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REFERENCES

1. Martinez VG, O'Driscoll L. Neuromedin U: a multifunctional neuropeptide with pleiotropic roles. *Clin Chem*. 2015;61:471-482.

2. Klose CSN, Mahlaköiv T, Moeller JB, et al. The neuropeptide neuromedin U stimulates innate lymphoid cells and type 2 inflammation. *Nature*. 2017;549:282-286.
3. Moriyama M, Sato T, Inoue H, et al. The neuropeptide neuromedin U promotes inflammation by direct activation of mast cells. *J Exp Med*. 2005;202:217-224.
4. Rao SM, Auger JL, Gaillard P, et al. The neuropeptide neuromedin U promotes autoantibody-mediated arthritis. *Arthritis Res Ther*. 2012;14:R29.
5. Inoue A, Ishiguro J, Kitamura H, et al. TGF- α shedding assay: an accurate and versatile method for detecting GPCR activation. *Nat Methods*. 2012;9:1021-1029.
6. Tatemoto K, Nozaki Y, Tsuda R, et al. Immunoglobulin E-independent activation of mast cell is mediated by Mrg receptors. *Biochem Biophys Res Commun*. 2006;349:1322-1328.
7. Mempel M, Voelcker V, Köllisch G, et al. Toll-like receptor expression in human keratinocytes: nuclear factor κ B controlled gene activation by staphylococcus aureus is toll-like receptor 2 but not toll-like receptor 4 or platelet activating factor receptor dependent. *J Invest Dermatol*. 2003;121:1389-1396.
8. Szöllösi AG, Vasas N, Angyal Á, et al. Activation of transient receptor potential vanilloid 3 regulates inflammatory actions of human epidermal keratinocytes. *J Invest Dermatol*. 2018;138:365-374.
9. Fujisawa D, Kashiwakura J, Kita H, et al. Expression of Mas-related gene X2 on mast cells is upregulated in the skin of patients with severe chronic urticaria. *J Allergy Clin Immunol*. 2014;134:622-633.

SUPPORTING INFORMATION

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Safety of ultra-rush protocols for hymenoptera venom immunotherapy in systemic mastocytosis

To the Editor,

Mastocytosis comprises a heterogeneous group of disorders characterized by the expansion and accumulation of clonal mast cells in one or more organ systems. It is a rare disease with an estimated prevalence of about 10 cases per 100 000 inhabitants.¹ Anaphylactic reactions are very common, affecting between 22% and 49% of patients with systemic mastocytosis (SM).² Hymenoptera venom allergy (HVA) seems to be particularly involved in anaphylactic reactions of patients with SM. Mastocytosis has been identified as a risk factor for severe anaphylaxis to hymenoptera venom and the prevalence of clonal mast cell disease in patients with HVA ranges from 1% to 7.9%, which is much higher than that of the general population.³ Elevation of baseline serum tryptase has been identified as a risk factor for severe anaphylaxis in HVA. Although recent EAACI (European Academy of Allergy and Clinical Immunology) guidelines on AIT recognize hymenoptera venom immunotherapy (HVI) as a safe and effective form of treatment for patients with mastocytosis

associated with anaphylactic reaction to hymenoptera venom,⁴ only a few studies are available on allergen immunotherapy (AIT) tolerance in those patients, and no protocols of HVI have been clearly recommended in patients with SM. We present hereinafter data recorded in patients with SM and anaphylactic reaction due to hymenoptera venom allergy and HVI based on an ultra-rush protocol.

Data were collected from patients with SM requiring HVI in the Mastocytosis Reference Centre at Toulouse University Hospital Centre. The inclusion criteria were as follows: (a) patients over 18 years old; (b) SM diagnosis based on World Health Organization diagnostic criteria,⁵ (c) allergy to hymenoptera venom with positive skin tests and/or positive specific IgEs to hymenoptera venom associated with a history of anaphylactic reaction following a hymenoptera sting; and (d) HVI initiation with an ultra-rush protocol as previously described.⁶

Demographic data, characteristics of the initial reaction and details of allergy skin tests were collected. Intradermal tests against

Vespula wasp, Polistes wasp and *Apis mellifera* bee have been performed using extracts of Alyostal st Vespula wasp venom, Alyostal Polistes wasp venom and Alyostal st *A. mellifera* bee venom, respectively (Stallergenes, Antony Cedex, France). Specific IgEs to Vespula wasp, Polistes wasp and *A. mellifera* bee venom were performed using ImmunoCAP® (bee *A. mellifera* bee, R + * Vespula spp., R + ** Polistes spp., Thermo Fisher Scientific/Phadia, Uppsala, Sweden).

Patients received antihistamine pretreatment and were given subcutaneous injections of 0.1, 1, 10 and 20 µg, every 30 minutes followed by 30 and 40 µg every 60 minutes on day 1, 50 µg twice on day 15 and 100 µg on day 45. They subsequently received a subcutaneous injection every 4 weeks for the first 3 years and every 6 weeks thereafter. All patients were checked for a new sting.

Eight patients were enrolled (4 women, 4 men) with a median age of 52.5 years old (Table 1). The initial reaction to hymenoptera was mostly severe because 6 of 8 patients experienced a grade 3 or grade 4 reaction based on Ring and Messmer's classification (Table 2). Three patients suffered from digestive symptoms and 1 from respiratory signs. One patient (patient 8) presented skin symptoms during the initial reaction to hymenoptera. The diagnosis of mastocytosis has been made in the presence of a major criterion in 3 patients and the presence of three minor criteria for five patients. All the patients had a c-KIT-D816V mutation in bone marrow. Baseline serum tryptase ranged from 10.1 to 41.7 µg/L, and 4 patients had a baseline tryptase value below 20 µg/L. Two patients suffered from aggressive SM whilst the other 6 had indolent SM. Hymenoptera venom-specific IgEs were low (0.11–1.51 kIU/L) except in one patient (35.6 kIU/L). When possible, the REMA (Red Espanola de Mastocytosis [Spanish Network on Mastocytosis]) score of patients was calculated.⁷

Hymenoptera venom immunotherapy was initiated with Vespula wasp venom in 3 patients, Polistes wasp venom in 1 patient, *A. mellifera* and Vespula wasp venom in 1 patient, as well as Vespula and Polistes wasp venom in three patients (Table 2). Patient 8 identified a wasp as the stinging insect, but the tests did not identify exactly which wasp was involved, and therefore, he received a double VIT. A total of 12 ultra-rush protocols have been initiated in eight patients. Six patients received a single VIT, 1 patient a double VIT and two patients received VIT twice because they have been restung after first VIT cessation. No adverse effects were observed during both the ultra-rush protocol and the maintenance protocol. Four patients (patients 1, 2, 4 and 6) were restung leading to a reaction. There was a dose increase in two patients (patients 2 and 4, 200 and 150 µg per month, respectively). Patients 1 and 6 were diagnosed with SM after the new sting. These patients received an ultra-rush VIT after a first reaction to hymenoptera, and they have been restung after VIT cessation. SM diagnosis has been carried out at this time. Given SM diagnosis, they received a second ultra-rush and VIT was maintained for life. After VIT cessation, patients

TABLE 1 Characteristics of population and diagnostic criteria for mastocytosis

Characteristics				Mastocytosis													
Sex	Age	Asthma	Rhino-conjunctivitis	Active or former smokers	Major criteria ^a			Minor criteria ^a					Mast cells c-kit+ CD2 + and/or CD25+	Baseline serum tryptase > 20 µg/L	Baseline tryptase (µg/L)	REMA score ^b	Age at diagnosis
					Presence of dense infiltrates of mast cells in bone marrow	>25% fusiform cells on BMB	Atypical mast cell morphology > 25%	A codon-816 c-kit mutation (in medullary tissue)	Mast cells c-kit+ CD2 + and/or CD25+								
1	F	70	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	41.7 µg/L	Aggressive	2	68
2	F	78	No	No	No	No	Yes	No	Yes	Yes	Yes	Yes	No	15.2 µg/L	Indolent		73
3	M	66	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	18.6 µg/L	Indolent	5	62
4	M	44	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No	10.1 µg/L	Indolent		42
5	F	59	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	30 µg/L	Aggressive		53
6	M	46	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	23.7 µg/L	Indolent		43
7	F	37	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	18.9 µg/L	Indolent	5	30
8	M	46	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	35.5 µg/L	Indolent	4	45

^aAccording to Ref (5).

^bAccording to Ref (7).

*natural allergenic source enriched with recombinant rVes v 5 allergen

**natural allergenic source enriched with recombinant rPol d 5 allergen

TABLE 2 Characteristics of anaphylactic reaction to hymenoptera

Reaction	Initial evaluation										Immunotherapy			
	Skin testing										Specific IgE (kIU/L)			
	Apis	Polistes	Vespula	Total IgE (kIU/L)	Apis	Polistes	Vespula	Apis	Polistes	Vespula	rVes v 1 ^b	rVes v 5 ^b	rPol d 5 ^b	Maintenance dose
1 Bee (?)	Neg	Neg	Neg	10	Neg	Neg	Neg	0	0	0.8	0	0.1	0	100 µg
	Yes													• 4 y • Restart due to new sting with anaphylactic reaction. Still ongoing
2 Bee	Neg	Neg	Neg	No data	Neg	Neg	Neg	1.5	No data	0.3	0	0.3	No data	100 µg then 200 µg
	Yes													• Bee initially • Then Vespula because of reaction to hornet sting. • Increase bee immunotherapy because of grade 3 reaction after repeat bee sting. Still ongoing
3 Wasp	Neg	Neg	+++	No data	Neg	Neg	+++	0	0	0	No data	No data	No data	100 µg
	No data	No data												• 3 y. Still ongoing • New sting at 2 y but no reactions
4 Wasp	Neg	+++	+++	67	Neg	+++	+++	0	1.1	1.1	No data	1.6	1.1	100 µg. then 150 µg
	Yes													• 7 y. Still ongoing • Anaphylactic reactions despite immunotherapy. Dose increase
5 Wasp	Neg	Neg	++	128	Neg	Neg	++	0	0	36	No data	No data	No data	100 µg
	Yes													• 12 y. Still ongoing
6 Wasp	Neg	Neg	Neg	15	Neg	Neg	Neg	0.6	0.8	0.6	0.34	0	0	100 µg
	No data	No data												• 8 y Polistes VIT • New sting with anaphylactic reaction 3 y after VIT cessation • Vespula VIT for 5 y. Still ongoing
7 Wasp	Neg	+	Neg	256	Neg	+	Neg	0.1	0.4	1.1	No data	No data	No data	100 µg
	No data	No data												• Lost to follow-up
8 Wasp	Neg	Neg	Neg	No data	Neg	Neg	Neg	No data	0	0	0	0	0	100 µg
	No data	No data												• 2 y. still ongoing

Sensitization profile and venom immunotherapy in 8 patients with systemic mastocytosis. A, *Apis mellifera*; HVI, hymenoptera venom immunotherapy; P, *Polistes*; V, *Vespula*. (?), The patient reported as being stung by a bee, but she was not sure. Allergic testing was discordant.

^aTryptase level of 303 µg/L was recorded 1 h after the reaction.

^bUsing ImmunoCAP® rVes v 1. rVes v 5. rPol d 5 (Thermo Fisher Scientific/Phadia).

^cAlyostal bee venom *Apis mellifera* (A). wasp venom *Vespula* (V). wasp venom *Polistes* (P) from Stallergenes, Antony Cedex. France.

with SM remain at high risk of anaphylactic reactions. This emphasized the necessity/need to continue VIT in patients with lifelong mastocytosis.

Although HVI is recommended in SM patients with severe reactions to hymenoptera venom, no clear-cut protocols have been established. According to the published case series, conventional, cluster and rush protocols are well tolerated and effective in patients with SM associated with anaphylaxis to hymenoptera venom-induced anaphylaxis.^{8,9} To the best of our knowledge, this is the first report on the safety of use of an ultra-rush protocol in SM patients. Although no adverse reactions have been observed, we nevertheless acknowledge the fact that the main limitation is the small patient cohort, thus a larger study is needed to corroborate our results.

Surprisingly, the bee was identified as the culprit insect in only one patient and the remaining patients showed severe reaction and positive skin testing or IgE to wasp. The severity of allergic reaction to wasp in patients with SM has been highlighted recently.¹⁰ However, we do not know whether this observation is a coincidence or whether there is a real association between the wasp reaction and SM.

Close collaboration between mastocytosis reference centres and allergy specialists is crucial in the management of HVI in patients with SM associated with severe hymenoptera venom-induced reactions.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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REFERENCES

1. Brockow K. Epidemiology, prognosis, and risk factors in mastocytosis. *Immunol Allergy Clin North Am*. 2014;34:283-295.
2. Bonadonna P, Pagani M, Aberer W, et al. Drug hypersensitivity in clonal mast cell disorders: ENDA/EAACI position paper. *Allergy*. 2015;70:755-763.
3. Bonadonna P, Lombardo C, Zanotti R. Mastocytosis and allergic diseases. *J Invest Allergol Clin Immunol*. 2014;24:288-297.
4. Sturm GJ, Varga EM, Roberts G, et al. EAACI guidelines on allergen immunotherapy: hymenoptera venom allergy. *Allergy*. 2018;73:744-764.
5. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;19:2391-405: <https://doi.org/10.1182/blood-2016-03-643544>.
6. Birnbaum J, Ramadour M, Magnan A, Vervloet D. Hymenoptera ultra-rush venom immunotherapy (210 min): a safety study and risk factors. *Clin Exp Allergy*. 2003;33:58-64.
7. Alvarez-Twose I, González-de-Olano D, Sánchez-Muñoz L, et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. *Int Arch Allergy Immunol*. 2012;157:275-280.
8. Bonadonna P, Zanotti R, Caruso B, et al. Allergen specific immunotherapy is safe and effective in patients with systemic mastocytosis and Hymenoptera allergy. *J Allergy Clin Immunol*. 2008;121:256-257.
9. de Olano DG, Álvarez-Twose I, Esteban-López MI, et al. Safety and effectiveness of immunotherapy in patients with indolent systemic mastocytosis presenting with Hymenoptera venom anaphylaxis. *J Allergy Clin Immunol*. 2008;121:519-526.
10. Vos BJ, van Anrooij B, van Doormaal JJ, Dubois AE, Elberink JNO. Fatal anaphylaxis to yellow jacket stings in mastocytosis: options for identification and treatment of at-risk patients. *J Allergy Clin Immunol Pract*. 2017;5:1264-1271.