

Depot extracts for rush venom immunotherapy

A new therapeutic opportunity for Hymenoptera sting allergy



Stings by Hymenoptera insects are relatively common in the general population and may cause different symptoms, ranging from mild and local reactions to life-threatening and fatal anaphylaxis.¹

Currently, the only causal treatment for Hymenoptera venom hypersensitivity is venom immunotherapy (VIT).²

VIT can be performed with aqueous or depot extracts.³ During build-up, aqueous extracts are preferred, especially in rush and ultra-rush protocols, because of the putative risk of delayed systemic reactions with depot ones.⁴ Depot extracts may be preferred instead during the maintenance phase because they seem to reduce the incidence of local reactions at the injection site compared with aqueous ones⁵ and also because they reportedly induce a significantly stronger specific IgG response.⁴

We performed an observational study to evaluate the safety and tolerability of a new rush protocol with aluminium hydroxide adsorbed insect venom extracts. Seventy-two patients (50 males and 22 females; mean age, 45.6 years; age range, 12–84 years) with a documented history of systemic reactions (17 patients with grade 2 urticaria-angioedema, 20 patients with grade 3 cutaneous and respiratory symptoms, and 35 patients with grade 4 cardiovascular anaphylaxis according to Mueller classification⁶) to Hymenoptera stings underwent VIT, with honeybee venom in 27 cases and yellowjacket venom in 45 cases.

A 4-day rush protocol was performed for honeybee venom, whereas a 2-day protocol was performed for yellowjacket venom

using aluminium hydroxide adsorbed insect venom extracts (Alutard SQ, ALK-Abellø A/S, Hørsholm, Denmark). We preferred a protocol with a more gradual build-up phase for honeybee venom because of the well-known higher risk of adverse reactions during honeybee VIT compared with yellowjacket VIT.⁷

A total of 7 and 17 subcutaneous injections (for yellowjacket and honeybee venom, respectively) were administered, every 20 minutes, during the build-up phase. The cumulative maintenance dose of 100 µg (1 mL of Alutard SQ 100,000 SQ-U) for yellowjacket was reached the second day, divided into 3 sequential injections: the first one containing 30 µg and the other two containing 35 µg each. As for honeybee, the cumulative maintenance dose was reached the fourth day, with 4 sequential injections of 25 µg each. Subsequently, on one hand, the intervals of the daily maintenance dose were progressively increased from 1 week to 2 weeks and finally to 4 weeks. On the other hand, the number of daily injections to reach the maintenance dose progressively decreased to a single 100-µg injection. The rush protocol schedules are detailed in Table 1.

All patients reached the expected maintenance dose with a good tolerability profile. Only 2 patients (1 man and 1 woman with honeybee allergy) developed flushing, with the man also presenting with palmar, plantar, and ocular itching that resolved within a few minutes without any treatment. These reactions occurred in the woman on the first day of the rush VIT, 15

Table 1
Yellowjacket and Honeybee Rush Protocol

Phase	Yellowjacket			Honeybee		
	Dose, SQ-U/mL	Dose, mL	Dose, µg of venom	Dose, SQ-U/mL	Dose, mL	Dose, µg of venom
Day 1	1000	0.1	0.1	100	0.1	0.01
	10,000	0.1	1	1000	0.1	0.1
	100,000	0.1	10	10,000	0.1	1
		0.2	20	100,000	0.05 ^a	5
Day 2	100,000	0.3	30	100,000	0.05 ^a	5
		0.35	35		0.05 ^a	5
		0.35	35		0.1	10
					0.1	10
Day 3				100,000	0.15	15
					0.15	15
					0.15	15
					0.15	15
Day 4				100,000	0.25	25
					0.25	25
					0.25	25
					0.25	25
Maintenance phase	After 7 days	100,000	0.3	100,000	0.25	25
			0.35		0.25	25
			0.35		0.25	25
	After 14 days	100,000	0.4	100,000	0.30	30
			0.6		0.35	35
					0.35	35
	After 28 days			100,000	0.4	40
					0.6	60
	Every 4 weeks	100,000	1	100,000	1	100

^aWithdraw 0.1 mL and inject 0.05 mL.

minutes after the administration of 5 µg of venom, and in the male on the second day, 10 minutes after the injection of 10 µg of venom. In these patients, the protocol was maintained, and no variation was needed.

During VIT, 12 patients experienced mild local reactions, with a diameter ranging from 5 to 15 cm, that consisted of redness and itching at the site of injection, well controlled by application of ice. These reactions did not interfere with the administration of VIT.

Only one patient, treated with yellowjacket VIT, experienced an extensive local reaction of approximately 20 cm at the injection site on the second day of the build-up (after a cumulative dose of 100 µg). This reaction did not occur at subsequent injections. At the end of the build-up phase, patients continued with the maintenance phase without any adverse event.

These data indicate a good tolerability profile of our rush protocol with depot extracts. No emergency treatment was used. In addition, the almost complete absence of severe local reactions at the injection site with aluminium hydroxide adsorbed extracts compared with aqueous extracts should be emphasized. Such reactions, although not dangerous, are sometimes characterized by extensive and painful edema, making difficult to continue VIT. Although mild systemic reactions concerned only 2 patients and the small sample size of this study does not allow definitive conclusions, we can point out that the onset of adverse effects, contrary to a common belief,^{4,8} occurred within a few minutes after the injection and was not delayed.

Although the purpose of the study was to evaluate the safety and tolerability of this new rush protocol, it should be emphasized that Alutard SQ vespuola and apis have been approved and marketed in a number of European and other countries for approximately 30 years and thus have a long record of well-established use. These products have demonstrated clinical efficacy in several studies.^{9,10}

If these results are confirmed in further studies, the safety concern to avoid the use of depot venom extracts in rush protocols should be reconsidered. In fact, the use of aluminium hydroxide adsorbed

venom in the build-up phase of rapid regimens could represent an important opportunity to offer a simplified treatment characterized by a good safety and tolerability profile.

Stefano Pucci, MD
Fedra Ciccarelli, MD
Tiziana De Pasquale, MD
Ilenia Illuminati, MD
Simona D'Alò, MD
Allergy Unit
General Hospital
Civitanova Marche, Italy
stefano.pucci@sanita.marche.it

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Olfactory dysfunction out of season in seasonal allergic rhinitis



Olfactory dysfunction (OD) is one of the major symptoms caused by seasonal allergic rhinitis (AR) and has been reported in patients with normal olfactory function (OF) before the allergy season.¹ In addition, inflammatory cells have been reported to infiltrate the olfactory mucosa in allergic rhinitis.² Moll et al³ found that the extra-seasonal score in the 1-butanol threshold test of patients with grass pollen allergy was lower than that of control subjects. It is therefore unclear whether OD persists out of pollen season in patients with seasonal AR, especially in patients who do not report symptoms of OD. We investigated extraseasonal OF in patients with severe AR caused by Japanese cedar pollen (the allergen that causes the largest number of problems in Japan) and who did not report OD symptoms out of season.

In this prospective trial, 50 control subjects (27 women and 23 men; mean [SD] age, 43.0 [1.6] years; age range, 22–55 years), 50 patients with Japanese cedar AR for 2 to 9 years after onset (disease duration, <10 years; 22 women and 28 men; mean [SD] age, 41.2 [1.5] years; age range, 21–54 years), and 50 patients with Japanese cedar AR for 10 or more years after onset (disease duration, ≥10 years; 24 women and 26 men; mean [SD] age, 42.2 [1.2] years; age range, 26–

54 years) were included in this study. No significant differences in age or sex were found among the 3 groups. The inclusion criteria for the patients were as follows: monosensitized patients with specific serum IgE to Japanese cedar pollen of class III or higher by the CAP system (Pharmacia & Upjohn, Uppsala, Sweden), a history of seasonal symptoms that required treatment for at least 2 years, and unawareness of OD out of season. Exclusion criteria included the existence of any nasal disease, such as sinusitis, nasal tumor, and nasal polyp; specific immunotherapy; age younger than 20 or older than 55 years; pregnancy; any other diseases except Japanese cedar pollinosis; the presence of asthma; or refusal of consent. The presence of a nasal polyp and rhinosinusitis was ruled out by examination with nasal endoscopy and computed tomography. Japanese cedar season runs from February until April, and olfactory tests were performed in August. This study was approved by the ethical committee in Nagoya City University, and informed consent was obtained from each participant.

Odor identification was evaluated using the Open Essence (OE) test (Wako Pure Chemical Industries, Saitama, Japan), which includes 12 odors.⁴ The OE score is defined as the number of correct answers. An olfactory threshold test was also performed using the T&T Olfactometry test (Daichi Yakuhin Sangyo, Tokyo, Japan),^{5,6} which is the standard method in Japan. The mean detection thresholds (DTs; the minimum concentration at which an odorant is detected) and recognition thresholds (RTs; the minimum concentration at which an

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