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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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

To the Editor,

Systemic anaphylactic reactions to Hymenoptera stings are reported to occur in 3.3% of the general Austrian population. Although field stings could be life-threatening for patients with insect venom allergy and despite the availability of venom immunotherapy (VIT) as an effective causal treatment, poor therapy adherence has been observed in our country.[1]

Venom immunotherapy is effective in 77%-84% of patients treated with honeybee venom and in 91%-96% of patients receiving vespid venom.[2] Adverse events are usually rare and mild, and symptoms occur in only 4.3%-11.4% of patients during the up-dosing.[3]

A variety of therapy regimes exists for the initial phase, from conventional to rush and ultrarush or clustered modalities.[2] Although several attempts have been made to shorten protocols for the up-dosing phase of immunotherapy, no prospective clinical trials have been performed recently. Current conventional protocols are still time-consuming for patients and, together with the poor therapy adherence, point to the need for further efforts to enhance the acceptance of this successful treatment. We therefore initiated a prospective clinical trial (EudraCT 2015-002769-44) evaluating an up-dosing protocol with 8 weekly injections in 7 weeks regarding efficacy and safety. The aim of the study was to develop a rapid and safe protocol that meets the requirements of the regulatory authorities to provide an official up-dosing protocol for the Summary of Product Characteristics (SmPC) for the depot *Vespula* venom, Alutard SQ®, ALK Abelló.

Seventy-six legally competent male and female subjects aged 18 to 70 years with a history of a systemic sting reaction to vespid stings (≥grade I according to the classification of Ring and Messmer)[4] were included. The study was approved by the ethics committee of the Medical University of Graz (approval no. 27-405 ex 14/15). External monitoring was performed during the clinical trial for the purpose of quality assurance. Sensitization was confirmed by IgE determination (ImmunoCAP® system, Thermo Fisher Scientific), intradermal tests (0.02 mL of 0.01, 0.1 and 1 μg/mL) and prick tests (10, 100, 300 μg/mL solutions). The basophil activation test (Bühlmann Laboratories) helped to distinguish between bee and vespid venom allergy in patients with equivocal history and test results (see Table S1), and only patients with mono-sensitization to vespid venom were included in the study. 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® vespid venom (ALK-Abelló) was administered with an initial dose of 1 μg followed by 5, 10, 20, 40, 60, 80, and 100 μg corresponding to 1.000, 5.000, 10.000, 20.000, 40.000, 60.000, 80.000, and 100.000 SQ at 1-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 100 μg. To demonstrate that immunotherapy is effective immediately after up-dosing, sting challenges with live vespids (*Vespula germanica* or *Vespula vulgaris*) were performed, whenever possible, one week after reaching the maintenance dose.

We registered one withdrawal from the study according to the patients' wish, the other 75 completed up-dosing without dose reductions. Only 3 (3.9%, one-sided exact 97.5% confidence interval [CI] 0.0-11.1) patients showed objective symptoms which were mild and limited to the skin, and 5 (6.6%, one-sided exact 97.5% CI 0.0-14.7) patients developed mostly mild and subjective systemic reactions (SR; see Tables 1 and 2). Twenty-two (28.9%)

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TABLE 1 Demographic data and medical history (n = 76) as well as frequency of adverse events (large local and systemic reactions) during up-dosing and maintenance phases

Age range (median age) (y)	19-70 (50)
Sex	
Male	43 (56.6%)
Female	33 (43.4%)
Antihypertensive treatment	10 (13.2%)
ACE inhibitor	3 (3.9%)
Beta blocker	5 (6.6%)
ACE inhibitor and beta blocker	2 (2.6%)
Grade of SR (index sting)[a]	
I°	3 (3.9%)
II°	56 (73.7%)
III°	16 (21.1%)
IV°	1 (1.3%)
Up-dosing phase (n = 76)	
No side effect	45 (59.2%)
Large local reaction	22 (28.9%)
Subjective systemic symptoms	5 (6.6%)
Objective systemic symptoms	3 (3.9%)
Maintenance phase (n = 67)	
No side effect	56 (83.6%)
Large local reaction	10 (14.9%)
Subjective systemic symptoms	1 (1.5%)
Objective systemic symptoms	0 (0.0%)

[a]According to the classification of Ring & Messmer.[4]

patients experienced large local reactions (LLR; see Table 1), the majority just once or twice. Elevated (>11.4µg/L) tryptase levels (P = .365), age >40 years (P = .604), the prevalence of cardiovascular diseases (P = 1.000), or antihypertensive treatment (P = .282) were not related to the occurrence of SR (demographic data see Table 1).

Four (5.3%) patients registered field stings with vespids during up-dosing, one of them developed mild paresthesia in the legs three minutes after the sting, all others tolerated the sting. In total, 73 sting challenges have been performed and all patients (100%) tolerated the sting challenge with live vespids. Thirty-one (42.5%) sting challenges were performed within the first two weeks after reaching the maintenance dose. Due to the lack of availability of wasps during the winter season, the remaining sting challenges had to be performed later, with a median of 14 weeks and a maximum of 95 weeks.

In total, 8 patients (10.7%) were lost to follow-up for the first annual check-up (latency 8 to 20 months to initial phase). We registered accidentally prolonged injection intervals in 11 patients (16.4%). Premedication was widely used (68.2%), but almost half of the patients took it irregularly (21 of 45 patients, 47.7%). Ten patients (14.9%) reported LLRs, and one patient (1.5%) a SR (see Table 1). This patient developed two episodes of laryngeal dyspnea 6 and 7 months after reaching the maintenance dose, each of them 15 minutes after a dosage of 100 µg with subsequent treatment by the doctor. After dose reduction and up-dosing again, all further injections were tolerated well. Fifteen patients (22.4%) reported field stings, all without any systemic sting reaction.

Adverse events appear to be less frequent in conventional protocols during the up-dosing phase compared to rush and ultrarush protocols.[2] However, patients may remain unprotected for months and it takes a considerable time to reach the maintenance dose. Our goal was to find a good balance between quick up-dosing and safety, with particular consideration of the latter. In an observational multicenter study in Spain, a 9-week outpatient protocol was evaluated in 55 patients and indicated a very good safety profile[5] while another study demonstrated that starting immunotherapy with 1µg was safe.[6] Therefore, we hypothesized that the 7-week protocol with a starting dose of 1µg should be well tolerated. Indeed, only 3 out of 76 (3.9%, one-sided exact 97.5% CI 0.0-11.1) patients exhibited objective systemic adverse events during up-dosing which is in the lower range of previously published protocols ranging from 3% to 25%.[3,7-9]

It is still a debated issue whether mastocytosis/elevated tryptase levels or antihypertensive treatment are risk factors for SR.[2] To obtain "real life data," we did not exclude patients with such potential risk factors and we did not identify any risk factor for the occurrence

TABLE 2 Systemic reactions during the up-dosing phase of venom immunotherapy

Patient ID	Age	Sex	Grade[a]	Objective symptoms	Dose of last injection (µg)	Symptoms	Treatment
2	53	Female	I	Yes	80	Pruritus, urticaria	Oral antihistamine
49	34	Female	I	Yes	60	Pruritus, exanthema	Oral antihistamine
75	43	Female	I	Yes	40	Urticaria	No
4	32	Male	I	No	40	Pruritus	No
27	25	Female	II	No	40	Vertigo	No
35	70	Male	I	No	100	Paresthesia (fingers)	No
58	60	Female	I	No	5	Tingling lips	No
61	60	Female	II	No	1	Vertigo, dysphagia, globus sensation	No

[a]According to the classification of Ring & Messmer.[4]

of SR. However, the small number of patients with adverse events may hamper statistical analysis.

Venom immunotherapy[10] and tolerated sting challenges during VIT[11] improve the health-related quality of life. For the first time, we could show that patients treated with vespid venom are protected one week after reaching the maintenance dose.

Our 7-week outpatient protocol proved to be safe and effective in patients pretreated with antihistamines and is practical as well as efficient in terms of time and costs for patients and medical staff, which will lead to a better patient acceptance of VIT. Furthermore, it could be applied not only in hospitals, but also in private practices and outpatient clinics.

CONFLICT OF INTEREST

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