereas in children the percentage of patients presenting allergic reactions to wasp venom and bee venom did not differ significantly.

In both adults and children, most allergic sting reactions were Mueller grade III and IV (95.2% and 73.2% of patients treated with VIT-UR, respectively). In both adults and children, there was no difference in the severity of insect sting reactions between those sensitized to wasp venom and those sensitized to bee venom.

There were no significant differences in the frequency of atopy and asthma between the groups (Table 1).

Immunological Parameters

Compared with children, HVA adults showed higher responsiveness to wasp and bee venom in the intradermal tests (both $P<.001$). Higher skin responsiveness to Hymenoptera venom in adults was manifested by both a larger average wheal diameter and lower venom concentrations that elicited a positive test result. The concentrations of specific IgE did not differ significantly between the groups in patients sensitized to

Table 1. Demographic and Clinical Characteristics of the Study Sample

Variable	Category	Adults		Children		*P* Value
Sex	Male	99	47.8	94	70.1	<.001
	Female	108	52.2	40	29.9	
Mean (SD) age, y		42.4 (14.0)	14.0	12.6 (3.7)	3.7	<.001
Place of residence	City	81	61.8	43	34.1	<.001
	Country	50	38.2	83	65.9	
Sensitizing insect	Wasp	151	72.9	65	48.5	<.001
	Bee	56	27.1	69	51.5	
Mueller grade	I	0	0.0	12	9.0	
	II	10	4.8	24	17.9	
	III	106	51.2	64	47.8	
	IV	91	44.0	34	25.3	
Atopy	Yes	42	20.3	31	23.8	NS
Asthma	Yes	15	7.2	12	9.0	NS
Total		207	100	134	100	

Abbreviation: NS, nonsignificant.

Table 2. Immunological Characteristics of Adults and Children With Respect to the Sensitizing Insect

Variable	Group	Median	Q1	Q3	*P* Value
Wasp Venom–Allergic Patients					
Total IgE, kU_A/L	Adults	72.8	37.8	180.0	NS
	Children	83.9	63,4	199.5	
Wasp venom sIgE concentration, kU_A/L	Adults	2.53	0.70	10.30	NS
	Children	3.28	1.05	9.31	
Wasp venom sIgE class	Adults	2	2	3	NS
	Children	2	2	3	
sIgE/total IgE	Adults	0.035	0.009	0.077	NS
	Children	0.023	0.008	0.062	
IDT concentration, µg/mL	Adults	0.001	0.001	0.010	<.001
	Children	0.100	0.001	0.100	
IDT diameter, mm	Adults	12	10	15	<.001
	Children	6	6	7	
Bee Venom–Allergic Patients					
Total IgE	Adults	37.8	16.6	62.9	<.001
	Children	191.0	80.8	467.0	
Bee venom sIgE concentration, kU_A/L	Adults	2.93	0.48	14.00	<.001
	Children	23.70	9.09	66.80	
Bee venom sIgE class	Adults	2	0	3	<.001
	Children	4	3	5	
sIgE/total IgE	Adults	0.027	0.000	0.058	.001
	Children	0.128	0.064	0.236	
IDT concentration, µg/mL	Adults	0.001	0.001	0.100	.007
	Children	0.055	0.010	0.100	
IDT diameter, mm	Adults	11	9.5	15.0	<.001

Abbreviations: IDT, intradermal test; NS, nonsignificant.

wasp venom, although they were higher in children sensitized to bee venom (Table 2).

Tryptase Levels

Median (IQR) tryptase levels were lower in HVA children than in adults (3.48 [2.6-5.16]) vs 3.05 [2.3-3.87]; *P*=.009).

VIT-SARs

VIT-SARs occurred in 21 out of 341 patients (6.2%). Although the frequency was half as low in children as it was in adults, the result is not statistically significant (3.7% vs 7.7%; *P*=.134). Adults treated with bee venom experienced VIT-SARs more frequently than those treated with wasp venom (21.4% vs 2.6%; *P*<.001). A similar tendency was observed in children (7.2% vs 0%; *P*=.058).

The percentage of children with grade I-II reactions differed from that of adults (27% vs 4%), VIT-SARs occurred exclusively in children with grades III-IV. In order to ensure that overrepresentation of grade I and II HVA children as compared with adults did not affect the complication rate, we investigated the frequency of VIT complications in children and adults who were qualified for VIT on the basis of grade III and IV reactions (children and adults with grade I and II reactions were excluded). The frequency of VIT complications in grade III and IV patients did not differ significantly (*P*=.342) between adults (16/181; 8.1%) and children (5/93; 5.1%) (Table 3). To ensure that numerical proportions between children and adults with grade III and grade IV reactions did not affect the frequency of VIT complications in either group, we performed separate calculations for grade III symptoms

Table 3. Frequency of VIT complications in adults and children with hymenoptera venom allergy: grade III and IV symptoms

P=.342	VIT Systemic Symptoms		Total
	No	Yes	
Adults, No (%)	181 (91.9%)	16 (8.1%)	197 (100.0%)
Children, No (%)	93 (94.9%)	5 (5.1%)	98 (100.0%)
Total, No. (%)	274 (92.9%)	21 (7.1%)	295 (100.0%)

Abbreviation: VIT, venom immunotherapy.

Table 4. Severity of VIT-SARs in the Study Groups

	Adults		Children		*P* Value
	No.	(%)	No.	(%)	
Total systemic reactions	16	100.0	5	100.0	NS
Grade I	9	56.3	1	20.0	
Grade II	2	12.5	0	0.0	
Grade III	4	25.0	4	80.0	
Grade IV	1	6.3	0	0,0	
Systemic reactions to wasp venom	4	100.0	0		
Grade I	2	50.0	0		
Grade II	1	25.0	0		
Grade III	1	25.0	0		
Systemic reactions to bee venom	12	100.0	5	100.0	NS
Grade I	7	58.3	1	20.0	
Grade II	1	8.3	0	0.0	
Grade III	3	25.0	4	80.0	
Grade IV	1	8.3	0	0	

Abbreviations: NS, nonsignificant; VIT-SAR, venom immunotherapy systemic adverse reaction.

Table 5. Characteristics of Individuals With SARs to Venom Immunotherapy During an Ultrarush Protocol

Patient	Age, y	Gender F=1/M	Venom	Initial Reaction, Mueller Grade	sIgE, kU_A/L	IDT Concentration, µg/mL	IDT Diameter, mm	BST, ng/mL	Dose of extract with SAR, µg	SAR, Mueller Grade
1	66	Female	Wasp	3	1.99	0.10000	11.0	16.70	20 000	1
2	65	Female	Bee	4	17.50		20.0		40 000	3
3	58	Male	Bee	4	14.80	0.00100	15.0		20 000	1
4	56	Female	Bee	3	0.00	0.10000	15.0		40 000	1
5	50	Male	Bee	4	76.60		17.0		30 000	1
6	50	Female	Bee	4	0.63	0.00100	13.0		40 000	1
7	49	Male	Bee	4	0.99		14.0		10 000	4
8	45	Male	Bee	3	16.90	0.00100	12.0	3.52	20 000	2
9	43	Female	Bee	3	101.00	0.00100	8.0			1
10	43	Male	Bee	4	0.00				30 000	1
11	38	Female	Wasp	4	1.09		15.0		40 000	3
12	36	Male	Bee	3		0.00100	8.0		30 000	1
13	35	Male	Wasp	4	1.86	0.10000	11.0	4.28	40 000	1
14	35	Female	Bee	4	101.00		14.0		10 000	3
15	34	Female	Wasp	3	0.42	0.01000	6.0	3.15	20 000	2
16	20	Male	Bee	3	13.20	0.00100	18.0	6.77	10 000	3
17	16	Female	Bee	4			10.0		10 000	3
18	13	Female	Bee	4	101.00	0.00100	6.0		40 000	1
19	12	Male	Bee	3	101.00	0.00100	6.0		20 000	3
20	10	Male	Bee	4	101.00		5.0		30 000	3
21	4	Male	Bee	4	44.30	0.10000	6.0	5.23	30 000	3

Abbreviations: BST, basal serum tryptase; IDT, intradermal test; SAR, systemic adverse reaction.

and grade IV symptoms. The results of the calculations did not show significant differences between the frequency of VIT in grade III children and adults and grade IV children and adults.

An analysis of the frequency of VIT-SARs in the separate subgroups of patients treated with bee venom extract and wasp venom extract showed that VIT-SARs to bee venom were more frequent in adults than in children (21.4% vs 7.2%; *P*=.034). No such correlation between adults and children was observed in patients treated with wasp venom extract, despite the fact that there were no VIT-SARs in children treated with wasp venom (2.6% vs 0%; *P*=.318).

The most frequent manifestations of VIT-SARs concerned the skin (grade I [2.9%]) and the respiratory system (grade III [2.3%]); Mueller grade II systemic reactions were rarer (0.6%). There was 1 case of anaphylactic shock in an adult who underwent VIT-UR (0.3%). All VIT-SARs resolved with pharmacological treatment.

In the whole study group, the severity of VIT-SARs determined by the frequency of the occurrence of allergic reactions of different Mueller grades did not differ significantly between children and adults. The most frequent reactions in children were grade III; therefore, it was not necessary to use adrenaline to treat VIT-SARs (Table 4).

No significant differences were observed between children and adults with regard to the dose that caused the VIT-SARs.

A thorough analysis of the adults and children who experienced VIT-SARs did not reveal significant differences with respect to asthma and atopy, the severity of the previously experienced field sting reaction, or the results of diagnostic tests (intradermal tests, determination of sIgE) (Table 5).

Children who experienced VIT-SARs differed from those who did not with respect to the severity of the previously experienced field sting reactions (*P*=.016); children with a grade IV field sting reaction experienced VIT-SARs 7 times more frequently than children with a grade III field sting reaction (11.8% and 1.6%, respectively), while no children with previous grade I and II reactions experienced VIT-SARs. Other factors that distinguished children who experienced VIT-SARs from those who did not were median absolute sIgE value (101 kU_A/L vs 21.25 kU_A/L; *P*=.005) and bee venom sIgE (class 6 vs 4: *P*=.011). Such correlations were not observed in adults (Table 5).

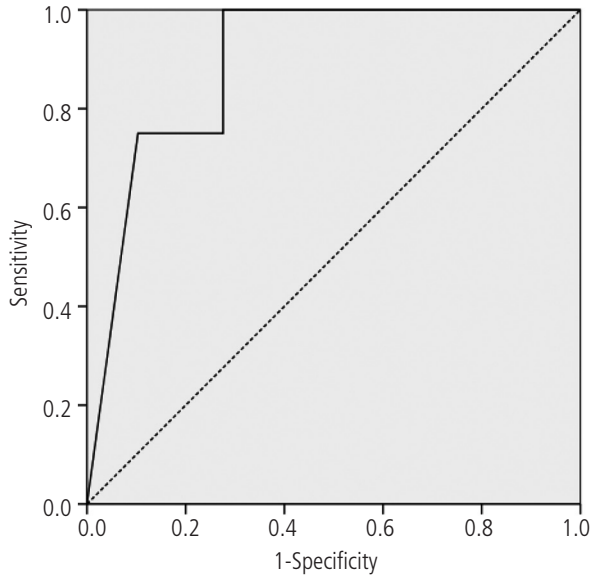

Figure. Receiver-Operating Characteristic Curve for sIgE in Children Allergic to Bee Venom.

Immunological Markers for Prediction of VIT-SARs

The diagnostic performance of immunological markers used to predict VIT-SARs were evaluated using ROC curve analysis, which showed that sIgE to bee venom in bee venom–allergic children had the best predictive value (AUC, 0.89; 95%CI, 0.78%-1.00%; *P*=.009). In children, the sensitivity and specificity for this parameter at a venom concentration of 95.45 kU_A/L were 0.75 and 0.9, respectively; higher values increased the risk of SARs (Figure).

Discussion

The objective of the present study was to assess whether VIT-UR is safe in children. We compared the frequency and severity of SARs during VIT-UR in patients aged <18 years and adults. Safety of VIT-UR has not yet been thoroughly investigated in children and is often assumed by extrapolating results from studies conducted in adults. In order to verify our assessment of the safety of our approach in children, we based our comparison on a parallel evaluation in a group of adult patients treated with the same protocol. VIT-SARs were monitored using a unified protocol in which the severity of SARs was classified based on the Mueller scale, as in the European multicenter study by Mosbech et al [10] and the single-center Swiss study performed in children by Köhli-Wiesner et al [15].

Our multicenter study demonstrates that VIT-UR is a safe and well-tolerated induction regimen for VIT in children. The frequency of SARs during the course of VIT-UR was low in children. Only 3.7% of the children treated developed VIT-SARs; this frequency did not differ statistically between children and adults. The frequency of VIT-SARs was not affected by the difference between the number of children with grade I-II and IV reactions in comparison with adults. VIT-SARs to bee venom were more predominant that those to wasp venom in both adults and children. In patients with allergy to bee venom, the percentage of VIT-SARs was even lower in children than in adults. Our results for the frequency of VIT-SARs in children are similar to those of Steiss et al [17], who found the frequency of VIT-SARs to be 2.7%; the authors followed a 2-day VIT protocol with a cumulative venom extract dose of 251.1 µg (first day of treatment, 152.11 µg) [17]. A higher percentage of VIT-SARs in children was reported by Kohli-Wiesner et al (16%) [15] and Birnbaum et al (10.8%) [16], although only the former investigated the problem of VIT in children alone. The results of our study are similar to those reported elsewhere in another respect; when VIT-SARs do occur, they are more likely to be caused by bee venom than by wasp venom [7,9,10,12]. The safety of VIT-UR in both age groups is evidenced not only by the low

frequency of VIT-SARs, but also by the relatively low severity of the reactions. After analyzing cases of VIT-SARs, we found that systemic reactions in children and adults manifested predominantly in the skin and were mild to moderate and that no child experienced anaphylactic shock. We conclude that VIT-UR is safe in children. However, since VIT-SARs to bee venom occur with greater frequency than VIT-SARs to wasp venom, children treated with bee venom extracts should be closely monitored.

Observations supporting the safety of VIT-UR in children are of practical importance in the daily routine of HVA centers. Considering the abundant data suggesting greater risks of VIT-UR compared with slower protocols, natural concern over the safety of the former means that VIT-UR is avoided in the treatment of young patients. Such is the conclusion of the study by Brown et al [19] in Australia, although the authors examined reactions to another representative of the Hymenoptera order, namely, the jack jumper ant (Myrmecia pilosula) of the Formicidae family [19].

Our results do not fully reflect the overall percentage of VIT-SARs in adults. Adult data are underestimated, because by recruiting adults to serve as a background for comparisons with children, we eliminated individuals with mastocytosis and those receiving ACEIs and ß-blockers, since both drugs involve the risk of potentially more frequent VIT-SARs. Such a study design could have resulted in an underestimation of VIT-SARs in adults and a corresponding overestimation of the safety of VIT-UR in adults in general. However, the system of patient selection was motivated by our intention to make both age groups as clinically compatible as possible. As a result, the safety of VIT-UR in children was assessed against the baseline safety data collected from adults free from high-risk factors that could complicate the outcome of VIT. In addition, disproportion in the number of patients in the study groups may have led the study parameters to be considered as having uneven statistical value, thus potentially affecting the assessment of the safety of VIT-UR between the groups. However, we wanted to include all the available children and a numerous group of adults to obtain more representative results.

Our study has considerable strengths, notably a large number of children recruited from various centers. Another advantage is the fact that all the participating centers used the same treatment strategy and the same method to describe VIT-SARs in all the patients. Additionally, from the outset, the principal investigators were responsible for the diagnosis and treatment of all the patients from each center, thus ensuring the high reliability of the data obtained.

In conclusion, we hold that VIT-UR is a safe method of HVA treatment in young patients.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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