A safe and efficient 7-week immunotherapy protocol with aluminum hydroxide adsorbed bee venom

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Source of funding: This study was supported by the Austrian Science Fund (Grant-DOI: 10.55776/KLI836) and by an unrestricted grant from ALK Abelló, Hørsholm, Denmark.

Conflicts of interest: Dr. Sturm reports grants from ALK-Abelló, personal fees from ALK-Abelló, personal fees from Allergopharma, personal fees from Novartis, and personal fees

from Stallergenes-Greer, outside the submitted work. All other authors have no conflicts of interest to declare.

Keywords

accelerated up-dosing protocol; Hymenoptera venom allergy; sting challenge; systemic reaction; depot bee venom immunotherapy;

To the Editor:

Systemic anaphylactic reactions to Hymenoptera stings are reported to occur in 3.3% of the general Austrian population. Therapy adherence remains a significant challenge[1], despite the proven efficacy of venom immunotherapy (VIT) as a causal treatment. VIT provides protection from future systemic sting reactions (SSR) in 77–84% of patients treated with honeybee venom and 91–96% of those treated with vespid venom. [2]

Adverse events (AE) are usually rare and mild, and symptoms occur in only 4.3-11.4% of patients during up-dosing. [3] A variety of therapy regimes exists for the up-dosing phase, from conventional to rush and ultrarush or clustered protocols. [2]. Current conventional protocols are still time-consuming for patients. Therefore, we initiated a prospective clinical trial (EudraCT 2015-002769-44) evaluating the safety and efficacy of an accelerated up-dosing protocol with 8 weekly injections in 7 weeks using the purified depot preparation Alutard SQ® bee venom (ALK Abelló, Hørsholm, Denmark). External monitoring was performed during the clinical trial for the purpose of quality assurance.

Seventy-six patients aged 18-70 years with a history of a SSR to bee stings (≥ grade I, classification of Ring and Messmer[4]) were included (details see supplementary material S1). To demonstrate VIT efficacy, sting challenges with living bees (*Apis mellifera*) were performed, whenever possible, already one week after reaching the maintenance dose.

Two patients withdrew from the study at their request. Venom immunotherapy could not be initiated in one patient due to a medical contraindication, while the remaining 73 patients successfully completed the up-dosing phase. Seven patients (9.6%, CI 0.00-18.76) showed objective symptoms which were mild to moderate, and two (2.7%, CI 0.00-9.55) additional patients developed subjective systemic reactions (SR; see Table 1 and 2). Nineteen patients (26.0%) experienced large local reactions (LLR; see Table 1), the majority just once or twice. Elevated (>11.4µg/L) tryptase levels (p=0.330), age >40 years (p>0.999), the prevalence of

cardiovascular diseases (p=0.636) or antihypertensive treatment (p>0.999) were not related to the occurrence of SR.

Six patients (8.2%) experienced field stings from bees during the up-dosing phase; one of them developed an exanthema and palmar pruritus ten minutes after the sting, all others tolerated the sting. A total of 71 sting challenges were conducted after patients reached the maintenance dose, with 56 patients (78.9%) successfully tolerating the sting. Fifty-six patients returned to the clinic for the first annual check-up. Three patients (5.4%) reported a SR after VIT during the first year of the maintenance phase, exhibiting both, subjective and objective symptoms. Twenty-two patients (39.3%) reported field stings, all without any systemic sting reaction.

Adverse events appear to occur less frequently during up-dosing in conventional protocols compared to faster protocols.[2] However, reaching the maintenance dose in conventional protocols takes a considerable amount of time, leaving patients potentially unprotected for several months. Our objective was to achieve an optimal balance between rapid up-dosing and safety, with a strong emphasis on the latter. Notably, only 9.6% of patients in our study cohort experienced objective systemic adverse events during the up-dosing phase.

In the meantime, our published protocol for vespid venom has also been applied to bee venom by another group, though only in 16 patients. [5] Additionally, rush and cluster protocols using depot extracts have been published. [6,7] A common limitation of all these studies is that their design is underpowered to thoroughly evaluate the safety of bee venom immunotherapy. Moreover, our study is the only one to demonstrate efficacy through controlled sting challenges rather than relying on field sting evaluations. After reaching the maintenance dose of 100 µg, 78.9% of our patients tolerated the sting, aligning with the expected efficacy range of 77–84%. Our study demonstrated in a substantial cohort of bee venom-allergic patients that the 7-week outpatient protocol is safe and effective. This will, hopefully, result in improved acceptance of VIT.

Tables

Table 1: Demographic data and medical history (n=75) as well as frequency of adverse events (large local and systemic reactions) during up-dosing and maintenance phases.

Age range (median age) [years]	18-69 (37)
Sex	
- male	33 (44.0%)
- female	42 (56.0%)
Antihypertensive treatment	8 (10.7%)
- ACE inhibitor	4 (5.3%)
- Beta-blocker	5 (6.7%)
- ACE-inhibitor and beta-blocker	1 (1.3%)
Grade of SR (index sting) *	
- I°	10 (13.3%)
- II°	52 (69.3%)
- III°	13 (17.3%)
- IV°	0 (0.0%)
Up-dosing phase (n=73)	
- no side effect	49 (67.1%)
- large local reaction	19 (26.0%)
- objective systemic symptoms	7 (9.6%)
- only subjective systemic symptoms	2 (2.7%)
Sting challenge test (n=71)	
- sting tolerated	56 (78.9%)
- systemic reaction after sting	15 (21.1%)

*according to the classification of Ring & Messmer[4]

Table 2: Objective, **s**ystemic reactions during the up-dosing phase of venom immunotherapy.

Patient ID	Age	Sex	Reactions (n)	Grade*	Objective symptoms	Dose of last injection [µg]	Symptoms	Treatment
52	47	female	2	II; II	no	10; 60	vertigo; vertigo, globus sensation	oral antihistamine (2nd reaction)
72	37	male	3	I; I; I	no	5; 20; 40	paresthesia palmar/plantar (all three times)	no
19	39	female	1	I	yes	60	urticaria, pruritus	no
35	59	male	1	I	yes	40	flush	oral antihistamine
38	31	female	2	II; II	yes	1; 5	vertigo; vertigo, nausea, angioedema	antihistamine intravenous (2nd reaction)
47	24	female	1	II	yes	40	abdominal cramping, shivering, cold sweating	antihistamine (oral and iv.),metamizol-natrium, butylscopolamin, NaCl
53	48	female	1	I	yes	100	palmar pruritus and erythema	oral antihistamine
54	31	female	2	I; I	yes	60; 100	palmar pruritus and erythema; palmar pruritus and erythema, urticaria	oral antihistamine; oral antihistamine and corticosteroid iv.
61	64	male	1	I	yes	20	flush	oral antihistamine

*according to the classification of Ring & Messmer[4]

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The study was approved by the ethics committee of the Medical University of Graz (approval no. 27-405 ex 14/15) and all patients gave their written, informed consent.

Confirmation of sensitization

Sensitization was confirmed by IgE determination (ImmunoCAP® system, Thermo Fisher Scientific, Waltham, MA, USA), intradermal tests (0.02mL of 0.01, 0.1 and 1 μg/mL) and prick-tests (10, 100, 300 μg/mL solutions). The basophil activation test (Bühlmann Laboratories, Schönenbuch, Switzerland) helped to distinguish between bee and vespid venom allergy in patients with equivocal history and test results. Tryptase levels were determined using the ImmunoCAP® system.

Venom immunotherapy

During the up-dosing phase, patients were treated with oral non-sedative antihistamines (histamine (H1) receptor blockers) one hour before injection. The purified depot preparation Alutard SQ® bee venom (ALK-Abelló, Hørsholm, Denmark) was administered with an initial dose of 1μg followed by 5, 10, 20, 40, 60, 80 and 100μg corresponding to 1.000, 5.000, 10.000, 20.000, 40.000, 60.000, 80.000, and 100.000 SQ at one-week-intervals by single injections (injection interval: 7 to a maximum of 14 days).

The maintenance phase required single injections every 4-6 weeks with 100μg. All patients were observed for 30 minutes after receiving treatment.