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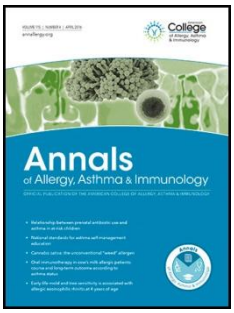


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# Evaluation of the safety of a protocol for switching venom immunotherapy products

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**IV**: Intravenous
**VIT**: Venom immunotherapy

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Venom immunotherapy (VIT) in patients allergic to hymenoptera stings is clearly acknowledged as effective and safe. Safety, in particular, is a pivotal issue that requires the use of standardized products and well-established protocols for the build-up and maintenance phases of VIT[1].

The risk of incurring an adverse reactions increases in case of deviation from the protocols with regards to timing, doses and kind of products used for VIT[2 3]. Recently a worldwide shortage of products for VIT for *Apis mellifera*, *Vespula species* and *Polistes species* from the manufacturer Stallergenes (Antony, France) occurred, requiring a replacement with another product in a large number of patients under maintenance therapy to ensure therapeutic continuity. A case report was published that described a near-fatal anaphylaxis in a subject who underwent a switching of manufacturer's venom for *Polistes* wasp allergy[4].

Our main concern was to set a protocol in order to perform a safe switch of VIT products in our patients.

A total of 155 patients with *Apis mellifera*, *Vespula* spp. or *Polistes* spp. venom allergy were in maintenance phase of VIT with the missing product, and underwent the switch to another manufacturer's venom extract. These subjects were outpatients of the Allergy Centers of the Azienda Ospedaliero-Universitaria of Parma and the ASST Lariana of Como, Italy. The protocol we used concerned 38 patients (21 males, mean age 49.9 years, range age 22-78 years) with *Apis mellifera* venom allergy, with an average VIT duration of 5.4 years (1-21 years), 2 of whom ~~2~~ suffered from systemic mastocytosis, as diagnosed according to WHO diagnostic criteria[5]; 102 subjects with *Vespula* spp. venom allergy (86 males, mean age 54.3 years, range age 13-78 years), with a mean VIT duration of 4.57 years (1-18 years), 3 of whom ~~with~~ had systemic mastocytosis; and 15 patients with *Polistes* spp venom allergy (10 males, mean age 51.6 years, range age 29-75 years), with an average duration of VIT of 3.33 years (1-11 years), none of whom had mastocytosis.

The 38 subjects treated with *Apis mellifera* venom were switched to the aqueous product from Alk-Abellò (Horsholm, Denmark) in 21 cases, to Allergy Therapeutics (Worthing, UK) products in 16, and to Anallergo (San Piero a Dieve, Italy) venoms in one case. Seventy-six of the 102 patients with *Vespula* spp. allergy were switched to aqueous preparations from Alk-Abellò, 7 to aqueous preparations from Anallergo and 19 to Allergy Therapeutics preparations. All the *Polistes* spp-allergic patients were switched to Anallergo aqueous preparation of *Polistes dominula*.

The switch was performed by increasing the doses of the new product according to this protocol: 0.1 ml of 1 mcg; 0.1 ml of 10 mcg; 0.1 of 100 mcg; 0.2 of 100 mcg; 0.3 mcg of 100; 0.4 of 100 mcg (Table 1). Each dose was administered at 30 minute intervals, after checking for any kind of adverse reactions. Patients stayed under observation for a total time of 200 minutes.

Globally, 3 adverse reactions occurred in patients allergic to *Vespula* venom. One patient, a 55-year-old male, treated with VIT for 4 years, developed heartburn ~~after~~ 6 hours after from the last dose of the protocol, that spontaneously resolved. Another patient, a 44-years-old woman, VIT-treated for 3 years, experienced a local reaction with angioedema and erythema extending from the injection site to the elbow and ~~interesting~~ involving the entire circumference of the arm after the last dose of the protocol. The subject was treated with ice application on the injection site and cetirizine 20 mg orally, with resolution of symptoms in about 24 hours. The third patient, a 65-years-old man, VIT-treated for 6 years, presented, 30 minutes after the cumulative dose of 60 mcg, epigastric pain and obnubilation. Vital parameters were normal and the patient was treated with intravenous (IV) hydration, with resolution of symptoms in 20 minutes. The first two patients received the maintenance dose of 100 mcg of venom without presenting further reactions. These subjects had been switched to Alk-Abellò aqueous product. The third patient completed the scheduled up-dosing during the same day. The two subsequent administrations of 100 mcg were fractioned in two doses of 50 mcg each, with no adverse effects. In this patient the new product used was the Anallergo aqueous formulation for *Vespula* spp venom.

No reaction was reported among patients allergic to *Apis mellifera* and *Polistes* spp and/or suffering from systemic mastocytosis during the 3-hours protocol. None of the 155 patient had adverse effects during the following VIT administrations.

The protocol we performed to switch the VIT products demonstrated a good safety profile. None of 155 patients had severe systemic reactions and the 3 patients with adverse effects receveid a minimal therapy and recovered with no consequences.

Interestingly, we noted the absence of adverse events in patients undergoing VIT for *Apis mellifera* allergy, that are generally affected by more frequent and more serious reactions than *Vespids* allergic subjects[6]. We can speculate that the homology among different manufacturers venom is greater for *Apis mellifera* than

the homology among *Vespa spp* extracts. In addition, as stated in the recent document from the American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma, and Immunology (AAAAI/ACAAI) task force on venom extract shortage, there are minimal differences in species of insects used to obtain honeybee venom, while vespid venoms are usually mixed from different species of *Vespula* or *Polistes*[7]. A further important observation concerns the 5 patients with mastocytosis, 3 with *Vespula* spp and 2 by *Apis mellifera* venom allergy, who tolerated the protocol without any systemic reactions. As far as we know, this is the first time that a protocol for venom-products switching was performed on patients with mastocytosis. In conclusion, in view of the previous report of a reaction[4] and in consideration of the potential risks to the patient and to the physician (from a forensic viewpoint), when it is necessary to switch venom products a rush protocol (as described above) is apparently safe and well tolerated by patients.

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125 **Table 1**: Switch of venom products protocol adopted.

| Timing (minutes) | ADMNISTERED DOSE | CUMULATIVE DOSE |
|---|---|---|
| 0 | 0.1 ml of 1 mcg | 0.1 mcg |
| 30 | 0.1 ml of 10 mcg | 1,1 mcg |
| 60 | 0.1 of 100 mcg | 11,1 mcg |
| 90 | 0.2 of 100 mcg | 41,1 mcg |
| 120 | 0.3 mcg of 100 | 71,1 mcg |
| 150 | 0.4 of 100 mcg | 111,1 mcg |

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