ORIGINAL ARTICLE

Factors Affecting the Safety and Effectiveness of Venom Immunotherapy

Arzt-Gradwohl L[1], Herzog SA[2], Aberer W[1], Alfaya Arias T[3], Antolín-Amérigo D[4,5], Bonadonna P[6], Boni E[7], Bożek A[8], Chełmińska M[9], Ebner B[10], Frelih N[11], Gawlik R[12], Gelincik A[13], Hawranek T[14], Hoetzenecker W[15], Jiménez Blanco A[16], Kita K[9], Kendirlinan R[17], Košnik M[18], Laipold K[1], Lang R[14], Marchi F[19], Mauro M[20], Nittner-Marszalska M[21], Poziomkowska-Gęsicka I[22], Pravettoni V[23], Preziosi D[20], Quercia O[24], Reider N[25], Rosiek-Biegus M[21], Ruiz-Leon B[26], Schrautzer C[1], Serrano P[26], Sin A[27], Sin BA[17], Stoevesandt J[28], Trautmann A[28], Vachová M[29,30], Sturm GJ[1,31]

[1]Department of Dermatology and Venereology, Medical University of Graz, Graz, Austria
[2]Institute for Medical Informatics, Statistics, and Documentation, Medical University of Graz, Graz, Austria
[3]Allergy Department, Hospital Universitario Fundación Alcorcón, Madrid, Spain
[4]Servicio de Enfermedades del Sistema Inmune-Alergia, Hospital Universitario Príncipe de Asturias, Departamento de Medicina y Especialidades Médicas, Universidad de Alcalá, Madrid, Spain
[5]Servicio de Alergia, Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain
[6]Allergy Unit, Verona General Hospital, Verona, Italy
[7]Laboratorio Unico Metropolitano, Maggiore Hospital, Bologna, Italy
[8]Clinical Department of Internal Diseases, Dermatology, and Allergology, Medical University of Silesia, Zabrze, Poland
[9]Allergology Department, Medical University of Gdańsk, Gdańsk, Poland
[10]Department of Dermatology, General Hospital Ordensklinikum Linz GmbH Elisabethinen, Linz, Austria
[11]University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia
[12]Department of Internal Medicine, Allergy, and Clinical Immunology, Silesian University of Medicine, Katowice, Poland
[13]Department of Internal Medicine, Division of Immunology and Allergic Diseases, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Türkiye
[14]Department of Dermatology and Allergology, Paracelsus Medical University Salzburg, Salzburg, Austria
[15]Department of Dermatology, Kepler University Hospital and Medical Faculty, Johannes Kepler University, Linz, Austria
[16]Allergy Unit, Hospital Central de la Cruz Roja. Faculty of Medicine, Alfonso X El Sabio University, ARADyAL, Madrid, Spain
[17]Department of Pulmonary Diseases, Division of Immunology and Allergy, Faculty of Medicine, Ankara University, Ankara, Türkiye
[18]University Clinic of Respiratory and Allergic Diseases, Golnik and Medical Faculty, Ljubljana, Slovenia
[19]SD Allergologia Clinica, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
[20]Allergy Unit, Sant'Anna Hospital, Como, Italy
[21]Department of Internal Diseases, Pulmonology and Allergology, Medical University of Wroclaw, Wroclaw, Poland
[22]Clinical Allergology Department, Pomeranian Medical University, Szczecin, Poland
[23]Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[24]High Specialization Unit of Allergology, Hospital of Faenza, AUSL (Local Health Unit) of Romagna, Romagna, Italy
[25]Department of Dermatology, Venereology, and Allergology, Medical University of Innsbruck, Innsbruck, Austria
[26]Allergy Section of University Hospital Reina Sofia, ARADyAL Network, Maimonides Biomedical Research Institute of Córdoba (IMIBIC), Córdoba, Spain
[27]Department of Internal Medicine, Division of Allergy and Immunology, Medical Faculty, Ege University, Izmir, Türkiye
[28]Department of Dermatology and Allergy, University Hospital Würzburg, Würzburg, Germany
[29]Department of Immunology and Allergology, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic
[30]Department of Immunology and Allergology, University Hospital Pilsen, Czech Republic
[31]Allergy Outpatient Clinic Reumannplatz, Vienna, Austria

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Abstract

Background: The safety profile of venom immunotherapy (VIT) is a relevant issue, and considerable differences have been reported in the safety and efficacy of this treatment modality. The primary aim of this study was to evaluate the safety of angiotensin-converting enzyme inhibitors and ß-blockers during VIT. In a second analysis, we evaluated data on premedication and venom preparations and their association with systemic adverse events (AEs) during the up-dosing phase and the first year of the maintenance phase, as well as the outcome of field stings and sting challenges.
Methods: Ours was an open, prospective, observational, multicenter study that recruited 1425 patients, of whom 1342 underwent VIT.
Results: Premedication with oral antihistamines was taken by 52.1% of patients during up-dosing and 19.7% of patients during the maintenance phase. Antihistamines had no effect on the frequency of systemic AEs (*P*=.11), although large local reactions (LLRs) were less frequent (OR, 0.74; 95%CI, 0.58-0.96; *P*=.02). Aqueous preparations were preferred for up-dosing (73.0%), and depot preparations

were used for the maintenance phase (64.5%). The type of venom preparation had no influence on the frequency of systemic AEs or on the effectiveness of VIT (*P*=.26 and *P*=.80, respectively), while LLRs were less frequent with depot preparations (*P*<.001).
Conclusions: Pretreatment with oral antihistamines during VIT significantly reduces the frequency of LLRs but not systemic AEs. All venom preparations were equally effective and did not differ in terms of the frequency of systemic AEs.

Key words: Anaphylaxis. Bee venom. Effectiveness. Premedication. Systemic adverse events. Venom immunotherapy. Venom preparation. Vespid venom.

Resumen

Antecedentes: El perfil de seguridad de la inmunoterapia con veneno (VIT) es un tema relevante y se han descrito diferencias considerables en su seguridad y eficacia. El objetivo principal de este estudio fue evaluar la seguridad de los inhibidores de la ECA y los betabloqueantes durante la VIT, que ya han sido descritos. En un segundo análisis, se han evaluado los datos sobre premedicación y los distintos extractos de veneno en relación con los eventos adversos (EA) sistémicos durante la fase de aumento de dosis y el primer año de la fase de mantenimiento. También se evaluaron los efectos sobre el resultado de las picaduras espontáneas y las provocaciones mediante picadura.
Métodos: El diseño del estudio fue abierto, prospectivo, observacional y multicéntrico. En total, se inscribieron 1.425 pacientes y se realizó VIT en 1.342 pacientes.
Resultados: La premedicación con antihistamínicos orales fue tomada por el 52,1% de los pacientes durante la fase de subida de dosis y el 19,7% de los pacientes durante la fase de mantenimiento. La toma de antihistamínicos no tuvo efecto sobre la frecuencia de EA sistémicos (p=0,11), pero las reacciones locales exageradas (LLR) se observaron con menor frecuencia (OR: 0,74; IC 95%: 0,58-0,96; p=0,02). Se utilizaron preferentemente preparaciones de extractos acuosos para la fase de subida de dosis (73,0%) y preparaciones *depot* para la fase de mantenimiento (64,5%). El tipo de preparación del veneno no tuvo influencia en la frecuencia de EA sistémicos ni en la efectividad de la VIT (p=0,26 y p=0,80, respectivamente), mientras que las LLR se observaron con menor frecuencia cuando se utilizaron preparaciones *depot* (p<0,001).
Conclusiones: El tratamiento previo con antihistamínicos orales durante la VIT reduce significativamente la frecuencia de LLR, pero no los EA sistémicos. Todas las preparaciones de veneno utilizadas fueron igualmente efectivas y no difirieron en la frecuencia de EA sistémicos.

Palabras clave: Anafilaxia. Veneno de abeja. Efectividad. Premedicación. Reacciones adversas sistémicas. Inmunoterapia frente a veneno de himenópteros. Preparación del veneno. Veneno de avispa.

Summary box

- **What do we know about this topic?**
  Venom immunotherapy (VIT) is the only treatment that can potentially prevent further systemic sting reactions, and its safety profile is a relevant issue. Differences in the safety and efficacy of VIT have been reported.
- **How does this study impact our current understanding and/or clinical management of this topic?**
  The frequency of systemic adverse events is similar for the different protocols. Therefore, quicker up-dosing protocols are preferred, since patients are protected faster from future systemic sting reactions. Importantly, all venom preparations used in the present study are equally effective.

Introduction

Hymenoptera venom allergy is the most common cause of anaphylaxis in adults in Europe and a potentially life-threatening disease [1]. The frequency of self-reported systemic sting reactions (SSRs) ranges from 2.3% to 5.4% in European and US epidemiological studies [2-4]. Venom immunotherapy (VIT) is the only treatment that can potentially prevent further SSRs [5] and is effective in 77%-84% of patients treated with honeybee venom [6,7] and in 91%-96% of patients receiving vespid venom [6,7].

The safety profile of VIT is a relevant issue, and differences in the safety and efficacy of VIT have been reported [6-10]. The most important risk factor for systemic adverse events (AEs) during VIT is treatment with bee venom [9,11]. A rapid dose increase during the up-dosing phase is also a weaker but established risk factor for systemic AEs [8,9]. In Europe, VIT is administered with both purified venom extracts (obtained by a filtration process that mostly removes vasoactive substances) and nonpurified venom extracts [12]. Purified aluminum hydroxide–adsorbed preparations and tyrosine-adsorbed preparations (the so-called depot preparations) seem to cause large local reactions (LLRs) less frequently than aqueous preparations, although these findings may be biased by the up-dosing protocol used, since depot preparations are generally used for slower up-dosing protocols [13]. In addition, reduced effectiveness of VIT due to a lack of venom components in some venom preparations has been postulated [14].

Pretreatment with different types of antihistamines has been reported to reduce the frequency of LLRs during the up-dosing phase [15-18], as well as that of generalized, cutaneous reactions such as urticaria or angioedema [16,19,20]. However, the potential risk of masking onset of an allergic reaction by premedication with antihistamines has also been discussed [19].

We recently published the results of an open, prospective, observational, multicenter study that recruited 1425 patients from 26 centers in 8 European countries. We showed that β-blockers and angiotensin-converting enzyme inhibitors (ACEIs) did not increase the number of systemic AEs during VIT [21]. In this second analysis, we aimed to assess whether premedication with oral antihistamines and various venom preparations affected the frequency of systemic AEs and the effectiveness of VIT in a large study cohort. Furthermore, we compared treatment strategies for systemic sting reactions and systemic AEs throughout Europe.

Materials and Methods

Objectives

Our main objective was to evaluate whether patients taking antihypertensive treatment with β-blockers or ACEIs experience more systemic AEs during VIT than patients not taking antihypertensive treatment. Furthermore, we evaluated whether well-known and controversial risk factors were correlated with a higher frequency of systemic AEs in our study cohort. These data have already been published [21]. As a secondary objective, we assessed how initial sting reactions and systemic AEs were treated and evaluated the influence of premedication. In addition, we determined whether some venom preparations were safer than others in terms of systemic AEs and LLRs (defined as swelling >10 cm persisting for at least 24 hours) and whether there were differences in the effectiveness of VIT based on the outcome of sting challenges and field stings. We also evaluated treatment strategies for initial sting reactions and systemic AEs throughout Europe.

Study Design and Oversight

Ours was an open, prospective, observational, multicenter study (Clinicaltrials.gov: NCT04269629). Patients were recruited from 26 centers in 8 European countries (5 centers in Austria, 1 in the Czech Republic, 1 in Germany, 5 in Italy, 5 in Poland, 1 in Slovenia, 4 in Spain, and 4 in Türkiye). The study was approved by the ethics committee of the study sponsor (Medical University of Graz; approval no. 26-442 ex 13/14), as well as the local ethics committee in each country. The patients gave their written informed consent.

Legally competent male and female patients aged 35 to 85 years with a history of SSR (≥grade I according to the classification by Ring and Messmer [22]) were eligible for the study. The exclusion criteria were absolute contraindications to VIT according to the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI), such as active multisystem autoimmune disorders, active malignant disease, and pregnancy [5]. Patients were included after giving their written informed consent and once the inclusion and exclusion criteria were carefully reviewed (at visit 1). All data concerning the index sting reaction and concomitant diseases and medications were recorded. If patients agreed to receive VIT, data concerning the up-dosing phase (premedication, venom preparation, up-dosing protocol, systemic AEs graded according to Ring and Messmer [22]), and changes in concomitant diseases and medication were recorded at visit 2. There was no standard up-dosing protocol for VIT. All centers used in-house protocols (conventional, cluster, ultrarush, and rush) [5]. Visit 3 was at 1 year after the maintenance dose was reached. At this visit, changes in premedication, venom preparation, and concomitant diseases and medication were recorded, as were systemic AEs during the maintenance phase and, if applicable, the outcome of field stings or sting challenges. No additional study-related visits were required. All procedures (diagnosis and treatment of Hymenoptera venom allergy) had to be in concordance with current EAACI guidelines [5,23,24] and were conducted individually by each study center. Premedication with antihistamines (standard or double dose) was usually administered 30-60 minutes before the first injection of VIT per treatment day. All centers used a maintenance dose of 100 µg in most cases and 200 µg for high-risk patients, as suggested in the EAACI guidelines [5].

Statistical Analysis

The variables are expressed as mean (SD), median (IQR), or as absolute and relative frequencies. Group comparisons regarding parameters of interest, for example, between different

Table 1. Demographic Data.[a]

	Visit 1 (n=1425): index sting	Visit 2 (n=1342): immunotherapy induction	Visit 3 (n=1186): maintenance phase
Age range (mean age), y	35-80 (52)	35-84 (54)	36-85 (55)
Sex, No. (%)			
Male	810 (56.8)	774 (57.7)	679 (57.3)
Female	615 (43.2)	568 (42.3)	507 (42.7)
Grade of SSR (index sting), No. (%)			
Grade I	122 (8.6)	–	–
Grade II	700 (49.1)	–	–
Grade III	589 (41.3)	–	–
Grade IV	14 (1.0)	–	–
Causal venom, No. (%)			
Bee	320 (22.5)	351 (26.2)	297 (25.0)
Vespid/*Vespa*/*Polistes*	838 (58.8)	924 (68.9)	832 (70.2)
Bee and vespid/*Vespa*/*Polistes*	206 (14.5)	67 (5.0)	57 (4.8)
Unknown	61 (4.3)	0 (0.0)	0 (0.0)

Abbreviations: SSR, systemic sting reaction.
[a]The percentages refer to the total number of observations. Age at visit 1 was the age at the index sting; age at visit 2 was the age when venom immunotherapy was started.

systemic sting reaction grades, were performed using the *t*, Mann-Whitney, or Fisher exact test. Percentages and ORs are reported with a 95%CI calculated using the Clopper–Pearson interval. A *P* value <.05 was considered statistically significant. All statistical analyses were performed using R Version 4.2.2 [25].

The sample size was calculated for the primary aim of this study, that is, to evaluate the safety of ACEIs and ß-blockers during VIT, as reported previously [21].

Results

Patients

From August 2014 until January 2018, a total of 1425 patients were included in the study: 330 of these patients were included in Austria, 41 in the Czech Republic, 68 in Germany, 254 in Italy, 269 in Poland, 279 in Slovenia, 44 in Spain, and 140 in Türkiye. The patients' demographic data are shown in Table 1.

Seventy-five patients refused VIT, and 8 patients were lost to follow-up; therefore, a total of 1342 patients attended visit 2. During the first year of VIT, a further 156 patients were lost to follow-up. Most patients returned to the clinics for the first annual check-up, and 1186 patients attended visit 3.

Initial Sting Reactions

Systemic sting reactions were predominantly moderate and severe: these were grade I in 122 cases (8.6%), grade II

Table 2. Location of Initial Sting Reactions.[a]

Location	Grade I and II	Grade III and IV	Overall
Head, No. (%)	199 (24.5)	155 (26.1)	354 (25.2)
Trunk, No. (%)	91 (11.2)	83 (14.0)	174 (12.4)
Upper extremities, No. (%)	257 (31.6)	193 (32.5)	450 (32.0)
Lower extremities, No. (%)	159 (19.6)	77 (13.0)	236 (16.8)
Several locations, No. (%)	26 (3.2)	27 (4.5)	53 (3.8)
Unknown, No. (%)	81 (10.0)	59 (9.9)	140 (10.0)

[a]Missing data are not explicitly stated in the table.

Table 3. Treatment of Systemic Sting Reactions.[a]

	Grade I	Grade II	Grade III	Grade IV	Total
No treatment, No. (%)	12 (10.6)	52 (8.6)	37 (6.9)	0 (0.0)	101 (7.9)
Antihistamines and/or corticosteroids, No. (%)	91 (80.5)	388 (63.8)	225 (41.8)	0 (0.0)	704 (55.4)
Epinephrine, No. (%)	10 (8.9)	168 (27.6)	276 (51.3)	12 (100.0)	466 (36.7)

[a]Missing data are not explicitly stated in the table.

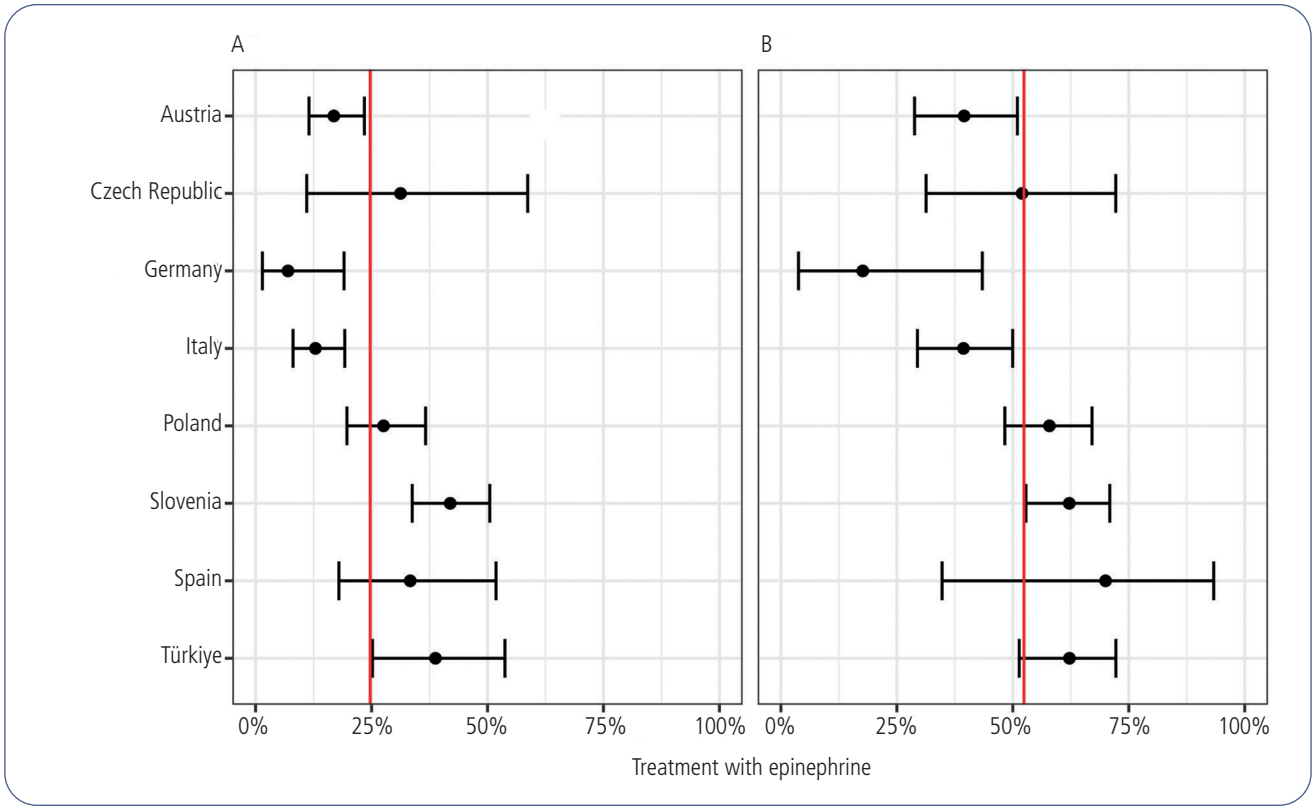

Figure 1. Frequency of epinephrine use in participating countries: 24.7% of grade I and II reactions were treated with epinephrine (A) compared to 52.4% of grade III and IV reactions (B) (vertical red lines). In the Czech Republic, Germany, and Slovenia only 1 center each participated in the study.

in 700 (49.1%), grade III in 589 (41.3%), and grade IV in 14 (1.0%). The median time span between the sting and the onset of symptoms was 6.5 (5.00-15.00) minutes. Onset of severe reactions, such as loss of consciousness or cardiac arrest, was after a median of 5 (3-10) minutes; the median time to onset of skin symptoms, such as flush, urticaria, and angioedema, was 10 (5-15) minutes (P<.001). In 1166 patients (81.8%), initial sting reactions occurred after only 1 sting, while 243 patients (17.1%) had multiple stings.

Stings on the head and neck did not cause more severe reactions (grades III and IV): 26.1% of patients with severe systemic sting reactions were stung on the head, compared to 73.9% stung on other parts of the body (14.0% on the trunk, 32.5% on the upper extremities, 13.0% on the lower extremities, and 14.4% at unknown and several locations [Table 2]).

While stings on the trunk and upper extremities did not cause severe reactions more frequently (P=.120 and P=.729, respectively), stings on the lower extremities caused significantly more frequent mild reactions (grades I and II). The relative frequency of severe SSRs on the lower extremities and at other sites was 32.6% and 44.2%, respectively (OR, 0.61; 95%CI, 0.45-0.83; P=.001).

Antihistamines and corticosteroids were the treatment of choice for mild SSRs and were used to treat 80.5% of grade I reactions and 63.8% of grade II reactions (Table 3). Epinephrine was administered significantly more frequently with the severity of the reaction (24.7% of grade I and II reactions and 52.4% of grade III and IV reactions; P<.001). Differences concerning the frequency of epinephrine use were detected between the participating countries: in Austria, Germany, and Italy, epinephrine was less commonly used to treat both mild and severe SSRs (Figure 1).

Systemic AEs During the Up-dosing Phase

In total, 93 patients (7.0%) who underwent VIT experienced systemic AEs, which were generally mild to moderate. Only 1 patient experienced a grade III reaction (flush and bronchospasm). Most systemic AEs occurred within the first 30 minutes of the injection (64.8%), after between 10 µg and 50 µg of venom preparation (60.9%). Systemic AEs were less frequently treated with antihistamines, corticosteroids, or epinephrine than initial systemic sting reactions (Table 4), and 50.0% of grade I reactions and 31.6% of grade II reactions were not treated. The treatment of choice for grade I reactions and the only grade III reaction was antihistamines and/or corticosteroids, while most of the grade II reactions were treated with epinephrine.

Interestingly, the frequency of epinephrine for the treatment of grade I and II reactions was clearly above average in Slovenia (62.5%) (Figure 2).

Systemic AEs During the Maintenance Phase

Twenty patients (1.4%) had a systemic AE to VIT during the first year of the maintenance phase: 7 patients had a grade I reaction, 9 patients a grade II reaction, and 4 patients a grade III reaction. Two patients with grade III reactions developed bronchospasm; the other 2 lost consciousness. Interestingly, all patients with grade III reactions were treated with bee venom. The median time between the systemic AE and the end of the up-dosing phase was 10 weeks (minimum and maximum, 1 and 41). In total, 14 patients (70.0%) were treated (Table 5).

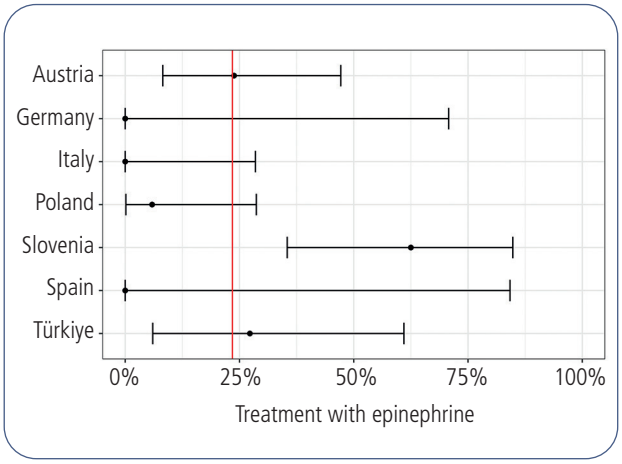

Figure 2. Frequency of epinephrine to treat grade I and II reactions during up-dosing.

Table 4. Treatment of Systemic Adverse Events During Up-dosing.[a]

	Grade I	Grade II	Grade III	Total
No treatment, No. (%)	26 (50.0)	12 (31.6)	0 (0.0)	38 (41.8)
Antihistamines and/or corticosteroids, No. (%)	20 (38.5)	11 (28.9)	1 (100.0)	32 (35.2)
Epinephrine, No. (%)	6 (11.5)	13 (34.2)	0 (0.0)	19 (20.9)
Other treatment, No. (%)	0 (0.0)	2 (5.3)	0 (0.0)	2 (2.2)

[a]Most of the patients were treated with antihistamines, corticosteroids, or epinephrine. Two patients were treated with ipratropium bromide/fenoterol hydrobromide and benzodiazepine and ipratropium bromide, respectively. The drug was not recorded in an additional 2 patients. Missing data are not explicitly stated in the table.

Table 5. Treatment of Systemic Adverse Events During the Maintenance Phase.

	Grade I	Grade II	Grade III	Total
No treatment, No. (%)	3 (42.9)	2 (12.5)	1 (40.0)	6 (30.0)
Antihistamines and/or corticosteroids, No. (%)	4 (57.1)	5 (62.5)	0 (0.0)	9 (45.0)
Epinephrine, No. (%)	0 (0.0)	2 (25.0)	3 (60.0)	5 (25.0)

Grade I and II reactions were solely or mainly treated with antihistamines and/or corticosteroids, respectively, while grade III reactions were additionally treated with epinephrine.

Premedication

Premedication with oral antihistamines was taken by more than half of the patients (52.1%) during the up-dosing phase (Table 6). Loratadine and desloratadine were the most frequently used agents, followed by cetirizine and levocetirizine. Taking antihistamines as premedication had no statistically significant effect on the frequency of systemic AEs (*P*=.106); however, the LLRs were significantly less frequent in patients taking premedication than in those who were not (23.5% vs 29.3%; *P*=.021) (Table 7).

During the maintenance phase, premedication was taken by only 19.7% of patients. Of the 20 patients who had a systemic AE during the first year of the maintenance phase, 11 had taken premedication. Thirty-five patients had an LLR, and of these, 15 had taken premedication. Taking antihistamines had no influence on the frequency of skin symptoms (flush, urticaria, and angioedema) or during the up-dosing phase (*P*=.891) or maintenance phase (*P*=.197).

Oral antihistamines are prescribed as premedication on a center-by-center basis and not following a national protocol: the patients of 6 centers never took antihistamines during the up-dosing phase, while all the patients from the other 4 centers (respectively in Austria, Poland, Spain, and Türkiye) took antihistamines during the up-dosing and maintenance phases. In Slovenia, all patients took antihistamines during the up-dosing phase, but none did so during the maintenance phase. In all the other centers, premedication was less commonly administered during the maintenance phase than during the up-dosing phase.

Venom Preparation

Bee venom is generally obtained by electrostimulation, whereas vespid venom is obtained by venom sac extraction. Venom preparations from Anallergo SpA are obtained by capillary extraction. All purified venom preparations were from ALK-Abelló AS, while most nonpurified preparations were obtained from HAL Allergy Holding B.V., followed by ALK-Abelló, Stallergenes Greer International AG, and Allergy Therapeutics Ltd.

The study centers in the Czech Republic, Germany, Spain, and Türkiye used solely preparations from ALK-Abelló, while the other centers used venom preparations from at least 2 different companies.

Aqueous preparations, both purified and nonpurified, were preferred for up-dosing, while depot preparations were the first choice for the maintenance phase (Table 8 and Online Supplement 1).

The type of venom preparation did not affect the frequency of systemic AEs during up-dosing. AEs were recorded in 18 patients (5.6%) treated with purified depot preparations, 23 patients (7.7%) treated with purified aqueous preparations, and 51 patients (7.6%) treated with nonpurified aqueous preparations (*P*=.258).

Table 6. Use of Premedication During the Up-dosing and Maintenance Phases.

	Visit 2 (up-dosing phase)	Visit 3 (maintenance phase)
No premedication, No. (%)	643 (47.9)	953 (80.4)
Cetirizine-levocetirizine, No. (%)	140 (10.4)	90 (7.6)
Loratadine-desloratadine, No. (%)	435 (32.4)	98 (8.3)
Dimetindene, No. (%)	45 (3.4)	0 (0.0)
Other antihistamines, No. (%)	79 (5.9)	45 (3.8)

Table 8. Venom Preparations Used During the Up-dosing and Maintenance Phases.

	Visit 2 (up-dosing)	Visit 3 (maintenance)
Purified depot preparation, No. (%)	326 (24.4)	675 (60.0)
Purified aqueous preparation, No. (%)	305 (22.8)	9 (0.8)
Nonpurified depot preparation, No. (%)	34 (2.5)	62 (5.5)
Nonpurified aqueous preparation, No. (%)	671 (50.2)	379 (33.7)

Table 7. Impact of Premedication on the Frequency of Systemic Adverse Events and Large Local Reactions During the Up-Dosing Phase of Venom Immunotherapy.

	No premedication	Premedication	OR (95%CI)	*P* Value
Systemic adverse event, No. (%)				
No	606 (94.2)	634 (91.9)	1.45 (0.92-2.29)	.106
Yes	37 (5.8)	56 (8.1)		
Large local reaction, No. (%)				
No	454 (70.7)	520 (76.5)	0.74 (0.58-0.96)	.021
Yes	188 (29.3)	160 (23.5)		

The frequency of LLRs, on the other hand, was significantly increased when aqueous preparations were used: these affected 77 patients (24.1%) treated with purified depot preparations, 138 patients (46.5%) treated with purified aqueous preparations, 129 patients (19.3%) treated with nonpurified aqueous preparations, and 1 patient (2.9%) treated with a nonpurified depot preparation. The probability of developing an LLR was 2.7 times higher for patients treated with purified aqueous preparations than for patients treated with purified depot preparations (OR, 2.73; 95%CI, 1.94-3.86; *P*<.001).

Effectiveness of VIT

The effectiveness of VIT is monitored based on the outcome of sting challenges or field stings. In total, 210 patients (17.7%) were stung: sting challenges were performed in 18 patients, and 192 patients experienced field stings within the first year of the maintenance phase. Most patients (91.0%) tolerated the sting without developing systemic symptoms.

Eighteen SSRs occurred after field stings: 11 patients experienced a grade I reaction, 5 patients had a grade II reaction, and 2 had a grade III reaction. These reactions were treated primarily with antihistamines and corticosteroids; 7 patients (38.9%) used their prescribed epinephrine autoinjector. Only 1 systemic reaction occurred after a sting challenge: the patient experienced a grade I reaction with general fatigue and a feeling of warmth 10 minutes after the sting.

Taking antihistamines as premedication had no influence on the effectiveness of VIT: 7 patients (8.3%) who had taken premedication had a systemic reaction after a field sting or sting challenge, compared to 12 patients (9.5%) not taking antihistamines as premedication (OR, 0.86; 95%CI, 0.28-2.51; *P*=.812).

Similarly, the type of venom preparation used for the maintenance phase did not influence the effectiveness of VIT: 11 patients (10.2%) who were treated with purified venom preparations did not tolerate a sting, compared to 7 patients (8.3%) treated with nonpurified venom preparations (OR, 1.25; 95%CI, 0.42-3.98; *P*=.804).

Discussion

All the venom preparations used in the present study were equally effective and caused similar frequencies of systemic AEs. However, the risk of developing LLRs was 2.7 times higher for patients treated with purified aqueous preparations than for patients treated with purified depot preparations. Aqueous preparations have been shown to cause LLRs more frequently [12,13,26].

Unexpectedly, the frequency of LLRs was higher in patients treated with purified aqueous preparations than in patients treated with nonpurified aqueous preparations in our study. Contradictory results were reported by Bilò et al [27] for bee venom immunotherapy: purified aqueous preparations resulted in fewer systemic AEs and smaller local reactions than nonpurified preparations using the same rush protocol. The superiority of purified aqueous and/or purified depot preparations over nonpurified aqueous extracts in terms of safety (fewer LLRs) has also been reported elsewhere [28-31]. Therefore, we do not have an explanation for our conflicting results.

The major reason for fewer LLRs with purified venom preparations is the absence of peptides and active amine components: purified venom extracts do not contain low-molecular-weight components, such as vasoactive amines, and comprise only a reduced concentration of small peptides, which are present in native venom extracts [27]. Another reason for fewer LLRs after depot preparations is the fact that allergens adsorbed to substances such as aluminum hydroxide or tyrosine are released slowly from the injection site [29,30,32].

In 2001, it was reported that the switch from aqueous to depot extracts for VIT occurred almost exclusively in German-speaking European countries [30,33]. This assumption has changed over the years, since depot preparations in our European multicenter study were used not only in German-speaking countries but also in Italy, Poland, and the Czech Republic. In Türkiye, the only venom extract available for VIT was a purified depot preparation. However, given that most patients were treated using rush, cluster, or ultrarush up-dosing protocols, more than 70% were treated with aqueous preparations, which are commonly used for these dosing regimens. In the present study, quicker up-dosing protocols (conventional vs rush, cluster, and ultrarush) did not cause more frequent systemic AEs during VIT, although LLRs were more frequent when quicker up-dosing protocols were used [21]. Systemic AEs appear to occur more frequently in patients on rush VIT [13], and rapid dose increase has been established as a risk factor for systemic reactions [8,9]. Rueff et al [13] also concluded that the aluminum hydroxide–adsorbed bee venom preparation caused fewer LLRs than the aqueous preparation, although different up-dosing protocols were used for the various venom preparations.

Depot preparations were generally used in up-dosing phases lasting up to 16 weeks. However, this is time-consuming and unacceptable for Hymenoptera venom–allergic patients, who need immediate protection. Two safe and efficient up-dosing protocols using aluminum hydroxide–adsorbed venoms for 7-week up-dosing have been reported since 2019 [34,35].

All venom preparations used in the present study were equally effective, as indicated by the outcome of field stings and sting challenges, consistent with other reports [13,28,29,36,37]. Furthermore, pretreatment with antihistamines did not negatively influence the effectiveness of VIT [15,38], as confirmed by the results of the present study.

Several studies have shown that pretreatment with H1 antihistamines reduces the number of local as well as systemic reactions [15,16,19,20]. While the number of systemic AEs, especially cutaneous reactions, decreased significantly with levocetirizine, local reactions and cutaneous systemic AEs occurred less frequently during the up-dosing phase of bee VIT [15] with fexofenadine-based pretreatment [16]. In the present study, more than half of the patients took antihistamines as pretreatment during up-dosing. Loratadine and desloratadine were the most frequently used, followed by cetirizine and levocetirizine. The frequency of systemic AEs was not reduced, and we did not even detect a positive effect on the frequency of systemic skin symptoms. However, the number of LLRs was significantly lower in patients taking premedication than in those who were not.

Antihistamines, together with corticosteroids, have also been the treatment of choice for mild SSRs. Even though SSRs were predominantly moderate and severe, only 8% of all reactions were treated with antihistamines, corticosteroids, or epinephrine. The median time between the sting and the appearance of mild systemic reactions was 10 minutes, while severe SSRs occurred as soon as after 5 minutes. As expected, stings in the head and neck region did not cause more severe reactions, in contrast with data reported elsewhere [39,40]. However, stings in the lower extremities caused milder reactions significantly more frequently in our study cohort. Systemic AEs usually occurred within 30 minutes of injection and after 10-50 μg of venom preparation. In previous studies, most systemic AEs occurred after 40-60 μg of venom [17,34], consistent with our findings.

The present analysis has 2 main limitations. First, the study was designed primarily to assess whether taking β-blockers and ACEIs affected the frequency of systemic AEs during VIT. Therefore, as the sample size was not calculated to show these effects, the results for the secondary endpoints must be interpreted with caution. Second, it has been reported that both quicker up-dosing protocols and aqueous venom preparations more frequently cause AEs, especially LLRs. However, given that aqueous preparations are preferred for rush, cluster, and ultrarush protocols, the present study cannot generate sufficient evidence, since various preparations were used in the up-dosing protocols and some dosing regimens were based on more than 1 venom preparation.

The safety profile of VIT is a relevant issue, and considerable differences in safety and efficacy have been reported in the past, for several reasons. The strength of recommendations concerning risk factors and the management of AEs in the current EAACI guidelines are often weak, since only case series or case reports are available [5]. The present prospective multicenter study, with 1425 patients, clearly shows that taking β-blockers and ACEIs does not increase the frequency of systemic AEs during VIT [21] and that all venom preparations used were equally effective, with none proving superior to the others in terms of the frequency of systemic AEs. Pretreatment with oral antihistamines during VIT significantly reduced the frequency of LLRs. The potentially higher frequency of LLRs with aqueous preparations for rapid up-dosing can be reduced by using antihistamines as pretreatment. Depot preparations are commonly used and well tolerated during the maintenance phase. Owing to the similar frequency of systemic AEs, quicker up-dosing protocols are preferred, since patients are protected much faster from future systemic sting reactions.

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Conflicts of Interest

Dr Alfaya reports payment of honoraria as a speaker from Roxall, outside the submitted work. Dr Antolín-Amérigo reports the following: grants from Sociedad Española de Alergología e Inmunología Clínica (SEAIC); consulting fees from ALK-Abelló, AstraZeneca, Chiesi, and Gebro; and speaker fees from AstraZeneca, Chiesi, Gebro, GSK, Leti Pharma, Mundipharma, Novartis, Roxall, and Sanofi, outside the submitted work. Dr Hawranek reports personal fees from ALK-Abelló, personal fees from Novartis, personal fees from Takeda, and personal fees from Sanofi, outside the submitted work. Dr Lang reports travel support from Bencard, travel support from ALK-Abelló, and travel support from Thermo Fisher Scientific, outside the submitted work. Dr Trautmann reports personal fees from ALK-Abelló, outside the submitted work. Dr Vachová reports personal fees from ALK-Abelló, personal fees from AstraZeneca, and personal fees from Takeda, outside the submitted work. Dr Sturm reports grants from ALK-Abelló, personal fees from ALK-Abelló, personal fees from Allergopharma, personal fees from Novartis, personal fees from Mylan, personal fees from Stallergenes-Greer, and personal fees from Bencard, outside the submitted work. The remaining authors declare that they have no conflicts of interest.

Previous Presentations

Parts of the manuscript were presented as a poster at the EAACI Congress 2023.

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Gunter Sturm

Department of Dermatology and Venereology
Medical University of Graz
Auenbruggerplatz 8
8036 Graz, Austria
E-mail: gunter.sturm@medunigraz.at