
Rush venom immunotherapy in patients experiencing recurrent systemic reactions to conventional venom immunotherapy

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Background: An unknown number of venom-allergic patients fail to reach the maintenance dose (MD) during the build-up period of conventional venom immunotherapy (VIT) due to recurrent systemic reactions (SRs).

Objective: To establish an alternative VIT protocol that will enable these patients to reach a full protective MD.

Methods: Venom-allergic patients who had experienced recurrent SRs during the build-up period of conventional VIT underwent rush VIT.

Results: Of the 9 patients who participated in this study, the 6 who underwent 8 treatment courses tolerated the rush VIT well and reached the MD within 3 days. In 3 of these patients, mild cutaneous SRs were overcome with loratadine. In 2 patients who experienced recurrent and more severe SRs, the original 3-day rush VIT had to be modified and extended to 5 days until the MD was reached. In a single patient who experienced an anaphylactic reaction, VIT was discontinued.

Conclusions: Rush VIT is an appropriate therapeutic alternative that enables most patients with recurrent SRs throughout the build-up period of conventional VIT to reach a full protective MD.

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INTRODUCTION

Venom immunotherapy (VIT) is considered protective against future insect stings only after the maintenance dose (MD) has been achieved. However, an unknown number of venom-allergic patients fail to reach the MD during the build-up period of conventional VIT due to recurrent systemic reactions (SRs). Most practicing allergists favor the 100- μ g dose, although in a few patients even this dose has been shown to be nonprotective and increased doses have been required to ensure protection.¹ Some researchers advocate that a MD of 50 μ g is sufficient,² although others have shown that this dose protects only 79% of adults from challenge sting reactions.³ No works have studied the efficacy of smaller dosages, but in general, they are considered nonprotective and most clinicians aim to achieve the full MD. The incidence of SRs that result from administration of VIT varies from 5.8% to 58.8%, according to different studies.^{4–13} The incidence is higher during the build-up period compared with the maintenance treatment.^{4–6}

Occasionally, patients experience recurrent SRs immediately after venom injections. In most of these patients, lowering the dose after the SR and subsequent minute gradual increments of the dose will enable the patient to eventually reach the full MD. In a few patients, recurrent trials of decreasing and slowly increasing the dose are repeatedly associated with SRs.

The build-up period of conventional VIT is composed of gradual increments of the venom dosage, at weekly intervals, for 3 to 4 months until the MD is reached. Previous studies with various protocols have demonstrated both the efficacy and safety of rapid VIT.^{5,14–16} In rush VIT, the build-up period is significantly shortened by administration of many venom injections at 15-minute intervals, for several days, until the MD has been reached. The underlying mechanism responsible for the long-term protection may be similar in both procedures. However, the early protection achieved within several days by rush VIT probably implies a different mechanism compared with the one responsible for long-term protection. Therefore, we hypothesized that rush VIT might be a possible alternative for patients who develop SRs during the build-up period of conventional VIT, thus enabling them to achieve the full MD and gain maximal protection.

METHODS

Patients who had experienced a SR inflicted by an insect sting and were found to have a positive skin test result to bee venom (BV) and/or yellow jacket (YJ) venom began receiving conventional VIT at weekly intervals. VIT was begun with a dose of 0.01 to 0.1 μ g and was gradually increased. Patients who developed recurrent SRs after the venom injections were instructed to take loratadine 1 hour before the next injection. After a SR, the dose was reduced by 50% or more and was then gradually increased at a slower pace. Patients who continually developed SRs despite these measures were offered a trial of rush VIT. None of them refused and their characteristics are described in Table 1. All patients were in general good health and were taking no medications on a regular basis. None of the patients had any symptoms or

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Table 1. Patient Characteristics Before Rush VIT

Patient no./sex/age, y	Severity of initial SR (Muller grading)	Time elapsed since SR to insect sting, y	Conventional VIT	Symptoms of SRs after VIT (No.)	Maximal venom dose of VIT, μg
1/F/30	4 (LOC)	2	YJ	Dyspnea, wheezing (4)	50 (divided into 2 doses)
2/M/46	2	6	BV	Rash, pruritus, tearing, rhinitis (12)	40
3/F/18	3	2	BV	Dyspnea, wheezing, rash (8)	0.1
4/F/42	2	14	BV	Chest tightness, pruritus (9)	50 (divided into 2 doses)
5/M/58	2	1	BV and YJ	Dyspnea, diffuse rash (5)	20
6/M/53	3	2	BV and YJ	Dyspnea, pruritus, nausea, redness (7)	85
7/F/60	3	0.4	BV	Rash (6)	7.5
8/M/35	2	0.5	BV	Pruritus, dyspnea, perspiration (3)	20
9/F/67	4 (LOC)	0.2	BV	LOC, vomiting, low blood pressure (1)	5

Abbreviations: BV, bee venom; LOC, loss of consciousness; SR, systemic reaction; VIT, venom immunotherapy; YJ, yellow jacket.

findings on physical examination that suggested systemic mastocytosis. Patient 9 experienced only a single, remarkable, severe SR after a relatively low dose of venom (5 μg) was administered to her during conventional VIT. However, her allergist was reluctant to continue VIT, and therefore we agreed to attempt rush VIT on her after only a single SR to conventional VIT.

After obtaining informed consent from the patients, venom skin tests were repeated just before the initiation of rush VIT. After their results were examined, an intravenous line was inserted and heart rate and blood pressure were monitored at 10-minute intervals. Rush VIT was administered subcutaneously, with increasing doses of venom as described in Table 2.

RESULTS

Nine patients participated in this study. In all 9 patients, venom skin test results were positive to the venoms they had been previously treated with. Patient 3 developed 2 urticarial lesions after a prick skin test with a concentration of 1 $\mu\text{g}/\text{mL}$

was performed. Therefore, rush VIT was begun with a dose of 0.01 μg . Other than this exception, patients 1 through 6 received the rush VIT with the protocol we had been using for all other venom-allergic patients, as presented in Table 2.

Patients 1 and 2 tolerated the entire protocol well. One week after reaching the MD, a live bee-sting challenge was performed on patient 2 without any adverse reactions. Patient 1 continued to receive the MD twice at 1-week intervals, twice at 2-week intervals, twice at 3-week intervals, and at a 1-month interval thereafter.

Patient 3 developed a small number of urticarial lesions at the end of day 1. Later, after the injection of 100 μg on day 3, she complained of pruritus of the neck and both forearms. She was instructed to take loratadine before the following injections, which were all well tolerated thereafter. After reaching the 1-month interval, the maintenance interval (MI) in this patient was gradually increased as previously described and then to twice at 6 weeks, twice at 2 months, and eventually 3 months.

We acted similarly with patients 4 and 5, who developed pruritic rash and facial pruritus after receiving the 100- μg dose on day 3 and the first 20- μg dose of BV on day 1, respectively. With loratadine being taken before the following treatment days, no further adverse reactions were observed in both these patients. In patient 5, BV was administered during the first rush VIT, whereas YJ venom was administered during the second course, performed 3 weeks later. In these 2 patients, the MI had been gradually increased up to a 1-month interval as previously described.

In patient 6, other than pruritus of hands and lips after the first 20- μg dose on day 1, rush VIT with BV was completed uneventfully, according to the original protocol. This patient reached the 100- μg dose of BV on day 3, and 10 days later rush VIT with YJ venom was performed uneventfully. One week later, the patient was given the MD of both venoms simultaneously without any adverse reaction. Two weeks later, the same dosage resulted in mild generalized pruritus and mild, nonprogressing dyspnea, necessitating loratadine

Table 2. Rush Venom Immunotherapy Protocol*

Day	Venom concentration, $\mu\text{g}/\text{mL}$	Volume, mL	Dose, μg	Daily accumulative dose, μg
1	1	0.05	0.05	58.55
	1	0.1	0.1	
	1	0.2	0.2	
	1	0.4	0.4	
	1	0.8	0.8	
	10	0.2	2	
	10	0.5	5	
	10	1.0	10	
	100	0.2	20	
	100	0.2	20	
2	100	0.2	20	100
	100	0.3	30	
	100	0.5	50	
3	100	1.0	100	100

* There were 15-minute intervals between venom injections.

and salbutamol inhalation. Similar SRs occurred recurrently during the next 2 treatment courses. Therefore, instead of administering the 100- μ g MDs simultaneously, we gave them at 1-hour intervals. This way, VIT was well tolerated, and after giving the full MDs at 1-week intervals 4 times, we gradually extended the interval to 4 weeks and have similarly continued for the past 5 months with no adverse reactions.

After administration of the first 20- μ g dose on day 1, both patients 7 and 8 developed mild diffuse rashes and patient 8 also developed nasal congestion and mild, nonprogressing dyspnea. He was treated with loratadine and salbutamol inhalation. Similar symptoms developed in both patients during the next day, after the 30- μ g dose, despite having taken loratadine (patient 8) or fexofenadine (patient 7) during that morning. Therefore, the rush VIT protocol was modified. Whenever such symptoms developed, the following dose was not increased but was rather repeated after 30 to 60 minutes, and if no worsening of the symptoms was observed, the dose was increased again, at a slower pace. On day 4 both patients received 100 μ g/mL (0.4, 0.6, and 0.8 mL), and on day 5 the full 100- μ g MD was administered. Patient 7 still developed mild erythema after administration of the MD on day 5, but it did not recur on day 8 after another MD was administered. An in-hospital live bee-sting challenge was performed on this patient on day 12 without any adverse reaction, and she has continued receiving the MD uneventfully ever since. Patient 8 continued with the 100- μ g MD on day 8, day 12, and then twice at weekly intervals. He continued to receive his treatment by the referring allergist, who practiced closer to his home. Two weeks later, the MD was administered uneventfully, and the patient was instructed to continue with the 2-week interval. He returned for the next treatment only 3 weeks later and developed rhinorrhea and generalized pruritus after the administration of the 100- μ g MD. He was treated with subcutaneous epinephrine and all symptoms subsided. The patient was lost to follow-up thereafter, claiming he was unwilling to continue VIT.

Patient 9 tolerated all doses of day 1 well until she reached the 20- μ g dose. Five minutes after the administration of this dose, she developed facial erythema, she vomited several times, her blood pressure dropped to 75/40 mm Hg, and she lost consciousness for 30 seconds. She was treated with subcutaneous epinephrine and intravenous metoclopramide and recovered within 10 to 20 minutes. No further attempt to give her VIT took place. A summary of all 7 patients is presented in Table 3.

DISCUSSION

The goal of VIT is to reach the MD and maintain it regularly for 3 to 5 years or even longer. The efficacy of this protocol in preventing future SRs inflicted by insect stings varies between 77% and 99% according to different researchers.^{7,17,18} Most allergists aim at reaching 100 μ g as the appropriate MD, although some researchers claim that 50 μ g may still be as efficient as the 100- μ g dose. No works have documented the efficacy of smaller doses.

Failure to reach the MD has been encountered in 8% of the patients treated with VIT.¹⁹ However, according to the data presented by Lockey et al,¹⁹ it is impossible to determine whether the inability to reach the MD was due to the patient's failure to comply or to recurrent SRs inflicted by the venom injections. Although the incidence of this phenomenon is unknown, almost every allergist has encountered a patient in whom the MD could not be achieved because of recurrent SRs throughout the VIT. Some allergists may simply continue with the highest tolerable dose, disregarding its probable lack of efficacy in the face of SRs to higher doses. Others may try to increase the total administered dose by injecting separate smaller doses, at 15- to 30-minute intervals, which would accumulate to a dose higher than the one that had induced the SR. The efficacy of both techniques is unclear. Alternatively, patients with these SRs occasionally give up VIT either because of their unwillingness to experience further SRs or because they feel that the desired protection from future stings will not be achieved unless they reach the full MD. Occasionally, these patients may receive the same advice from the allergist.

Systemic reactions after venom injections throughout immunotherapy are more common during the build-up period compared with the maintenance treatment.⁴⁻⁶ Their incidence is not associated with the severity of the initial SR after the insect sting.²⁰ This incidence varies significantly according to the type of the injected venom and the different VIT protocols.^{4-16,21}

The underlying immunoregulatory mechanism of VIT remains poorly understood. Works examining this question differ significantly in regard to the antigens administered during the immunotherapy, the protocol of immunotherapy, duration before reaching the MD, time points at which the immunological assays were performed, cell populations that were studied, the method of cell stimulation (specific antigen or a mitogen), and the cytokines or chemokines that were measured. It is accepted that immunotherapy is associated with a shift in cytokine response from a T_H2 to a T_H1 dominant pattern.¹⁹⁻²⁶ However, most works studying this issue have exclusively examined either conventional immunotherapy or rush immunotherapy and did not compare the effect of each of the protocols on the cytokine shift, one along with the other. In a single work that examined this subject specifically, the timing of cytokine response shifting from T_H2 to T_H1 was different in conventional VIT and in rush VIT.²⁷ Nevertheless, the desired goal of immunotherapy, namely, the induction of tolerance to the specific allergen, has been shown to occur following the completion of rush VIT. Thus, histamine depletion of basophils,²⁸ decreased release of histamine and sulfidoleukotrienes by human peripheral blood leukocytes,²⁹ and partial basophil degranulation together with basophil surface membrane antigen alternation³⁰ have all been described immediately after the achievement of MD. A partial explanation for this may be associated with interleukin 10, which is considered a key cytokine throughout the entire process of immunotherapy,²⁹ and probably originates in dif-

Table 3. Results of Rush VIT

Patient No.	Adverse reactions to original rush VIT protocol	Action taken	Adverse reactions to MD VIT	Action taken and follow-up	Present situation	
					MD VIT duration	MD interval
1	None		None		12 mo	4 wk
2	None		None		3 mo	3 wk
3	Mild urticaria after second 20- μ g dose on day 1, pruritus after 100- μ g dose on day 3	Loratadine before next injections	None		22 mo	3 mo
4	Rash after 100- μ g dose on day 3	Loratadine before next injections	None		14 mo	4 wk
5	Facial pruritus after first 20- μ g dose on day 1	Loratadine before next injections	None		17 mo	6 wk
6	Pruritus of hands and lips after first 20- μ g dose on day 1	None	Pruritus and dyspnea 3 times while taking MD	Separate administration of bee and yellow jacket venoms, well tolerated	9 mo	4 wk
7	Diffuse erythema after first 20- μ g dose on day 1	Slower modified rush VIT protocol, several episodes of erythema, eventually well tolerated	Rash after administration of first MD		2 mo	2 wk
8	Dyspnea, pruritus, and erythema of hands and neck twice after first 20- μ g dose on day 1 and 30- μ g dose on day 2	Slower, modified rush VIT protocol, well tolerated	Rhinitis and pruritus of eyes and hand after "premature" 3-week interval	Subcutaneous epinephrine, patient lost to follow-up		
9	Vomiting, drop in blood pressure, short loss of consciousness after the first 20- μ g dose on day 1	Subcutaneous epinephrine, intravenous metoclopramide, rush VIT discontinued				

Abbreviations: MD, maintenance dose; VIT, venom immunotherapy.

ferent cell populations, according to the different stages of immunotherapy.^{31,32}

The rationale for attempting rush VIT on patients with recurrent SRs during conventional VIT was that the possibly different immunoregulatory mechanism that induces allergen tolerance in rush VIT may be used to overcome the recurrent SRs induced by another immunoregulatory mechanism in the few patients with this problem throughout conventional VIT. Indeed, most of our patients (6 of 9) tolerated well the build-up period of our rush VIT and reached the 100- μ g MD on day 3. Included were patients with severe initial SRs after the sting (Muller grade 3 or 4) and patients in whom VIT could not be continued beyond relatively small venom doses (0.1–20 μ g). In 4 of our patients, mild cutaneous symptoms developed throughout this phase, but they were easily overcome by giving the patients loratadine before the next injections. The beneficial effect of the preventive administration of another antihistaminic drug (terfenadine) on the incidence of SRs after VIT has already been described.^{12,13} Since terfenadine is no longer available in Israel, based on previous researchers' impression that antihistamines in general might

reduce adverse effects of VIT,^{12,33} we chose loratadine for our patients. Indeed, its beneficial effect on our patients may suggest the routine use of antihistamines in rush VIT, especially in patients with previous recurrent SRs to conventional VIT. In 2 patients (patients 7 and 8), more severe systemic symptoms developed during the build-up period. By modifying our protocol and attenuating the rate of venom administration, these patients could reach the 100- μ g dose on day 5. In 2 patients, a live bee-sting challenge performed 1 week after reaching the MD was tolerated uneventfully.

A single patient (patient 9) developed a recurrent anaphylactic reaction while undergoing rush VIT. This happened after she had tolerated well, on the same day, an accumulative dose 3 times larger than the dose that had previously induced a similar reaction. We hesitated about whether to attempt a modified, slower build-up protocol on her. After consulting the patient and her family, we concluded that the risk of another anaphylactic reaction after a venom injection outweighs the likelihood of this patient, who seldom leaves her home, experiencing another field sting. We therefore decided not to retry VIT on her. Obviously, this decision is not a

general recommendation and applies to the specific patient only. Probably, with another subject, a young patient who works outdoors, for example, our recommendation would have been to attempt a modified, slower build-up protocol. In any case, the final decision should, of course, be made mutually by the allergist and the patient.

After reaching the MD, 2 patients developed SRs while taking the MD. In patient 8, this might be explained by an unplanned, premature extension of the MI. In patient 6, it was probably the administration of MDs of both BV and YJ venom together that induced the SR. Indeed, when these venoms were administered separately, SRs no longer recurred.

For unknown reasons, these patients seemed to be extremely vulnerable to SRs following venom administration. Administration of BV has been associated with an increased frequency of adverse reactions to VIT.^{6,7,12} Systemic mastocytosis has been mainly associated with severe anaphylaxis to insect stings,^{34,35} occasionally evolving into fatal outcome.³⁶ Two patients with systemic mastocytosis had to stop VIT because of SRs,³⁵ and in another patient who developed a single SR during the build-up period of VIT with BV, a modified rush VIT protocol was successful in reaching the MD.³⁷ Another clue for the role of mastocytosis in severe anaphylactic reactions that result from insect sting allergy emerged from the observation that significantly more patients with raised tryptase concentrations had a history of severe sting reaction when compared with patients with lower tryptase concentrations.³⁸ Although measurement of tryptase levels in our patients might have shed some light on the plausible diagnosis of mastocytosis in this specific group, the practical approach of attempting rush VIT on them would have probably remained unchanged, disregarding the tryptase levels. Although these specific patients were eventually able to reach the MD by rush or modified rush VIT protocol, this state of "vulnerability" seemed to persist even after they had reached the MD. Therefore, extending the MI in these patients should be very slow, and patients receiving more than one venom at a time should receive them separately. Although in most venom-allergic patients MI can be rapidly extended to a 3-month interval,³⁹ this policy should be cautiously adapted for these specific patients. It is probably best to have them follow a 1-week interval for several weeks and only then begin to slowly and gradually extend it.

Recurrent SRs to conventional VIT cause patients either to completely stop receiving this treatment or to continue receiving small, probably nonprotective doses. We suggest that rush VIT may be an appropriate therapeutic alternative that enables most of these patients to reach the full protective MD. Nevertheless, pursuing rush immunotherapy, as suggested by our study, is an option that may not be acceptable to all physicians and patients. Some physicians may view the rush approach as too dangerous. Some patients may conclude that moderate dose therapy and use of epinephrine automatic injector whenever needed is preferable to risking anaphylaxis with rush therapy. Considering the risk-benefit relationships of rush VIT, the decision of how to continue VIT in these

unique patients should be made on the basis of a thorough discussion of these issues by the physician and patient.

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