

Both SM patients presented with abdominal pain, diarrhea, urticaria, and rash (Table 1). Patient 6 had anaphylaxis, whereas patient 7 reported severe, debilitating bone pain. Bone marrow biopsy confirmed mast cell infiltrates in both patients. Patient 6 achieved symptomatic improvement with antihistamines and cromolyn. Patient 7 failed maximal medical therapy with antihistamines, montelukast, cromolyn, and hydroxyurea.⁴ He was subsequently started on omalizumab, with dramatic improvement.

The diagnosis of mast cell disorders can be challenging given the heterogeneous clinicopathologic spectrum and the short half-lives of the available biomarkers. Tryptase is optimally collected within 4 hours after symptom onset. This timepoint is often overlooked by physicians tasked with emergently stabilizing a patient. In our cohort, patients 1–3 had elevated tryptase levels. Patients 2 and 3 had elevated urine markers as well. Patient 4's tryptase level was not collected until 24 hours after symptom onset and was within normal limits at that timepoint; the urinary marker, however, was persistently elevated. A weakness of our report is the failure to obtain 2 or more collections of urinary mediators during a symptomatic episode or elevation of tryptase over baseline for patients 1 and 4 to meet all MCAS criteria.¹ Patient 2 did have a meaningful tryptase elevation; however, the timing was not delineated in the record. These omissions reflect the “real-world” challenges with patients presenting at multiple sites for emergent care.

There is limited information available to assist clinicians in choosing effective therapies for mast cell disorders. Given the rarity of these conditions, case reports are of unique value for practitioners to guide treatment decisions and monitor outcomes. Our therapeutic approach mirrors the available literature incorporating escalating doses of antihistamines, addition of a cysteinyl leukotriene receptor blocker or 5-lipoxygenase inhibitor and/or mast cell stabilizer, particularly for GI symptoms.⁵ Aspirin therapy can be considered, especially in patients with coexisting coronary artery disease, given evidence that prostaglandins, including prostaglandin D₂, may play a role in mast cell activation.⁶ As exemplified by our cohort, response to therapy is quite variable. Although 1 patient was adequately controlled on antihistamines as needed, the majority of patients required combination therapies. Two patients failed maximal medical therapy but achieved symptom relief with omalizumab 300 mg every 4 weeks.

Previous case reports have suggested that omalizumab can provide symptomatic relief in patients with SM and monoclonal MCAS.^{7–9} Omalizumab has been reported to be effective in a pedi-

atric patient with MCAS.¹⁰ Our patient 5 represents the first adult (nonclonal) MCAS patient successfully treated with omalizumab to the best of our knowledge. The mechanism by which omalizumab mediates symptom relief in mast cell disorders has not been well delineated.

Our cases highlight the variable presentation, diagnostic challenges, and response to treatment of mast cell disorders. Importantly, 2 of these cases demonstrated that symptoms refractory to traditional medical management may be alleviated with omalizumab.

Meng Chen, MD*

Alexander Kim, MD*

Bruce Zuraw, MD*†

Taylor A. Doherty, MD*

Sandra Christiansen, MD*

*Department of Medicine
University of California San Diego

San Diego, California

†Veterans Affairs

San Diego, California

scchristiansen@ucsd.edu

References

- [1] Akin C. Mast cell activation syndromes. *J Allergy Clin Immunol*. 2017;140:349–355.
- [2] McNeil BD, Pundir P, Meeker S, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature*. 2015;519:237–241.
- [3] Abdelghany M, Subedi R, Shah S, Kozman H. Kounis syndrome: a review article on epidemiology, diagnostic findings, management and complications of allergic acute coronary syndrome. *Int J Cardiol*. 2017;232:1–4.
- [4] Pardanani A. Systemic mastocytosis in adults: 2017 update on diagnosis, risk stratification and management. *Am J Hematol*. 2016;91:1146–1159.
- [5] Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. *New Engl J Med*. 2015;373:163–172.
- [6] Ravi A, Butterfield J, Weiler CR. Mast cell activation syndrome: improved identification by combined determinations of serum tryptase and 24-hour urine 11β-prostaglandin2α. *J Allergy Clin Immunol Pract*. 2014;2:775–778.
- [7] Jagdis A, Vadas P. Omalizumab effectively prevents recurrent refractory anaphylaxis in a patient with monoclonal mast cell activation syndrome. *Ann Allergy Asthma Immunol*. 2014;113:115–116.
- [8] Lieberoth S, Thomsen SF. Cutaneous and gastrointestinal symptoms in two patients with systemic mastocytosis successfully treated with omalizumab. *Case Rep Med*. 2015;2015:1–3.
- [9] Kibsgaard L, Skjold T, Deleuran M, Vestergaard C. Omalizumab induced remission of idiopathic anaphylaxis in a patient suffering from indolent systemic mastocytosis. *Acta Derm Venerol*. 2014;94:363–364.
- [10] Bell MC, Jackson DJ. Prevention of anaphylaxis related to mast cell activation syndrome with omalizumab. *Ann Allergy Asthma Immunol*. 2012;108:383–384.

Safety of a 2-day ultrarush immunotherapy in vespid allergic patients

Focus on elevated serum tryptase

Systemic mastocytosis (SM) is a disorder caused by the abnormal proliferation of mast cells (MCs) in one or more organs, leading to heterogeneous clinical presentations. Patients with SM are more at risk for Hymenoptera sting-induced anaphylaxis,¹ and in these patients indolent SM is the most frequent form of this disorder.

Venom immunotherapy (VIT) is a highly effective and safe treatment that is able to reduce the risk of a subsequent systemic reaction (SR).² VIT is also considered well tolerated and effective in

patients with mastocytosis, albeit to a lesser extent.^{1,3} However, bee venom allergy and an ultrarush schedule represent risk factors for an SR during VIT.⁴ Accordingly, some authors recommend that patients with mastocytosis receive conventional slow VIT while under strict observation.¹

Since 2000 we have been prospectively collecting clinical data from vespid allergic patients referred to our unit and who underwent VIT. A preliminary assessment (hematopoietic examination, cardiologic examination with electrocardiography and spirometry) was performed in all patients, regardless of age, to diagnose or rule out any concomitant disease. Only those with a history of SRs and a positive standard diagnostic workup result (ie, skin prick, intradermal testing, specific IgE CAP radioallergosorbent test)⁵

Table 1

Features of 29 Vespid Allergic Patients With bSTC Greater Than 20 µg/L

Patient no.	Sex	Severity of reaction ^a	Serum tryptase, µg/L	Diagnosis of MC disorder	Type of VIT	Time from reaction to start VIT, mo	Dose of venom, µg	Adverse reaction
1	M	IV	51	ND	Vespula	5	100	None
2	F	IV	32	ND	Vespula	5	100	None
3	M	IV	39.2	ND	Vespula	3	100	None
4	M	IV	20.6	ND	Polistes	6	100	None
5	M	IV	40.9	ND	Vespula	8	100	None
6	M	IV	23.8	ND	Polistes	6	100	None
7	M	IV	25.7	ND	Polistes	4	100	None
8	M	IV	22	ISM	Vespula	3	100	None
9	M	IV	21.6	ND	Polistes	3	100	None
10	M	IV	23.1	ND	Polistes	3	100	None
11	M	III	65.3	ND	Polistes	4	100	None
12	M	IV	22.2	ISM	Vespula	5	100	None
13	M	IV	26.8	ISM	Polistes	18	100	None
14	M	IV	45.8	ISM	Polistes	6	100	None
15	M	IV	34.3	ISM	Vespa crabro	11	100	None
16	F	IV	22.4	ISM	Polistes	2	100	None
17	M	IV	34	ISM	Polistes	12	100	None
18	F	IV	50.4	ISM	Vespula	8	100	None
19	F	IV	37.8	ISM	Vespula	6	100	None
20	M	IV	86.9	ISM	Polistes	2	100	None
21	M	IV	36.8	ISM	Vespula	11	100	None
22	F	III	112	ISM	Vespula	6	100	None
23	M	IV	32	ISM	Vespula	4	100	None
24	M	IV	52	ISM	Vespula	72	100	None
25	M	IV	36.6	ISM	Vespula	4	100	None
26	F	IV	51.48	ISM	Vespula	36	100	None
27	M	IV	20.7	ND	Polistes	7	100	None
28	M	IV	28	CM	Polistes	60	100	None
29	M	IV	22.5	CM	Vespula	36	100	None

Abbreviations: bSTC, basal serum tryptase concentration; CM, cutaneous mastocytosis; ISM, indolent systemic mastocytosis; MC, mast cells; ND, not determined; VIT, venom immunotherapy.

^aAccording to Mueller's classification.

were eligible for treatment. In compliance with the standard practice, all patients signed an informed consent to data privacy and diagnostic and therapeutic procedures. Basal serum tryptase concentrations (bSTCs) were measured (immunofluorimetric CAP assay, Unicap 100, Thermo Fisher Scientific, Uppsala, Sweden) in all patients. A dermatologic evaluation was performed in those with a bSTC greater than 11.4 µg/L, whereas patients with a bSTC greater than 20 µg/L were referred to the hematologist to consider a bone marrow (BM) biopsy. A BM biopsy was also performed in one patient with a bSTC less than 20 µg/L and a history of 2 episodes of documented hypotension without triggers. The diagnosis of SM in Hymenoptera venom allergic (HVA) patients and anaphylaxis were considered part of the standard care regimen; hence, no institutional review board approval was required.

In all patients, a 2-day ultrarush protocol was performed; no conventional protocol was applied. In the ultrarush induction, 4 subsequent shots of 0.1, 1, 10, and 20 µg every 45 minutes were given on the first day; on the second day, patients received doses of 35, 35, and 30 µg. No premedication was given. The patients were continuously monitored for local and systemic symptoms. Injections in the build-up phase were given by a physician at our clinic, whereas the maintenance dosages were administered by a physician or a nurse with VIT experience, with full resuscitation facilities at hand.

Of 1,141 VIT treated patients, 43 (3.8%) had a bSTC greater than 11.4 µg/L, among whom 29 (2.5%) had a bSTC greater than 20 µg/L. Seventeen patients (one of whom had a bSTC less than 20 µg/L) gave consent for a BM biopsy; the remainder did not for either logistic reasons or fear of the invasive procedure. The BM biopsies confirmed the presence of indolent SM in all patients,

whereas a histopathologic examination of the skin biopsy revealed urticaria pigmentosa in 3 patients. Thirty-nine patients had experienced a class IV sting SR, and 4 patients had experienced a class III SR (according to Mueller's classification).⁵ Table 1 gives the features of vespid allergic patients with a bSTC greater than 20 µg/L.

The interval between the last SR and VIT initiation was less than 6 months in 53.5% of patients, between 7 and 12 months in 25.5% of patients, and more than 13 months in 21% of patients. The prescribed VITs were 7 *Vespula* Species and 2 *Polistes* Species (Stallergenes, Antony, France), 14 *Vespula* Species and 4 *Polistes dominula* (ALK, Copenhagen, Denmark), 1 *Vespula crabro*, 1 *Vespula* species, and 14 *Polistes dominula* (Anallergo, Florence, Italy).

No SRs during VIT occurred in patients with a bSTC greater than 11.4 µg/L. Of 43 patients with a bSTC greater than 11.4 µg/L, 3 patients (6.9%) experienced a local reaction (edema and injection site erythema) during the build-up phase (dose of 70 µg), after which the maximum single dose of 100 µg was reached after 1 week.

Of 1,098 patients with normal bSTCs, 2 patients (0.2%) developed a mild SR (urticaria) during the build-up phase (a bSTC of 2.7 µg/L in one case and 3.1 µg/L in the other). In these patients, we did not consider large local reactions because they are common, are usually not a risk factor for a SR, and do not usually necessitate a reduction in the venom dose or prevent the protective dose from being reached.

The maintenance dose of 100 µg per venom was successfully given after 1 week, 2 weeks, and then every 4 to 6 weeks for at least 3 years, with no adverse effects.

According to the recent European guidelines, VIT is effective and safe and may be recommended in patients with underlying SM.² VIT is usually well tolerated by most patients with SM,⁶ although SRs tend to be more frequent.³ Whether an elevated bSTC alone increases the risk for adverse events remains an open question; only one study found a significant association between risk for adverse events and bSTC in vespid venom allergic patients and when using a 1-day ultrarush protocol.⁴

We report the safety of VIT in real life using an ultrarush protocol in 1,141 vespid allergic patients. VIT was well tolerated in all patients, including those with a bSTC greater than 11.4 µg/L, among whom 20 patients were diagnosed with indolent SM or urticaria pigmentosa. Moreover, in some patients with severe anaphylaxis and a bSTC between 20 µg/L and 11.4 µg/L or at even lower concentrations, a diagnosis of clonal mastocytosis disorder is presumable.⁷ We are aware that an early diagnosis would help to prevent certain SM complications. However, the hematologic workup was possible in only 59% of our patients because of logistic issues or patient apprehension.

No comparative studies are available with which to evaluate different build-up protocols in patients with mastocytosis diseases. In more recent observational studies, conventional or cluster protocols have been used in patients with mastocytosis, of whom 12.5% to 14% developed mild SRs.^{3,6} The frequency of VIT SRs in large multicenter studies of HVA patients ranges from 8% to 20%.² In a more recent study, which recruited 84 HVA patients with clonal mastocytosis disorders, 24 patients received conventional VIT, 75 received a rush-modified induction, and 3 received a 4-day rush induction.¹ Even though SRs only occurred in 4 patients (4.7%) (only one reaction with vespid venoms) and were not statistically significant, the authors suggest a less aggressive induction in these patients. VIT was also well tolerated in 9 wasp venom allergic patients with mastocytosis using a 3-day rush protocol, with 1 SR.⁸ Of note, therapy was with extracts from various manufacturers, which the evaluation's time span made inevitable.^{1,3,6} We evaluated VIT safety of a 2-day ultrarush schedule and not its effectiveness because the treatment efficacy is unaffected by the type of buildup phase.⁹

In conclusion, this is the first real-life study evaluating the safety of a 2-day ultrarush protocol in a substantial number of vespid allergic patients with SM and/or an elevated bSTC. Further studies on a larger scale will be necessary to confirm our findings, and until such data are available, ultrarush protocol should

only be performed by VIT specialists in an emergency department setting.

Acknowledgment

We thank Paul Bowerbank for his help in reviewing the English of the paper.

Maria Beatrice Bilò, MD*

Alice Corsi, MD†

Stefano Agolini, MD†

Chiara Tontini, MD†

Leonardo Antonicelli, MD*

*Allergy Unit

Department of Internal Medicine

University Hospital Ospedali Riuniti di Ancona Via Conca

Ancona, Italy

†Postgraduate School of Allergy and Clinical Immunology

Università Politecnica delle Marche

Ancona, Italy

mariabeatrice.bilo@ospedaliuniti.marche.it

References

- [1] Bonadonna P, Gonzalez-de-Olano D, Zanotti R, et al. Venom immunotherapy in patients with clonal mast cell disorders: efficacy, safety, and practical considerations. *J Allergy Clin Immunol Pract*. 2013;1:474–478.
- [2] Sturm GJ, Varga EM, Roberts G, et al. EAACI Guidelines on Allergen Immunotherapy: Hymenoptera venom allergy. *Allergy*. 2018;73:744–764.
- [3] González de Olano D, Alvarez-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.
- [4] Ruëff F, Przybilla B, Biló MB, et al. Predictors of side effects during the buildup phase of venom immunotherapy for Hymenoptera venom allergy: the importance of baseline serum tryptase. *J Allergy Clin Immunol*. 2010;126:105–111.
- [5] Biló BM, Ruëff F, Mosbech H, et al. Diagnosis of Hymenoptera venom allergy. *Allergy*. 2005;60:1339–1349.
- [6] 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.
- [7] Zanotti R, Lombardo C, Passalacqua G, et al. Clonal mast cell disorders in patients with severe Hymenoptera venom allergy and normal serum tryptase levels. *J Allergy Clin Immunol*. 2015;136:135–139.
- [8] Verburg M, Oldhoff JM, Klemans RJ, et al. Rush immunotherapy for wasp venom allergy seems safe and effective in patients with mastocytosis. *Eur Ann Allergy Clin Immunol*. 2015;47:192–196.
- [9] Goldberg A, Confino-Cohen R. Bee venom immunotherapy: how early is it effective? *Allergy*. 2010;65:391–395.

Anaphylaxis care guidelines and the effect on health care resource use in the United States



For patients with anaphylaxis, US guidelines recommend first-line therapy with epinephrine to prevent fatalities, as well as prescription of an epinephrine autoinjector (EAI), referral to an allergist/immunologist, and training to identify and avoid the

responsible allergen.^{1–3} However, adherence to these guidelines is low,^{4–6} and generally, patients face increased health care resource use and associated costs.⁴

We evaluated concordance with pre-event and postdischarge care guidelines and health care resource use among adults (aged ≥18 years) and children (aged <18 years) using inpatient or emergency department (ED) claims for anaphylaxis in the MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases. These databases comply with the Health Insurance Portability and Accountability Act of 1996. Because this study was composed of deidentified data, it was exempt from review and approval by an institutional review board.

Patients were selected if they had 1 or more claim for anaphylaxis between January 1, 2009, and December 31, 2012, and continuous medical/pharmaceutical coverage for 1 year or more

Disclosures: Dr Song reported payment for lectures, including service on speakers' bureaus, by Teva and Novartis. Dr Corvino reported that he is an employee of Genesis Research LLC, which received funding to perform this research. Dr Lehnigk reported that he is an employee of Allergopharma GmbH & Co KG, Reinbek, Germany. Dr Lieberman reported receiving consulting fees or honorarium and support for travel to meetings from Kaleo and Mylan, provision of writing assistance for Allergopharma, and advisory board membership of Kaleo. No other disclosures were reported.

Funding Sources: This real-world evidence study was funded by EMD Serono Inc., Rockland, Massachusetts. Medical writing was funded by Allergopharma GmbH & Co KG, Reinbek, Germany.