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Simultaneous up-dosing of bee and vespid venom immunotherapy is safe

To the editor,

Venom immunotherapy (VIT) is generally safe and prevents almost all patients from further systemic sting reactions. In recent studies, objective systemic adverse events (AE) were reported in 2.7 to 17.8% of patients.[1-3] It is well known that systemic AEs occur more frequently during the up-dosing phase of bee VIT compared with vespid VIT.[1,4,5] However, the rate of AEs was usually analyzed in mono-venom immunotherapy or in stepwise dual immunotherapy maintaining a 30-min interval between the injections of venom. A systematic literature research for the EAACI guidelines on venom immunotherapy detected no study comparing the safety of simultaneously injected dual VIT with mono-VIT. Therefore, recommendations on dual VIT in the recently published EAACI guidelines are based on expert consensus only.[6]

This prompted us to retrieve and retrospectively analyze data of 650 patients from our database of hymenoptera venom allergic patients. All of them visited our outpatient clinic in the time from May 2010 to July 2017, have had systemic sting reactions in the past, and were treated with VIT. The institutional review board of the Medical University of Graz approved this database (approval no. 25.-465 ex 12/13), and all patients have signed an informed consent form. The therapeutic venom was selected following our routine diagnostics with specific IgE determination, skin testing (prick and intradermal tests), and in some patients also with basophil activation testing (BAT). If a simultaneous bee and vespid VIT was started, the venoms were injected simultaneously, one venom in each upper arm. Only if a systemic AE occurred during the up-dosing phase, venoms were administered time-shifted, usually 30 minutes apart. The frequency of systemic AEs during up-dosing was compared between patients with bee VIT, vespid VIT, and simultaneous bee and vespid VIT. A systemic AE was defined as an anaphylactic reaction grade I or higher according to Ring and Messmer[7] after administering VIT. The up-dosing protocol was chosen by the patients and was either: (a) conventional, outpatient: 15 injections with 7- to 14-day intervals, (b) accelerated conventional, outpatient: 8 injections with 7- to 14-day intervals, (c) rush: multiple injections on 4 consecutive days on an inpatient setting, followed by 2 injections, 7 and 14 days apart, or (d) cluster: multiple injections in 2 days, which are 1 week apart, followed by 3 injections, each 14 days apart. While depot preparations have been used for the conventional and accelerated conventional up-dosing protocol, aqueous preparations have been used when the rush or cluster protocol was chosen.

Ninety-two patients were treated with bee venom, 435 with vespid venom, and 123 simultaneously with bee and vespid venom; the rate of systemic AEs was 10.9%, 6.4%, and 10.6%, respectively. Some of the patients experienced more than one systemic AE (see Table 1 for further demographic data and Online Table S1 for demographic data listed separately for each up-dosing protocol). All systemic AEs, except one, occurred when administering 20 µg or more of therapeutic venom, most of them at 50 µg or more. There were three grade III reactions, with one reaction in each treatment group: syncope (vespid and bee VIT), nausea, and emesis (vespid VIT) or tachycardia, angioedema, and bronchospasm (bee VIT); all other patients had milder reactions.

The rate of AE during simultaneous VIT was almost identical with that of bee VIT (P = 1.000). Both groups did not differ significantly in age, sex, concomitant antihypertensive medication (either angiotensin-converting enzyme (ACE)—inhibitors, beta blockers, and/or angiotensin receptor blockers (ARB)), up-dosing protocol, grade of initial systemic sting reaction, tryptase levels, and grade of the systemic AE (see Table 1). Compared to bee VIT and simultaneous VIT, systemic AEs were less frequent during vespid VIT, although this was not statistically significant (P = .164). The frequency of large local reactions (LLR) at the injection site was similar in patients treated with bee, vespid, and both venoms, with slightly more LLR in patients with dual VIT (10.9%, 11.0%, and 14.6%, respectively). However, the difference was not statistically significant (P = .530).

In conclusion, no differences regarding systemic AE and LLR between mono-VIT and dual VIT could be found in this retrospective data analysis. Furthermore, the rate of systemic AEs in our mono-VIT groups did not differ from previous published data.[1-3] Although the number of included patients with dual VIT is limited, our data suggest that systemic and local AEs are not more frequently seen in patients simultaneously receiving bee and wasp venoms. For prospective studies, two methodological approaches are possible: (a) a non-inferiority approach with one-sided testing to demonstrate that dual VIT does not cause more side effects, or (b) a randomized trial comparing patients with simultaneously injected venoms and stepwise dual immunotherapy. For both approaches, multi-center studies with a large number of patients are required.

Taken together, our data indicate that simultaneous VIT is safe and timesaving and may therefore be another step to enhance patient adherence. However, prospective multi-center studies with sample size estimation and larger patient numbers are needed for future guidelines.

TABLE 1 Demographic data of included patients and comparison of VIT groups

	Bee venom (N = 92)	Vespid venom (N = 435)	Bee and vespid venoms (N = 123)	Bee vs vespid VIT (p-value)	Bee vs double (bee and vespid) VIT (p-value)	Vespid vs double (bee and vespid) VIT (p-value)
Age range (mean age) [years]	12-74 (40)	9-77 (48)	16-87 (42)	0.008	0.334	0.048
Sex	Female 45 (48.9%)	Female 216 (49.7%)	Female 56 (45.5%)	0.909	0.679	0.475
Concomitant medication with ACE inhibitors, beta blockers, and/or ARB	9 (9.9%)	52 (11.9%)	15 (12.2%)	0.551	0.601	0.944
Up-dosing protocol	Cluster 56 (60.9%) Rush 22 (23.9%) Conventional 2 (2.2%) Accelerated conventional 12 (13.0%)	Cluster 238 (54.7%) Rush 124 (28.5%) Conventional 22 (5.1%) Accelerated conventional 51 (11.7%)	Cluster 70 (56.9%) Rush 45 (36.6%) Conventional 7 (5.7%)	0.362	0.958	0.138
Grade of initial sting reaction according to Ring and Messmer[7]	Grade I 5 (5.4%) Grade II 60 (65.2%) Grade III 26 (28.3%) Grade IV 1 (1.1%)	Grade I 17 (3.9%) Grade II 268 (61.6%) Grade III 144 (33.1%) Grad IV 5 (1.1%)	Grade I 1 (0.8%) Grade II 75 (61.0%) Grade III 45 (36.6%) Grade IV 2 (1.6%)	0.329	0.080	0.226
Elevated tryptase levels (>11.4 µg/l)	4 (4.3%)	24 (5.5%)	13 (10.6%)	0.802	0.128	0.062
Large local reactions	10 (10.9%)	48 (11.0%)	18 (14.6%)	1.000	0.540	0.342
Systemic AEs (grading according to Ring and Messmer[7])	10 (10.9%) Grade I 6 (6.5%) Grade II 3 (3.3%) Grade III 1 (1.1%)	28 (6.4%) Grade I 18 (4.1%) Grade II 9 (2.1%) Grade III 1 (0.2%)	13 (10.6%) Grade I 6 (4.9%) Grade II 6 (4.9%) Grade III 1 (0.8%)	0.179	1.000	0.168
Multiple systemic AEs	4 (4.3%)	5 (1.1%)	1 (0.8%)	0.054	0.167	1.000

Abbreviations: ACE, angiotensin-converting enzyme; AE, adverse event; ARB, angiotensin receptor blocker; VIT, venom immunotherapy.

CONFLICTS OF INTEREST

GJ Sturm reports consulting and lecture fees from Novartis, Bencard, Stallergenes, HAL, Allergopharma, and Mylan outside of the submitted work. U Cerpes reports fees from Mylan outside of the submitted work.

Urban Čerpes[1]
Lisa Arzt-Gradwohl[1]
Christoph Schrautzer[1]
Lukas Koch[1]
Danijela Bokanovic[1]
Karin Laipold[1]
Patrik Tripolt[1]
Barbara Binder[1]
Gunter J. Sturm[1,2]

[1]*Department of Dermatology and Venereology, Medical University of Graz, Graz, Austria*
[2]*Allergy Outpatient Clinic Reumannplatz, Vienna, Austria*

Correspondence
Gunter J. Sturm, Department of Dermatology and Venereology, Medical University of Graz, Auenbruggerplatz 8, 8036 Graz, Austria.
Email: gunter.sturm@medunigraz.at

ORCID

Lisa Arzt-Gradwohl https://orcid.org/0000-0002-5489-2070
Gunter J. Sturm https://orcid.org/0000-0002-7245-121X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.