

Clinical Communications

One-day ultrarush desensitization for Hymenoptera venom anaphylaxis in patients with and without mast cell disorders with adjuvant omalizumab

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Clinical Implications

- We describe a novel 1-day venom desensitization protocol coupled to an option for omalizumab that enables successful venom immunotherapy in patients with life-threatening anaphylaxis after Hymenoptera sting, mast cell activation disorders, and/or recurrent systemic reactions during conventional venom immunotherapy. Patients at the highest risk of anaphylaxis from Hymenoptera venom may benefit from rapid attainment of maintenance-dose venom immunotherapy.

TO THE EDITOR:

Systemic hypersensitivity reactions to Hymenoptera venom occur in 1.2% to 3.5% of the population. In patients with systemic mastocytosis, the incidence of Hymenoptera-induced systemic reactions is 20% to 50%, considerably greater than that in the general population.¹ Fatalities are rare but have been reported in patients with and without mastocytosis.

The association of Hymenoptera venom hypersensitivity and mastocytosis was first reported in 1983 by Müller et al.² Further studies have shown that patients with mastocytosis develop disproportionately severe reactions including hypotension and severe anaphylaxis.¹ This observation has led to a strong recommendation for venom immunotherapy (VIT) in patients with mastocytosis (VIT), for whom it has been shown to be overall safe and effective.³ However, immunotherapy in patients with mast cell disorders is often challenging and up to 30% of patients have adverse reactions to VIT including anaphylaxis.³ Reactions may delay progression to maintenance and may lead to discontinuation of immunotherapy. Such barriers to treatment are of particular concern in patients with mastocytosis because VIT is a potentially lifesaving therapy.

Accelerated VIT protocols have been developed to attain rapid protection, and the rate of adverse reactions appears to be similar to that with conventional VIT. Ultrarush protocols have been used successfully in VIT. Few protocols have demonstrated successful accelerated VIT in patients with clonal mast cell disorders, including a 3-day protocol.^{4,5} In addition to accelerated protocols, omalizumab has been used to facilitate VIT progression in challenging patients with and without systemic mastocytosis.⁶

Here, we report the development and successful implementation of a rapid (ultrarush) 1-day venom desensitization protocol for patients with Hymenoptera venom anaphylaxis. The protocol safely achieves maintenance doses in 6 hours in high-risk patients

with and without clonal mast cell disorders. In this highly sensitized and reactive patient population, the benefit of rapid desensitization is important because future stings may be fatal.

This study included a total of 13 patients from age 33 to 71 years. Eight patients were women (62%) and 5 were men (38%). Seven (54%) had a clonal mast cell disorder: 5 with indolent systemic mastocytosis (ISM) and 2 with monoclonal mast cell activation syndrome. Of note, 1 patient with ISM had a normal baseline serum tryptase level. The mean baseline serum tryptase level was 23.8 ng/mL in patients with ISM and 21.4 ng/mL in patients with monoclonal mast cell activation syndrome. Clinical and demographic characteristics are reported in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

All patients had anaphylaxis within 30 minutes of sting. Ten of 13 (77%) had syncope or documented hypotension. Three patients received *cardiopulmonary resuscitation* in the field and were intubated. One patient with ISM had a serum tryptase level of 2640 ng/mL several hours after a sting. Most patients (11 of 13 [85%]) were sensitized to multiple Hymenoptera. Honeybee sensitization was most common and observed in 9 of 13 (69%) patients, with 2 patients monosensitized.

Eight (8 of 13 [62%]) patients received omalizumab before venom ultrarush desensitization. Five patients were started on omalizumab because of mast cell disorder in preparation for VIT. One was started on omalizumab because of recurrent VIT reactions. Two had been on omalizumab before consideration of ultrarush VIT.

A total of 24 desensitizations were conducted in 13 patients. Table I describes clinical characteristics and desensitization outcomes. Premedications are detailed in Table E3 in this article's Online Repository at www.jaci-inpractice.org. All desensitizations used purified venom extract from Hollister-Stier. All procedures were successful, and all patients received cumulative maintenance doses. The initial desensitization protocol was 16 steps, which was iteratively reduced to 12 after safety was established. Table II describes the mixed vespid protocol. The single venom protocol (wasp, honeybee, etc) is found in Table E2 in this article's Online Repository at www.jaci-inpractice.org. Ten of 24 (42%) procedures developed breakthrough reactions ranging from injection-site erythema/pruritus to tongue edema. One patient was administered intramuscular epinephrine but was able to resume VIT and successfully complete desensitization.

After ultrarush desensitization, 9 of 13 patients have remained on VIT at standard maintenance dosing. One discontinued because of difficulty with scheduling. Two were lost to follow-up. One patient had a systemic reaction on maintenance dose and has continued at a reduced dose. Three patients have experienced field stings after ultrarush desensitization and maintenance immunotherapy. One patient developed a large local reaction. One patient suffered 2 stings without symptoms. One patient is a beekeeper and has had multiple stings without symptoms. Long term outcomes including maintenance therapy and field stings are detailed in Table E3.

Our case series illustrate a novel and well-tolerated, ultrarush VIT protocol that can be completed in 1 day in patients without

TABLE I. Clinical data and ultrarush desensitization outcomes

Patient diagnosis (baseline tryptase)	Symptoms (onset, min)	Reaction treatment	Specific IgE (kU/L)	Skin testing (positive)	Venom desensitization	Omalizumab (no. of injections)	Reaction (step)	Reaction (symptom)	Reaction (treatment)
1 — (9.0)	S, R (1)	Epi	W: 7.2 YJ: 3.53 WH: 2.22		MV	No	6	R	H ₁
2* — (4.1)	S, R, CV (1)	Epi	WH: 0.99	HB: 0.01 YJ: 1.0 YH: 1.0	W HB	No	None		
3 mMCA (17.6)	R, CV (1)	CPR Intubation	W: 3.55 YJ: 2.69 WH: 0.91		MV	Yes (3)	9 13	9: S 13: S, R	9: H ₁ 13: none
4 — (2.7)	S, R, CV (5)	Epi		W: 1.0 YJ: 1.0 WH: 1.0	W MV	Yes (2)	None		
					W		3 6 12	3: R 6: R 12: CV	3: H ₁ , H ₂ , S, β_2 6: H ₁ β_2 12: Epi, H ₁ , S
5 ISM (123.0)	S, R, CV (2)	Epi $\times$ 4 Tryptase: 2640 ng/mL	W: 10.7 YJ: 0.53		MV	Yes (2)	None		
6 ISM (15.7)	CV (20-30)	Epi CPR Intubation	W: 0.36 YJ: 18.6	HB: 1.0	W YJ	Yes (3)	None		
					W HB		None		
7 mMCAS (25.2)	GI, CV (10)	Epi	HB: 2.0		HB	No	None		
8* ISM (58.1)	S, CV (1)	Epi CPR intubation	HB: 1.38 W: 7.26 YJ: 8.3 YH: 0.89 WH: 2.17	W: 1.0 YJ: 1.0 WH: 1.0	HB	Yes (3)	12	R	β_2
					MV		9	S	H ₁
9* ISM (40.1)	S, CV (10)	Epi		HB: 1.0 WH: 1.0	W WH	Yes (2)	None Post-VIT	S	H ₁

10* — (1.6)	S, CV (10)	Epi	HB: 4.05 W: 10.1 YH: 3.96 WH: 4.88	MV	No	1 5 13	1: R 5: R 13: S	1: H ₁ 5: H ₁ , β ₂ 13: H ₁ , S
				W		11	S	None
11 ISM (5.3)	S, CV (1)	None	HB: 2.42	HB	Yes	None		
12 — (3.1)	S, CV (30)	None	HB: 1.6 YJ: 3.05 YH: 0.84 WH: 1.58	HB	Yes	5	S	H ₁
				MV		None		
13* — (3.5)	S, R (10)	Epi	HB: 0.1	HB	No	7 11 12	7: R 11: R 12: R	7: H ₁ 11: β ₂ 12: β ₂
				HB		None		

mMCAS, Monoclonal mast cell activation syndrome.

Sting symptoms are coded as S (skin/cutaneous), R (respiratory), CV (syncope, cardiovascular), and GI (gastrointestinal). Hymenoptera species/venoms are coded as HB, honeybee; MV, mixed vespid; W, paper wasp; WH, white-faced hornet; YH, yellow-faced hornet; and YJ, yellow jacket. Only positive skin testing and specific IgE results are documented. Specific IgE values are listed in kU/L (normal range, <0.10 kU/L). The concentration (μg/mL) at which skin testing is positive is listed. Adverse reactions are coded on the basis of organ system as follows: S (skin/cutaneous), R (respiratory), CV (cardiovascular), and GI (gastrointestinal). Medications administered for adverse reactions are coded as follows: H₁, H₁-antagonist; H₂, H₂-antagonist; LT, montelukast; 5LO, zileuton; ASA, aspirin; β₂, albuterol; and S, systemic corticosteroid.

*One patient discontinued VIT because of a delayed reaction. She underwent repeat HB desensitization, which was well tolerated.

TABLE II. Rapid desensitization protocol for mixed vespid

Step	Time (min)	Dilution	Concentration ($\mu\text{g}/\text{mL}$)	Volume (mL) subcutaneously	Dose (μg)	Cumulative dose (μg)
1	0	1:1000	0.3	0.2	0.06	0.1
2	30	1:1000	0.3	0.4	0.12	0.2
3	60	1:1000	0.3	0.8	0.24	0.4
4	90	1:100	3	0.2	0.6	1.0
5	120	1:100	3	0.4	1.2	2.2
6	150	1:100	3	0.8	2.4	4.6
7	180	1:10	30	0.2	6	10.6
8	210	1:10	30	0.4	12	22.6
9	240	1:10	30	0.8	24	46.6
10	270	1:1	300	0.1	30	76.6
11	300	1:1	300	0.25	75	151.6
12	330	1:1	300	0.5	150	301.6

Three dilutions of standard venom extract are created (1:1000, 1:100, 1:10). Each dose is administered in 30-min intervals. The first maintenance dose was administered 2 wk after desensitization, followed by once-monthly injections.

mast cell disorders and, following omalizumab, in patients with mastocytosis. All patients successfully completed venom desensitization, including 1 patient with monoclonal mast cell activation syndrome who did not receive omalizumab.

Omalizumab likely increases the safety and tolerability of VIT, particularly in patients with mast cell disorders. In cluster dosing of specific allergen immunotherapy, omalizumab pretreatment decreased the frequency of systemic reactions and was associated with an increased rate of reaching maintenance dosing,⁷ with similar effect in conventional VIT in patients with mastocytosis. This cohort included 1 patient with recurrent systemic reactions during build-up who tolerated build-up after omalizumab pretreatment.

The safety and efficacy of this procedure is likely secondary to both desensitization and omalizumab. Although VIT is safe and effective, ultrarush protocols have been associated with a higher risk of systemic reaction. This report uses a novel protocol combined with omalizumab. The protocol was based on previous desensitization protocols that have been used to safely administer chemotherapy and mAbs. The initial study protocol had 16 steps and was based on previously published protocols.⁸ Once safety was established, the protocol was iteratively refined to 12 steps, and used for the last several procedures. It is also important to note that in other contexts, omalizumab, in the absence of desensitization, has not been sufficient to protect against hypersensitivity reactions and anaphylaxis.⁹

Based on the safety and success of this protocol, it should be offered as an option for the management of patients with severe anaphylaxis to Hymenoptera. Patients with high-risk features or clonal mast cell disorders should be offered omalizumab and ultrarush venom desensitization.

Further research is necessary to assess the duration of omalizumab therapy. All patients received a minimum of 2 omalizumab injections before immunotherapy, continuing throughout maintenance therapy. In conventional allergen-specific immunotherapy, IgG₄ is generated within 5 weeks, which is associated with protection, indicating that omalizumab could be discontinued at that time. Personalized studies should include the measurement of specific IgG₄ postdesensitization and during maintenance therapy. One study has reported successful discontinuation of omalizumab after 6 months of therapy and tolerance of maintenance of VIT. The approach described

necessitates resources and expertise of an intensive care unit setting. The long-term benefit of this protocol necessitates observational real-life studies, though protection against anaphylaxis from observed field stings is encouraging. The mechanism of induced tolerance in VIT is not fully elucidated, and it is not known how rapid desensitization can lead to T_H2/T_H1 shift alongside regulatory T-cell increase. Without further understanding of tolerance induction, the optimal approach to build-up and maintenance long-term is uncertain, though multiple approaches, including ultrarush VIT, offer demonstrable protection.

High-risk patients with mast cell activation disorder, those who fail conventional VIT, or others with time-sensitive treatment requirements (beekeepers, golfers, etc) have the most need for treatment, yet paradoxically the greatest treatment barriers. Such barriers stem from innate risk of reactivity from underlying mast cell disorder, heightened reactivity during traditional VIT, and increased risk of seasonal Hymenoptera exposure. This study provides evidence of safety and efficacy of ultrarush VIT by desensitization, achieving protective VIT dosing in 6 hours in patients refractory to traditional VIT or at highest risk of life-threatening Hymenoptera reactions.

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METHODS

Patient selection and initial evaluation

This study included 13 patients with systemic reactions after Hymenoptera stings. All patients were referred to the Brigham and Women's Hospital Allergy and Immunology Clinic and/or the Brigham and Women's Hospital Mastocytosis Center for evaluation.

Any patient undergoing evaluation for Hymenoptera anaphylaxis was considered for the study. Rapid venom desensitization was performed for 3 primary indications: (1) clonal mast cell disease, (2) failure of conventional VIT, or (3) a high-risk situation (such as a beekeeper with honeybee anaphylaxis). There were no formal exclusion criteria.

All data collected for this study were approved by the Partners Healthcare institutional review board under 2 protocols: 2012P002481 and 2018P000122. Patients provided mandatory written informed consent before venom desensitization.

Diagnosis of mast cell disorders

Initial evaluation screening for clonal mast cell disease included a complete blood cell count with differential, baseline serum tryptase level, and skin examination for cutaneous mastocytosis. Patients with elevated tryptase and/or cutaneous mastocytosis underwent additional evaluation including a bone marrow biopsy and KIT D816V mutation analysis in bone marrow or peripheral blood. Mast cell diseases were diagnosed according to the major (bone marrow aggregates of 15 mast cells) and minor (tryptase >20 ng/mL, spindle mast cells, CD25 expression, and KIT D816V mutation) World Health Organization criteria.

Evaluation for Hymenoptera sensitization

All patients underwent evaluation with serum specific IgE or skin testing. Sensitivity to Hymenoptera species including honeybee, yellow jacket, white-faced hornet, yellow-faced hornet, and paper wasp was evaluated. Specific IgE level was measured

using Immunocap (ThermoFisher, Waltham, Mass; positive ≥ 0.1 kU/L).

Skin testing was conducted with standardized end-point titration. Skin prick testing used 1 μ g/mL extract. Intradermal testing was conducted with 0.01, 0.1, and 1 μ g/mL concentrations. Purified venom extracts (Hollister-Stier, Spokane, Wash) were used.

Omalizumab injections

Patients were administered omalizumab if they had evidence of a clonal mast cell disease or recurrent adverse reactions during conventional immunotherapy. All patients received 2 or more injections of 300 mg of omalizumab at 2- to 4-week intervals before starting ultrarush venom desensitization.

Desensitization protocol and premedications

All desensitizations were performed in the medical intensive care unit at Brigham and Women's Hospital or Brigham and Women's Faulkner Hospital. Patients arrived at the intensive care unit the morning of procedure and were discharged the same day. All patients provided full informed consent consistent with hospital policy before initiation of immunotherapy. Patients were supervised by an attending allergist/immunologist and a 1-on-1 nurse throughout the procedure. Two intravenous access points were secured, and each patient was attached to a monitor for continuous observation and recording of vital signs. A grid was drawn on both shoulders designating injection sequence to identify injection-site reactions.

Premedications were administered 30 minutes before initiation of the procedure. As-needed medications for adverse reactions were kept at the bedside. Patients were instructed to return to the outpatient allergy and immunology clinical setting every other week for 2 injections. Patients were then transitioned to regular monthly maintenance injections.

The initial protocol was a 16-step procedure and based on previously published desensitization protocols for chemotherapy and mAbs. Over time, institutional experience permitted iterative refinement to a 12-step protocol with improved balance of safety, efficacy, and expediency.

TABLE E1. Clinical and demographic characteristics of patients

Patient no.	Age (y)	Sex	Total IgE (IU/mL)	Baseline tryptase level (ng/mL)	KIT D816V	Mast cell disorder
1	42	F	12	9.0	No	None
2	55	M	—	4.1	No	None
3	71	F	26	17.6	No	mMCAS
4	61	M	—	2.7	No	None
5	60	M	159	123.0	Yes	ISM
6	70	F	69	15.7	Yes	ISM
7	70	F	—	25.2	No	mMCAS
8	57	F	53	58.1	Yes	ISM
9	46	M	<8	40.1	Yes	ISM
10	34	F	806	1.6	—	None
11	48	M	34	5.3	No	ISM
12	33	F	126	3.1	No	None
13	41	F	—	3.5	—	None
52.9		62% Females	160.6 IU/mL ($\pm$ 265.6)	23.8 ng/mL ($\pm$ 34.3)	4/11	7/13 with MCAD

F, Female; M, male; MCAD, mast cell activation syndrome; MCAS, mast cell activation syndrome; mMCAS, monoclonal mast cell activation syndrome.

Data are represented as absolute values. The bottom row represents mean $\pm$ 1 SD. “—” represents data that are not available. Mast cell disorders are coded as mMCAD, ISM, and MCAS. Two of 5 patients with ISM had monomorphic maculopapular cutaneous mastocytosis; the remainder do not have skin lesions.

TABLE E2. Rapid desensitization protocol for single venom desensitization

Step	Time (min)	Dilution	Concentration (μ g /mL)	Volume (mL) subcutaneously	Dose (μ g)	Cumulative dose (μ g)
1	0	1:1000	0.1	0.2	0.02	0.0
2	30	1:1000	0.1	0.4	0.04	0.1
3	60	1:1000	0.1	0.8	0.08	0.1
4	90	1:100	1	0.2	0.2	0.3
5	120	1:100	1	0.4	0.4	0.7
6	150	1:100	1	0.8	0.8	1.5
7	180	1:10	10	0.2	2	3.5
8	210	1:10	10	0.4	4	7.5
9	240	1:10	10	0.8	8	15.5
10	270	1:1	100	0.1	10	25.5
11	300	1:1	100	0.25	25	50.5
12	330	1:1	100	0.5	50	100.5

Three dilutions of standard venom extract are created (1:1000, 1:100, 1:10). Each dose is administered in 30-min intervals.

TABLE E3. Desensitization premedications and outcomes

Patient	Venom	No. of steps	Premedications	Reaction (step)	Reaction (symptom)	Ultrarush complete	Duration of maintenance (mo)	Field stings (symptoms)
1*	MV	16	H ₁ , H ₂ , LT, 5LO	6	R	Yes	NA	
	W	14	H ₁ , H ₂ , LT, 5LO	None		Yes		
2	HB	10	H ₁ , H ₂ , LT	None		Yes	52	Multiple (none)
3	MV	13	H ₁ , H ₂ , LT	9 13	9: S 13: S, R	Yes	38	
	W	14	H ₁ , H ₂ , LT	None		Yes		
4*	MV	13	H ₁ , H ₂ , LT	None		Yes	NA	
	W	14	H ₁ , H ₂ , LT	3 6 12	3: R 6: R 12: CV	Yes		
5	MV	13	H ₁ , H ₂ , LT, 5LO, ASA, β_2	None		Yes	21	
	W	12	H ₁ , H ₂ , LT, 5LO, ASA, β_2	None		Yes		
6	YJ	14	H ₁ , H ₂ , LT, 5LO, ASA, β_2	None		Yes	24	Two (none)
	W	14	H ₁ , H ₂ , LT, 5LO, ASA, β_2	None		Yes		
	HB	12	H ₁ , H ₂ , LT, 5LO, ASA, β_2	None		Yes		
7	HB	12	H ₁ , H ₂ , LT, 5LO, ASA, β_2	None		Yes	17	
8	HB	12	H ₁ , H ₂ , LT	12	R	Yes	20	
	MV	13	H ₁ , H ₂ , LT, 5LO, ASA	9	S	Yes		
	W	12	H ₁ , H ₂ , LT, 5LO, ASA, β_2	None		Yes		
9	WH	12	H ₁ , H ₂ , LT, 5LO, ASA, β_2	Post-VIT	S	Yes	DC	
10	MV	14	H ₁ , H ₂ , LT, 5LO, ASA, β_2	1 5 13	1: R 5: R 13: S	Yes	16	
	W	12	H ₁ , H ₂ , LT, 5LO, ASA, β_2	11	S	Yes		
	HB	12	H ₁ , H ₂ , LT, 5LO, ASA, β_2	None		Yes	2	
12†	HB	12	H ₁ , H ₂ , LT	5	S	Yes	20	One (local reaction)
13‡	MV	12	H ₁ , H ₂ , LT	None		Yes		
	HB	12	H ₁ , H ₂ , LT, 5LO, ASA, β_2	7 11 12	7: R 11: R 12: R	Yes	10	
	HB	8	H ₁ , H ₂ , LT, 5LO, ASA, β_2	None		Yes		

DC, Dendritic cell; NA, not available/applicable.

Sting symptoms are coded as S (skin/cutaneous), R (respiratory), and CV (syncope, cardiovascular). Hymenoptera species/venoms are coded as HB, honeybee; MV, mixed vespid; W, paper wasp; WH, white-faced hornet; and YJ, yellow jacket. Medications administered for adverse reactions are coded as follows: H₁, H₁-antagonist; H₂, H₂-antagonist; LT, montelukast; 5LO, zileuton; ASA, aspirin; and β_2 , albuterol.

Each desensitization is described above. Long-term outcomes are reported as months of continuous maintenance injections and field stings.

*Two patients were lost to follow-up and duration of VIT is unknown.

†Patients 11 and 12 were on omalizumab before consideration of VIT and had received multiple injections before VIT.

‡Patient 13 discontinued immunotherapy because of delayed reaction and underwent repeat desensitization with an abbreviated (8-step) protocol.