



Letters

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



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 adverse reactions increases in case of deviation from the protocols with regard to timing, doses, and types 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 undergoing maintenance therapy to ensure therapeutic continuity. A case report was published that described a near-fatal anaphylaxis in a patient who underwent a switching of the manufacturer's venom for *Polistes* wasp allergy.⁴

Our main concern was to set a protocol to perform a safe switch of VIT products in our patients. A total of 155 patients with *A mellifera*, *Vespula* species, or *Polistes* species venom allergy were in the maintenance phase of VIT with the missing product and underwent the switch to another manufacturer's venom extract. These patients 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 men; mean age, 49.9 years; age range, 22–78 years) with *A mellifera* venom allergy, with a mean VIT duration of 5.4 years (range, 1–21 years), 2 of whom had systemic mastocytosis, as diagnosed according to World Health Organization diagnostic criteria⁵; 102 patients with *Vespula* species venom allergy (86 men; mean age, 54.3 years; age range, 13–78 years), with a mean VIT duration of 4.57 years (range, 1–18 years), 3 of whom had systemic mastocytosis; and 15 patients with *Polistes* species venom allergy (10 men; mean age, 51.6 years; age range, 29–75 years), with a mean duration of VIT of 3.33 years (range, 1–11 years), none of whom had mastocytosis. The 38 patients treated with *A mellifera* venom were switched to an aqueous product (Alk-Abellò, Horsholm, Denmark, products in 21 cases; Allergy Therapeutics, Worthing, England, products in 16 cases, and Anallergo, San Piero a Sieve, Italy, venoms in 1 case). A total of 102 patients with *Vespula* species allergy were switched to aqueous preparations (76 to products from Alk-Abellò, 7 to products from Anallergo, and 19 to products from Allergy Therapeutics). All the *Polistes* species allergic patients were switched to an aqueous preparation of *Polistes dominula* (Anallergo).

The switch was performed by increasing the doses of the new product according to this protocol: 0.1 mL of 1 µg, 0.1 mL of 10 µg,

Table 1
Switch of Venom Products Protocol Adopted

Timing, min	Administered dose, mL/µg	Cumulative dose, µg
0	0.1/1	0.1
30	0.1/10	1.1
60	0.1/100	11.1
90	0.2/100	31.1
120	0.3/100	61.1
150	0.4/100	101.1

0.1 mL of 100 µg, 0.2 mL of 100 µg, 0.3 mL of 100 µg, and 0.4 mL of 100 µg (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 man treated with VIT for 4 years, developed heartburn 6 hours after the last dose of the protocol, which spontaneously resolved. Another patient, a 44-year-old woman treated with VIT for 3 years, experienced a local reaction, with angioedema and erythema extending from the injection site to the elbow and involving the entire circumference of the arm after the last dose of the protocol. The patient was treated with an ice application on the injection site and cetirizine, 20 mg orally, with resolution of symptoms in approximately 24 hours. The third patient, a 65-year-old man treated with VIT for 6 years, presented 30 minutes after the cumulative dose of 60 µg with epigastric pain and obnubilation. Vital signs were normal, and the patient was treated with intravenous hydration, with resolution of symptoms in 20 minutes. The first 2 patients received the maintenance dose of 100 µg of venom without the occurrence of additional reactions. These patients had been switched to Alk-Abellò aqueous product. The third patient completed the scheduled up-dosing during the same day. The 2 subsequent administrations of 100 µg were fractioned in 2 doses of 50 µg each, with no adverse effects. In this patient, the new product used was the Anallergo aqueous formulation for *Vespula* species venom.

No reaction was reported among patients allergic to *A mellifera* and *Polistes* species and/or with systemic mastocytosis during the 3-hour protocol. None of the 155 patients 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 received a minimal therapy and recovered with no consequences.

Interestingly, we noted the absence of adverse events in patients undergoing VIT for *A mellifera* allergy, which are generally affected by more frequent and more serious reactions than *Vespids*

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allergic individuals⁶ We can speculate that the homology among different manufacturers' venom is greater for *A mellifera* than the homology among *Vespula* species 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 Task Force on Venom Extract Shortage, there are minimal differences in species of insects used to obtain honeybee venom, whereas 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* species and 2 with *A mellifera* venom allergy, who tolerated the protocol without any systemic reaction. As far as we know, this is the first time that a protocol for venom product switching was performed on patients with mastocytosis. In conclusion, in view of the previous report of a reaction⁴ and in consideration of the potential risks to the patient and 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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Jellyfish collagen A new allergen in the beach



Jellyfish stings are a common event in seas worldwide, with an estimated 150 million envenomations annually, usually resulting in acute cutaneous inflammation, although some allergic reactions have been documented.¹ Usually the allergy manifests with rashes, erythema, and pruritus and in some cases with even more severe reactions such as anaphylaxis. Among jellyfish (ie, Scyphozoa, Cubozoa, and the siphonophore Portuguese man o'war), there are different species, some of them very dangerous; their sting can lead to severe injuries and even death of the individual (mainly from Cubozoa and Siphonophora). Historically, reactions against jellyfish toxins are one of the hallmarks of medical history. In 1902, Portier and Richet² coined the term *anaphylaxis* ("lack of protection") after conducting experiments in dogs against the *Physalia physalis* toxins, in which dogs were exposed to sublethal doses of the toxin. They observed that sensitized dogs reacted instantaneously and fatally to subsequent contact with small amounts of the toxin. This discovery allowed to Richet to win the Nobel Prize for Medicine in 1913.

We describe the sting of *Pelagia noctiluca*, a bell-shaped pelagic jellyfish (open waters).³ *Pelagia noctiluca* is ubiquitous worldwide, especially in warm and temperate waters, and it is common in the Mediterranean Sea; moreover, it is one of the most abundant and venomous jellyfish in this area.⁴ The sting of the *P noctiluca* is poisonous but in humans typically does not cause more than a local cutaneous reaction. However, in some cases, humans can develop allergic reactions, including anaphylactic shock.⁵ Several studies have

described the cytolytic and hemolytic properties of the crude venom of *P noctiluca*⁶ and the complete proteome of this jellyfish¹; however, none have described the specific allergens responsible for these allergic effects. Only 1 study conducted with proteins from *Chironex yamaguchii* nematocysts identified several proteins as allergens: a protein toxin (CqTX-A) and an N-linked glycoprotein.⁷

A 76-year-old Spanish Caucasian man was accidentally stung by a jellyfish, identified by its morphologic appearance as *P noctiluca* at the Multidisciplinary Institute for Environmental Studies (University of Alicante, Spain) using photographs of this jellyfish taken by the patient. He was stung in Ibiza, Spain (38°54'31.79"N 1°25'58.66"E) and he felt only 1 sting. Immediately after the sting, he developed tongue edema, itchy palms, dizziness, and general discomfort. The patient did not go to the emergency department or a physician's office but rather treated his symptoms with 40 mg of oral methylprednisolone; he did not apply a topical treatment.

He had been stung several times previously by jellyfishes in the same sea area. He reported that he previously had itching with crab ingestion. He was evaluated in our outpatient clinic 4 weeks after the episode. The patient's tryptase levels were normal. Specific serum immunoglobulin E (IgE) results (Thermo Fisher Scientific, Waltham, Massachusetts) were 0.02 kU/L for crab; 0.0 kU/L for mussel, squid, and octopus; 0.58 kU/L for *Anisakis* species; 0.0 kU/L for rPen a 1 tropomyosin; 0.60 kU/L for rPol d 5 paper wasp *Polistes dominulus*; and 0.13 kU/L for *P dominulus*. The patient reported no reactions to Hymenoptera stings.

An in vitro study including sodium dodecylsulfate polyacrylamide gel electrophoresis analysis and immunoblot was performed with nematocyst extracts from the body or bell-shaped area and tentacles of *P noctiluca*. Two prominent bands of approximately 130 kDa were recognized by serum IgE of the patient (Fig 1). These

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