
Case report

Ultrarush venom desensitization after systemic reactions during conventional venom immunotherapy

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Background: Rush and ultrarush venom immunotherapy (VIT) protocols are safe and effective in patients with Hymenoptera hypersensitivity. However, these protocols have typically been used instead of conventional VIT and not in patients who have experienced adverse reactions during conventional VIT. To date, there are no reports of using an ultrarush VIT protocol to desensitize patients with a history of severe systemic reactions during conventional VIT.

Objective: To determine whether ultrarush VIT can be safely administered to a high-risk patient with a history of severe systemic reactions to conventional VIT.

Methods: Premedication with 40 mg of prednisone, 180 mg of fexofenadine, and 150 mg of ranitidine orally twice daily was initiated. The patient received VIT to mixed vespid and wasp in a medical intensive care unit via a 13-step buildup on day 1 followed by a 2-step buildup on day 2. Immunotherapy was begun with a dose of 0.005 μ g of mixed vespid and 0.002 μ g of wasp venom and achieved a total dose of 300 μ g of mixed vespid and 100 μ g of wasp venom.

Results: The patient tolerated the procedure with minimal adverse effects. She subsequently received maintenance dosing in the outpatient clinic weekly for 4 weeks and bimonthly for 8 weeks, and she continues monthly maintenance VIT.

Conclusions: We report the first successful use of ultrarush VIT in a high-risk patient with a history of severe systemic reactions during conventional VIT. This protocol should be considered in patients with a history of allergy to vespids or wasps who require VIT but cannot reach a maintenance dose with conventional VIT owing to systemic reactions.

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INTRODUCTION

Approximately 3% of the adult population in the United States is estimated to have had a systemic reaction to Hymenoptera venom.¹ The most serious systemic reactions involve the cardiovascular and/or respiratory system and are potentially life threatening, with an annual death rate of 40 adults per year in the United States.² The practice parameters of the American Academy of Allergy, Asthma, and Immunology recommend that patients with a history of a systemic reaction from an insect sting with venom specific IgE, based on results of skin or radioallergosorbent testing, should receive VIT.³

Venom immunotherapy has been practiced for more than 30 years and has an efficacy of 80% when patients can achieve the full maintenance dose of a standardized extract.⁴ Most patients in North America are treated with a “traditional” regimen of VIT that requires a buildup time of 4 to 6 months. More rapid schedules emerged that initially required 6 to 8 weeks to achieve a maintenance dose. In the 1980s, a

rush VIT schedule was created that reached maintenance levels in 3 days.^{5–7} More recently, ultrarush protocols have emerged that require 210 to 360 minutes for administration of a maintenance dose, with subsequent boosters before initiating a monthly schedule.⁸ These rush and ultrarush protocols have proved to be safe and effective but have typically been used in patients without a history of systemic reactions during conventional VIT.

A recent study explored the use of a rush VIT protocol in patients who had experienced systemic reactions during conventional VIT. Goldberg and Confino-Cohen⁹ studied 9 patients, of whom only 2 had severe systemic reactions during their conventional VIT schedule. Neither patient could complete the rush VIT protocol.

The patient described herein had experienced vascular collapse during field stings, thus qualifying her for VIT. However, she had experienced severe systemic reactions during conventional VIT and so had been deemed too risky to receive VIT. A repeated systemic reaction to a field sting prompted her to seek additional treatment options.

CASE REPORT

A 39-year-old woman with Hymenoptera sensitivity noted a history of a first field sting in 1990 that caused anaphylaxis manifested as vascular collapse and required epinephrine

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autoinjector (EpiPen; Dey Inc, Napa, CA) administration. She was evaluated at an allergy office at that time, had positive skin test results, and was given VIT with (probably, records unavailable) mixed vespid and wasp. She continued VIT for 2 years, with periodic reactions consisting of tongue swelling and lightheadedness, for which she was treated with epinephrine. She received VIT on a weekly basis, with a maximum dose of approximately 5 to 10 μg of wasp and 15 to 30 μg of mixed vespid venom. Because of these episodic adverse reactions, the patient could not reach a maintenance dose of VIT. She had an anaphylactic reaction after 1 injection, with tongue swelling and decreased blood pressure requiring epinephrine therapy, and she subsequently discontinued VIT.

She experienced another sting in 1999 while in the woods. She states that she was "grazed" by the insect. She was taken to a local emergency department for monitoring and did not manifest a systemic reaction. She did not require treatment. She was reevaluated by a different allergy practice with skin testing and venom IgG level measurement. She had a positive skin test reaction to wasp, yellow jacket, and white-faced hornet by means of intradermal testing at 0.01 $\mu\text{g}/\text{mL}$. Given her inability to tolerate conventional VIT, her physicians elected not to reattempt VIT.

In August 2005, the patient was stung on the extensor surface of the fingers on her right hand by a hornet or a yellow jacket. She took 50 mg of diphenhydramine (Benadryl; Pfizer Consumer Healthcare, Morris Plains, NJ) orally immediately and called 911. She did not self-administer epinephrine. She became anxious and developed abdominal cramping with subsequent emesis. Ten minutes later, emergency medical services arrived and administered epinephrine. She was told she had no detectable pulse or blood pressure and was given an additional dose of epinephrine and 2 L of intravenous fluids. She was seen in an emergency department and was discharged a few hours later.

The patient was referred to us to evaluate the potential for administering VIT. We also obtained a baseline total serum tryptase level to exclude systemic mastocytosis; the level was in the reference range at 2 ng/mL. Given her history of severe cardiovascular symptoms, we opted to admit her to the intensive care unit (ICU) for continuous hemodynamic and pulse oximetry monitoring during the buildup phase of mixed vespid and wasp venoms. We thought that this offered the safest environment for prompt recognition and treatment of a systemic reaction should one occur. To minimize the time spent in the ICU and increase cost-effectiveness, we used a modified version of an ultrarush 2-day desensitization protocol developed by one of us (S.C.). This protocol has been used successfully in patients who had failed conventional VIT owing to recurrent and recalcitrant systemic reactions.¹⁰

The patient was admitted to the ICU of the Massachusetts General Hospital in December 2005. She was given 180 mg of fexofenadine orally twice daily, 150 mg of ranitidine orally twice daily, and 40 mg of prednisone orally twice daily 3 days before the admission and was maintained on this regi-

men while in the ICU. The patient underwent continuous hemodynamic and pulse oximetry monitoring, and a peripheral intravenous catheter was placed. Informed consent was obtained. She received mixed vespid VIT in the left arm and wasp VIT in the right arm using aqueous venom extracts (Alk-Abello, Horsholm, Denmark) via a 13-step protocol (Table 1). A physician (E.O.) trained in the administration of VIT administered all the doses.

The patient exhibited local erythema reactions beginning at step 5 that were no larger than 4×4 cm in diameter for mixed vespid venom and 2×2 cm in diameter for wasp venom, except for the 5.1- μg dose of mixed vespid venom, which caused a 10×5 -cm area of erythema. Only the 90- μg dose of mixed vespid venom was accompanied by a wheal with flare. The patient complained of transient tingling of the tip of her tongue and bottom lip at steps 6 and 8. These symptoms resolved spontaneously within 5 minutes. She had no hemodynamic instability or hypoxia during the procedure.

On day 2, the patient received both doses in the ICU and again had local reactions of 1×1 -cm wheals and 3×3 -cm areas of erythema on both arms. She was discharged from the ICU 1.5 hours after administration of the second dose. The prednisone dose was tapered, and she continued taking a daily dose of 10 mg at the time of the first outpatient VIT injections 1 week later. Premedication with 180 mg of fexofenadine and 150 mg of ranitidine was continued before each subsequent VIT injection. The initial maintenance dose was given in split doses of 30, 90, and 180 μg of mixed vespid venom and 10, 30, and 60 μg of wasp venom, each separated by 30 minutes.

The patient received her second outpatient VIT the following week with the administration of split doses of 126 and 174 μg of mixed vespid venom and 42 and 58 μg of wasp venom (the doses were administered as on day 2 of the original protocol), each separated by 30 minutes. These split doses were chosen because of our desire for a conservative approach. Since then, the patient has received single injections of the maintenance dose for mixed vespid (300 μg) and wasp (100 μg) on a weekly basis for 2 additional injections and then every 2 weeks for 4 injections and monthly thereafter. She takes 180 mg of fexofenadine and 150 mg of ranitidine the day of VIT and undergoes baseline blood pressure measurements before the injection and then every 30 minutes afterward. She remains in the clinic for 1 hour after receiving the Hymenoptera vaccines.

DISCUSSION

Hymenoptera VIT is an important tool for the practicing allergist and offers almost complete protection from subsequent stings if the patient can reach an adequate maintenance dose. However, 8% of patients who begin VIT do not reach the maintenance dose.¹¹ Most of these failures of VIT are presumably due to systemic adverse reactions experienced during the escalation phases of VIT injections. The options in patients who have severe systemic reactions before achieving maintenance dosing are limited and include cessation of VIT

Table 1. Ultrarush Venom Desensitization Protocol*

	Time, min	Vial No.	Concentration, $\mu\text{g/mL}$	Volume, mL	Dose, μg
Day 1					
Mixed vespid, μg					
0.005	0	1	0.3	0.015	0.005
0.03	30	2	3	0.01	0.03
0.15	60	2	3	0.05	0.15
0.6	90	2	3	0.2	0.6
2	120	2	3	0.67	2.01
5	150	3	30	0.17	5.1
10	180	3	30	0.33	9.9
17	210	3	30	0.57	17.1
25	240	3	30	0.83	24.9
36	270	4	300	0.12	36
50	300	4	300	0.17	51
67	330	4	300	0.22	66
90	360	4	300	0.3	90
Wasp, μg					
0.002	0	1	0.1	0.02	0.002
0.01	30	2	1	0.01	0.01
0.05	60	2	1	0.05	0.05
0.2	90	2	1	0.2	0.2
0.67	120	2	1	0.67	0.67
1.7	150	3	10	0.17	1.7
3.3	180	3	10	0.33	3.3
5.7	210	3	10	0.57	5.7
8.3	240	3	10	0.83	8.3
12	270	4	100	0.12	12
17	300	4	100	0.17	17
22	330	4	100	0.22	22
30	360	4	100	0.3	30
Day 2					
Mixed vespid, μg					
126	0	1	300	0.42	126
174	30	1	300	0.58	174
Wasp, μg					
42	0	1	100	0.42	42
58	30	1	100	0.58	58

* Listed here are the 13 steps that compose the desensitization procedure on day 1 and the 2-step protocol for day 2. The cumulative dose is 302.8 and 100.93 μg for mixed vespid and wasp, respectively, on day 1. The cumulative dose is 300 and 100 μg for mixed vespid and wasp, respectively, on day 2.

or maintenance at a lower dose. Cessation of VIT is an undesired option given that patients who experience systemic reactions during VIT and subsequently discontinue treatment have a 46% chance of experiencing a systemic reaction with future field stings.¹²

Furthermore, maintenance at a lower dose than the target of 100 μg because of systemic reactions does not confer the same level of protection from re-sting. Specifically, choosing a dose of 50 μg because of anaphylactic reactions during VIT provides 79% protection from re-sting compared with the 96% to 100% protection of the 100- μg dose.¹³ It also seems that continuing VIT at subtherapeutic doses tends to increase IgE levels without any protective immune response.¹⁴

The patient described herein had experienced severe (Mueller grade IV) field stings and could not achieve an

adequate maintenance VIT dose owing to systemic adverse reactions. We used an aggressive premedication regimen and an ultrarush protocol developed based on the principle that early doses carry a lower risk of severe reactions and thus are amenable to larger incremental increases. The increment from the first to the second dose is a 6-fold increase in the amount of venom administered, and that from the second to the third dose is a 5-fold increase. The increments gradually decrease, resulting in a curvilinear rather than an arithmetic dose escalation, and lead to attainment of the maintenance dose cumulatively (Fig 1).

A large body of evidence has demonstrated that premedication with antihistamines decreases the rate of systemic adverse reactions without affecting the efficacy of rush VIT.^{15–17} No studies, to our knowledge, have evaluated the

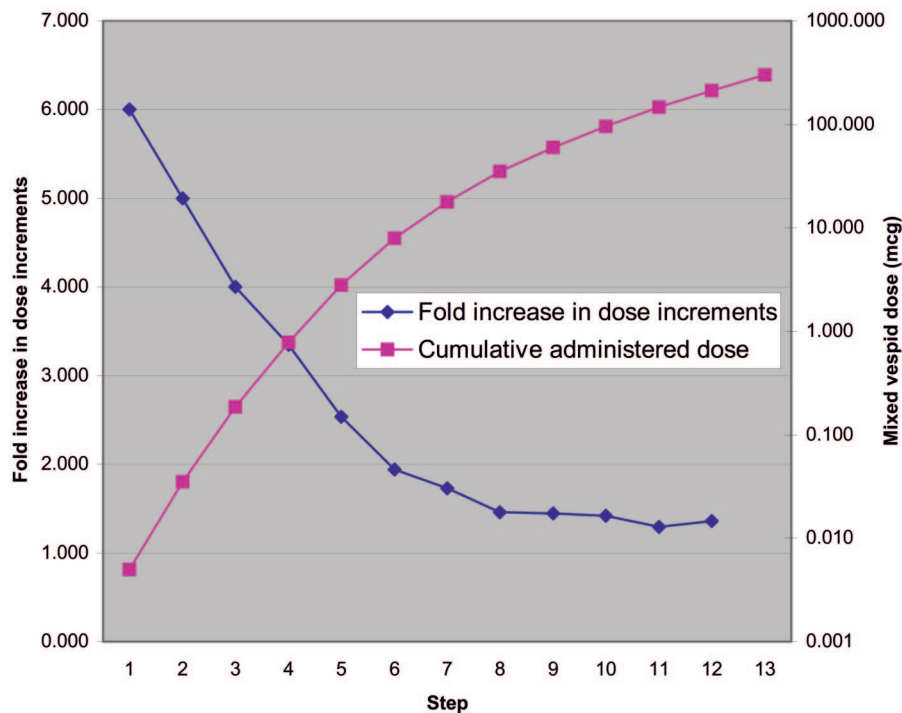


Figure 1. Curvilinear progression of the cumulative doses of mixed vespid immunotherapy administered in 13 steps and the incremental difference between doses. The increment between steps 1 and 2 is 6-fold, and that between steps 2 and 3 is 5-fold. The larger incremental changes at the start are based on the principle that early doses carry a lower risk of severe reactions and thus are amenable to larger incremental changes.

effect of premedication with corticosteroids on these variables or interference with the desired immunologic changes associated with successful VIT. We chose to use high doses of prednisone as pretreatment because of the severity of the patient's previous reactions to field stings and VIT. Her ability to receive subsequent doses of VIT without corticosteroid pretreatment suggests that corticosteroids offered transient protection without affecting the underlying immunologic mechanisms of VIT.

Our rationale for choosing an ultrarush protocol performed in the ICU came from the balance between administering the buildup phase of the VIT in a fast and safe manner without excessive use of a limited and costly hospital resource, the ICU. The ICU setting offered continuous hemodynamic and pulse oximetry monitoring and the availability of trained medical personnel who could quickly react to and manage a severe adverse reaction, which is a foreseeable hazard of ultrarush VIT. Performing an elective outpatient procedure in the ICU restricted the length of this admission to 24 hours, in which desensitization could be achieved with the current ultrarush protocol. One limitation of this experience is that the patient did not require VIT to honey bee venom, which has exhibited a higher incidence of systemic adverse reactions during rush VIT.⁸

We report the first successful use of an ultrarush venom desensitization protocol in a patient with a history of severe systemic reactions during conventional VIT. This protocol

should be considered in patients with a history of allergy to vespids or wasps who have an indication for VIT and who have been unable to reach a maintenance dose with conventional VIT. Because this experience is limited to the use of this protocol in an ICU setting, we recommend the same approach until the safety of the protocol can be established in other settings.

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