

Three Days Rush Venom Immunotherapy in Bee Allergy: Safe, Inexpensive and Instantaneously Effective

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Key Words

Hymenoptera • Insect venom allergy • Venom immunotherapy • Bee venom

Abstract

Background: Rush venom immunotherapy (VIT) is highly effective in vespid venom allergy, but comparable data regarding bee venom (BV) allergy are sparse. We evaluated its safety, efficacy and cost in BV-allergic patients. **Methods:** Conventional or rush VIT were offered to all patients with systemic reaction to insect sting. Rush VIT was also given to hyperreactive patients who failed to reach the maintenance dose with conventional VIT due to multiple systemic reactions. In BV-allergic patients, honeybee sting challenge was performed within 1 week after reaching the maintenance dose. **Results:** 179 patients, some of them allergic to more than one venom, received 246 rush VIT courses. Bee VIT was administered to 132 patients (73.7%); 173 patients (96.6%) reached the maintenance dose. The incidence of systemic reactions was 29.6%. They were more common in VIT with BV than with vespid venoms (31.1 and 16.3%, respectively, $p = 0.01$). After excluding the hyperreactive subgroup ($n = 20$), this difference was not significant (23.7 and 16%, respectively, $p = 0.19$). Despite the high incidence of systemic reactions (15 of 20, 75%) among hyperreactive patients, 17 patients (85%) achieved the maintenance dose. Sting challeng-

es resulted in systemic reaction in 4 of 8 (50%) hyperreactive patients and in 2 of 47 (4.3%) ordinary patients. The cost of rush VIT was 41% of that of conventional VIT. **Conclusions:** Rush VIT with BV is safe, instantaneously effective, less expensive and enables most patients with previous failures of conventional VIT to reach the maintenance dose.

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Introduction

Venom immunotherapy (VIT) is the recommended treatment for systemic reactions induced by *Hymenoptera* stings and has been shown to reduce the incidence of systemic reactions to re-stings from between 27 and 61% to between 2 and 3% [1]. Achieving the maintenance dose in conventional VIT usually requires 3–4 months. Therefore, different accelerated protocols, varying from several hours to a few days, have been developed in an attempt to shorten the build-up phase of VIT. Overall, rush venom immunotherapy (VIT) has been accepted as a common method of VIT, in addition to conventional VIT [2]. Most

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recently, in a review of accelerated immunotherapy schedules, Cox [3] concluded that most accelerated *Hymenoptera* studies had demonstrated both efficacy and safety comparable or superior to that of conventional schedules. However, this conclusion was based on results from rush VIT performed in large numbers of patients with vespid venom allergy [3–7]. The number of bee venom (BV)-allergic patients undergoing either regular rush VIT (a few days) [4, 8–11] or ultra-rush VIT (several hours) [5, 7, 13, 14] has not exceeded 90. Systemic reactions from both conventional VIT and rush VIT have been shown to be more prevalent with BV than with vespid venom administration [10], although a recent study that used a 4-hour ultra-rush VIT failed to demonstrate this difference [14]. In the present study, we performed rush VIT on a large number of BV-allergic patients in an attempt to better evaluate the safety and efficacy of rush VIT in this specific group of patients. We also examined its effect in hyperreactive BV-allergic patients who failed to reach the maintenance dose with conventional VIT due to multiple systemic reactions. In addition, we also evaluated whether it had any economic advantage over conventional VIT.

Methods

Patients

All patients had a history of systemic reactions inflicted by an insect sting and a positive skin test response to *Hymenoptera* venom [wheal diameter ≥ 5 mm in the presence of erythema diameter ≥ 11 mm following intradermal injection of venom at ≤ 1 μ g/ml, elevated titers of serum BV-specific IgE (≥ 0.70 kU/l), or both]. Patients were skin tested for BV, yellow jacket (YJ) venom and wasp venom. The degree of skin test reactivity was defined as the lowest intradermal concentration that produced a positive response.

After receiving a detailed description of both conventional VIT and rush VIT, patients chose one of the two protocols. In addition to ordinary patients who could choose their treatment modality, a hyperreactive subgroup of patients were intentionally referred to our allergy unit for rush VIT by other allergists after several attempts to reach the maintenance dose by conventional VIT failed due to multiple systemic reactions. Some of these patients have been described previously [15]. Patients receiving rush VIT, who belonged either to the ordinary or to the hyperreactive group were compared with a control group of randomly selected, age- and gender-matched patients, who chose conventional VIT and which was studied retrospectively. Pharmedal venoms were used for diagnostic (skin test) and treatment purposes (ALK-Abello, Horsholm, Denmark) and serum venom-specific IgE was measured with the AlaSTAT commercial kit (DPC, Los Angeles, Calif., USA). Positive skin tests and elevated titers of serum BV-specific IgE were defined in accordance with the manufacturers' recommendations.

Table 1. Conventional VIT protocol: concentrations, volumes and doses of venom administered at weekly intervals

1 μ g/ml	0.05, 0.1, 0.2, 0.4 ml (0.05, 0.1, 0.2, 0.4 μ g)
10 μ g/ml	0.05, 0.1, 0.2, 0.4 ml (0.5, 1, 2, 4 μ g)
100 μ g/ml	0.02, 0.05, 0.07, 0.1, 0.2, 0.4, 0.6, 0.8, 1 ml (2, 5, 7, 10, 20, 40, 60, 80, 100 μ g)

Table 2. Rush VIT protocol: concentrations, volumes and doses of venom administered at 15-min intervals

<i>Day 1</i>	
1 μ g/ml	0.05, 0.1, 0.2, 0.4, 0.8 ml (0.05, 0.1, 0.2, 0.4, 0.8 μ g)
10 μ g/ml	0.2, 0.5, 1 ml (2, 5, 10 μ g)
100 μ g/ml	0.2, 0.2 ml (20, 20 μ g)
<i>Day 2</i>	
100 μ g/ml	0.2, 0.3, 0.5 ml (20, 30, 50 μ g)
<i>Day 3</i>	
100 μ g/ml	1 ml (100 μ g)

VIT Protocols

Patients who demonstrated positive IgE to several venoms underwent VIT with all venoms, including YJ and wasp, unless the systemic reaction history was definitely supportive of a single culprit insect. This was evaluated according to patient's acquaintance with different species of *Hymenoptera*, the circumstances and location of the sting, the retention of sting apparatus and the extent of the insect's activity after the sting. If several venoms were to be administered to a patient receiving conventional VIT, they were injected simultaneously, whereas in a patient receiving rush VIT who was allergic to BV, this venom was administered on the first course and other venoms were given subsequently, in separate courses, 1–2 weeks apart. The maintenance dose of both conventional VIT and rush VIT was 100 μ g. The detailed protocols are presented in tables 1 and 2. Rush VIT was administered after insertion of an intravenous line with heart rate and blood pressure monitored at 10-min intervals. If a patient had a systemic reaction to the venom injection, the dose was reduced by 50% and gradually increased. Patients who developed more than one systemic reaction were instructed to take loratadine 1 h before the next injection visit. Severity of a systemic reaction was graded according to Brown's criteria [16]. According to this grading system, grade 1 (mild) involves skin and subcutaneous tissues only, grade 2 (moderate) includes features suggesting respiratory, cardiovascular or gastrointestinal involvement and grade 3 (severe) consists of hypoxia, hypotension or neurologic compromise. After reaching the maintenance dose the intervals between the injections were gradually extended in both protocols. Each of the following intervals was repeated twice: once a week, once every 2, 3, 4, 6 and 8 weeks. There-

Table 3. Patient characteristics

	RVIT (n = 179)	CVIT (n = 75)
Male/female	146/33 (82/18)	59/16 (79/21)
<i>Age</i>		
Mean $\pm$ SD, years	33.0 $\pm$ 15.0	34.1 $\pm$ 18.8
3–10 years	12 (7)	8 (11)
11–20 years	66 (37) ^a	11 (15) ^a
21–40 years	61 (34)	30 (40)
41–60 years	36 (21)	18 (24)
≥ 61	4 (2) ^b	8 (11) ^b
<i>Severity of SR that prompted VIT</i>		
Mild (grade 1)	37 (21)	13 (17)
Moderate (grade 2)	112 (63)	53 (71)
Severe (grade 3)	30 (17)	9 (12)
<i>Venoms administered for immunotherapy</i>		
BV only	93 (52)	36 (48)
BV + YJ	24 (13)	12 (16)
BV + W	1 (0.6)	1 (1)
BV + YJ + W	14 (8)	10 (13)
YJ only	33 (18)	11 (15)
YJ + W	14 (8)	5 (7)

Figures in parentheses are percentages. RVIT = Rush venom immunotherapy; CVIT = conventional venom immunotherapy; SR = systemic reaction. ^a $p = 0.0003$; ^b $p = 0.007$.

after, injections were given at 3-month intervals. Failure to reach the maintenance dose with rush VIT was defined as such after 4 or more grade 1–2 systemic reactions or after 1 or 2 grade 3 systemic reactions.

Sting Challenge

BV-allergic patients receiving rush VIT who provided written informed consent were deliberately stung by a live honeybee within 1 week after reaching the maintenance dose. We chose a rather short interval for the posttreatment challenge because these patients were also enrolled in another study addressing the early effectiveness of VIT [17]. An intravenous line was inserted prior to the sting, and heart rate and blood pressure were monitored, at 10-min intervals, for 2 h afterwards. A 50-ml plastic syringe containing the insect was used for the sting, as previously described [18]. The Meir Medical Center Institutional Review Board approved this study.

Cost of VIT

The costs of the different treatment protocols were calculated based on venom and medical equipment prices, allergist and nurse wages, and on clinic rental and maintenance fees. Data were recovered from Clalit Health Services which owns the Allergy Unit. Clalit Health Services is the largest HMO in Israel.

Statistical Analysis

The effect of different variables on the incidence of systemic reactions during VIT was analyzed using a logistic regression model where the odds ratio was accepted with a 95% confidence interval and 1 degree of significance, using SAS software, version 8. Correlation was expressed by the nonparametric Pearson correlation coefficient.

Results

Patients

Between August 1993 and August 2008, 179 patients received 246 courses of rush VIT. Their characteristics are described in table 3. Twenty patients (11.2%) belonged to the hyperreactive subgroup of patients who received rush VIT after recurrent failures to reach the maintenance dose by conventional VIT. Although rush VIT is more convenient for the patient, in the first few years, when our experience with rush VIT was less extensive and patients did not feel confident about it, most patients preferred conventional VIT. Over time, as our experience with the procedure increased, patients gradually tended to prefer rush VIT and over the past 7 years, most patients have chosen this alternative. The control group consisted of 75 patients who received conventional VIT. Although their mean age did not differ from that of rush VIT patients, fewer patients aged 11–20 years and more patients older than 60 years were in the conventional VIT group compared to the rush VIT group (table 3). We assume that this difference reflects the conservative approach usually taken by older individuals towards new treatment modalities such as rush VIT. Other characteristics did not differ from those of rush VIT patients.

Rush Immunotherapy

The 3-day protocol described in table 2 was applied in 175 patients. Initially, between August 1993 and April 1994, we used a slower protocol which lasted 21 days and was implemented in 4 patients who received 5 treatment courses. Maintenance dose was reached within 3 days in 158 patients (90.3%) who received 227 courses of treatment. Adverse reactions during the rush VIT resulted in prolongation of the treatment course to 4–5 days in 10 patients (7 of whom belonged to the hyperreactive subgroup) and to 9 days in 2 patients. Rush VIT lasted 5 days for 3 patients because they required a maintenance dose of 200–250 μ g due to failure of the 100- μ g maintenance dose to protect them from a systemic reaction after a field sting. Six patients (3.4%) did not reach the maintenance dose: 5 due to systemic reactions to the rush VIT (2.8%)

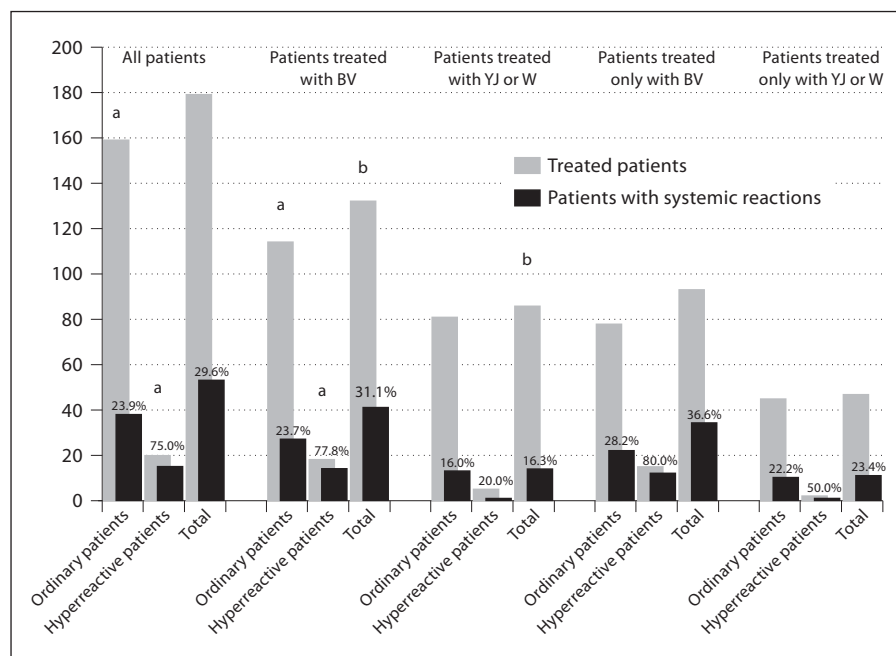


Fig. 1. Incidence of systemic reactions in rush VIT. W = Wasp. ^a $p < 0.0001$; ^b $p < 0.01$.

and 1 patient dropped out of the study for unknown reasons.

Systemic Reactions

Fifty-three patients (29.6%) experienced systemic reactions during rush VIT (fig. 1). These reactions were more common in patients who received BV than those who received vespid venom (YJ or wasp) (31.1 and 16.3%, respectively; $p = 0.01$). There was also a significant difference in the incidence of systemic reactions between conventional VIT patients receiving BV and those receiving vespid venom (25.4 and 9.1%, respectively; $p = 0.04$). Among rush VIT patients, this difference remained for both mild-to-moderate (grade 1 and 2) systemic reactions (29.6 and 16.3%, respectively; $p = 0.03$) as well as for moderate-to-severe (grade 2 and 3) systemic reactions (12.9 and 4.7%, respectively; $p = 0.04$) (fig. 2). However, when the incidence of systemic reactions in rush VIT was compared only among patients who belonged to the ordinary group, there was no difference between patients who received BV and those who received vespid venom (23.7 and 16%, respectively; $p = 0.19$). When rush VIT patients who received only BV (both ordinary and hyperreactive groups) were compared with rush VIT patients who received only vespid venom, there was no difference in the incidence of systemic reactions (36.6 and 23.4%, respectively; $p = 0.11$). The overall incidence of systemic

reactions in patients receiving conventional VIT was 20.8%, whereas it was 29.6% in patients receiving rush VIT ($p = 0.15$). Similarly, there was no difference in the incidence of systemic reactions between conventional VIT patients and rush VIT regular group patients and between conventional VIT patients and rush VIT patients receiving BV or vespid venom (either all patients or only the ordinary group) (data not shown).

Systemic reactions were more common in the hyperreactive subgroup (15 of 20, 75%) compared to the ordinary patients (38 of 159, 23.9%; $p < 0.0001$). This held true also for patients who received BV only (14 of 18, 77.8%, and 27 of 114, 23.7%, respectively; $p < 0.0001$). Severe (grade 3) systemic reactions were observed in 2 patients who belonged to the hyperreactive subgroup while receiving BV rush VIT.

The correlation between the incidence of systemic reactions and the severity of the last anaphylactic reaction before commencement of rush VIT in all patients approached statistical significance (Pearson correlation coefficient 0.02, $p = 0.08$). No such correlation was found between the incidence of systemic reactions and serum venom-specific IgE (Pearson's correlation coefficient -0.12, $p = 0.2$). Likewise, no correlation was found between the incidence of systemic reactions and the degree of venom skin test reactivity (Pearson's correlation coefficient 0.004, $p = 0.96$). Similarly, no correlations were

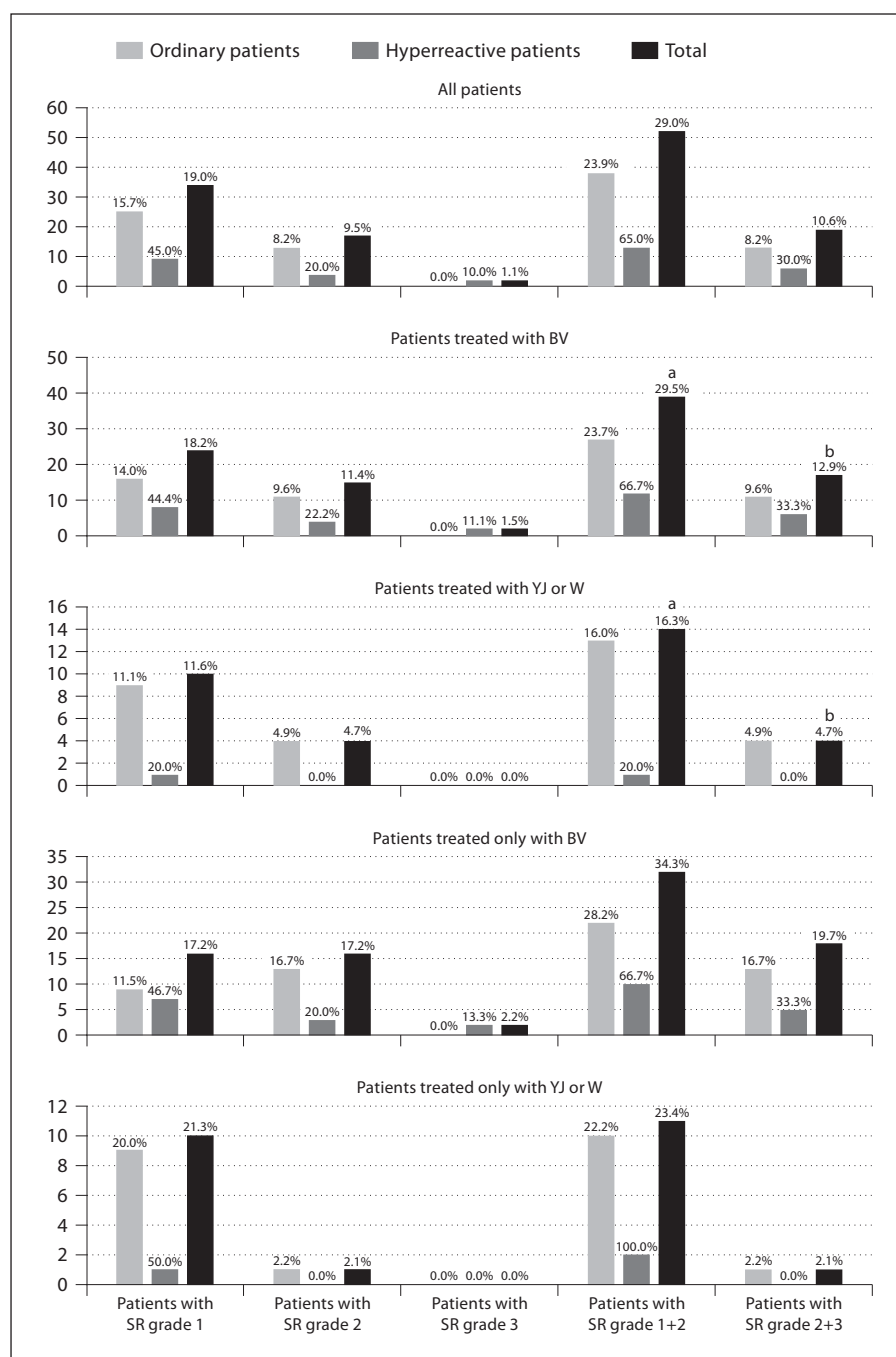


Fig. 2. Incidence of systemic reactions in RVIT according to their severity. W = Wasp; SR = systemic reaction. ^a $p < 0.03$; ^b $p < 0.04$.

found when these variables were compared separately either in patients who were allergic only to BV or in those who were allergic to BV and/or vespid venoms.

Medical Treatment of Systemic Reactions

Of 41 patients who developed a systemic reaction while receiving BV, the medical treatment administered

during the systemic reaction included antihistamines only in 27 patients (65.9%), bronchodilator inhalation in 4 patients (9.8%) and epinephrine in 7 (17.1%). Six of 13 patients (46.2%) who developed a systemic reaction while receiving vespid venom required antihistamines only and a single patient (7.7%) required epinephrine. All patients with grade 3 systemic reactions were treated with

fluid resuscitation and intramuscular epinephrine. Altogether, 2 of 159 patients (1.3%) in the ordinary group and 6 of 20 patients (30%) in the hyperreactive subgroup required epinephrine ($p < 0.0001$). Only 1 of 114 patients (0.9%) in the ordinary group and 6 of 18 patients (33.3%) in the hyperreactive subgroup ($p < 0.0001$) who received BV rush VIT required epinephrine.

Failure to Reach the Maintenance Dose

Six (3.4%) patients who began rush VIT did not reach the maintenance dose. Three patients discontinued rush VIT after they experienced one or two grade 1 systemic reactions, without attempting to reduce the dose and/or to take an antihistamine before the next injections. Two of these patients who belonged to the ordinary group switched to conventional VIT and reached the maintenance dose, whereas the third patient who belonged to the hyperreactive subgroup did not return for continued treatment. Another patient who belonged to the ordinary group completed the first two days of rush VIT without systemic reactions but failed to return for the last treatment for unknown reasons. Two patients who primarily had a grade 3 systemic reaction after field bee sting and belonged to the hyperreactive subgroup did not reach the maintenance dose. The first patient lost consciousness after receiving 5 μg of BV during conventional VIT and her allergist refused to continue the treatment. On the first day of BV rush VIT, after receiving the first dose of 20 μg , she vomited extensively and lost her consciousness for 2 min. Considering her general poor health and the fact that she had seldom left her home, we elected, together with the patient and her family, not to retry rush VIT. The other patient developed severe systemic reactions twice with rush VIT. Following the reactions, which involved severe choking, aphonia, wheezing and significant drop of blood pressure, treatment was discontinued. Thus, the incidence of failure to reach the maintenance dose with rush VIT, defined as discontinuation of the treatment due to multiple grade 1–2 systemic reactions or because of not more than two grade 3 systemic reactions, was 1.1% for all patients (2 of 175), none for the ordinary group, 10.5% for the hyperreactive subgroup (2 of 19) and 11.1% for patients in the hyperreactive subgroup who received BV rush VIT (2 of 18).

Sting Challenges

Honeybee sting challenge performed in 55 patients resulted in systemic reaction in 6 patients (10.9%). Two of 47 patients (4.3%) who belonged to the ordinary group and 4 of 8 (50%) who belonged to the hyperreactive subgroup

($p = 0.0001$) experienced systemic reaction. The severity of the systemic reactions in the ordinary group was grade 1 in one patient and grade 2 in the other patient, and in the hyperreactive patients, it was grade 1 in three patients and grade 2 in another patient. Four of 36 patients (11.1%) who were allergic only to BV experienced a systemic reaction: three patients grade 1 and another patient grade 2. Two of 19 patients (10.5%), who had first received rush bee VIT and were also allergic to vespid venom, experienced systemic reaction to the bee sting challenge: one patient grade 1 and the other patient grade 2. We continued with the 100- μg maintenance dose in 2 patients who had a very mild localized transient rash after the sting challenge and required no medical intervention.

Increasing the maintenance dose was offered to the other 4 patients. One patient who belonged to the ordinary group suffered a large local reaction to the sting challenge and declined continuation of VIT. In 3 patients, the dose was increased to 200 or 250 μg using rush VIT. Within a week after the increased maintenance dose was reached, rechallenge with a live honeybee sting was well tolerated by all 3 patients.

Cost and Time Requirement of Different VIT Protocols

Health services in Israel are publicly funded. In this health system, reaching the maintenance dose with conventional VIT by a compliant patient who does not miss scheduled visits and does not develop adverse reactions would have cost NIS 5,656 (equivalent to USD 1,414). The cost for a similar patient undergoing rush VIT to reach the maintenance dose would have been NIS 2,306 (USD 576). Thus, the expenses for an uncomplicated patient treated with rush VIT are 41% of conventional VIT. Assuming that an average visit for conventional VIT requires approximately 3 h (2 h for transportation back and forth and 1 h for administration of the injection and waiting period afterwards), reaching the maintenance dose, which requires 17 visits, would total 51 h. Considering that on each day of rush VIT, patients were observed for 2 h after the last injection, 5 h were required to complete the first day of rush VIT, 3 h for the second day and 2.5 h for the third day. Together with transportation time for the 3 days (6 h), the entire time to reach the maintenance dose by rush VIT for an uncomplicated patient was 16.5 h, which is 32% of the time required for conventional VIT.

The Hyperreactive Subgroup

Nineteen of the 20 patients who belonged to this subgroup were referred for rush VIT because of recurrent

failures to reach the maintenance dose with conventional VIT due to multiple systemic reactions. One aforementioned patient was included because her allergist refused to treat her after she developed a single grade 3 systemic reaction to a low dose of conventional VIT. Fourteen patients were treated only with BV, 4 patients with BV and YJ venom, and 2 patients were treated with vespid venom only. In 9 patients, maintenance dose was reached after 3 days. In 8 patients, maintenance dose was reached after 4–5 days, in 7 the protocol was slowed down due to systemic reactions, whereas another patient had to achieve a maintenance dose of 250 µg because he had suffered several failures of conventional VIT to reach this increased maintenance dose which was necessary to overcome recurrent systemic reactions following field bee stings, while on the regular 100-µg maintenance dose. In a single patient, the maintenance dose was reached after 9 days because of recurrent systemic reactions. Seventeen patients (85%) reached the maintenance dose. One patient did not return for the third treatment day after experiencing two grade 1 systemic reactions. We discontinued rush VIT in 2 patients after they had developed one or two grade 3 systemic reactions. Thus, failure to reach the maintenance dose in this subgroup was 10.5% (2 of 19).

Fifteen patients (75%) experienced systemic reaction during rush VIT. Fourteen systemic reactions occurred during BV rush VIT and one happened during YJ rush VIT. Their severity was grade 1 in 9 patients, grade 2 in 4 patients and grade 3 in 2 patients. Eight (53%) systemic reactions were treated with antihistamines, 6 (30%) with epinephrine and 1 (6.6%) with a bronchodilator.

Eight patients were sting challenged by a honeybee. Four (50%) experienced a systemic reaction after the sting (three patients grade 1 and one patient grade 2). In two patients who had a very mild localized transient rash following the sting, the 100-µg maintenance dose was continued, as planned. In the other two patients, the maintenance dose was increased to 200 or 250 µg. After reaching this dose, they were rechallenged and tolerated the sting uneventfully.

Discussion

Most advantages of rush VIT are obvious, namely shortening the lengthy period of frequent clinic visits until maintenance dose is finally reached and gaining protection from field restings within a couple of days. As reviewed by Cox [3], most studies on accelerated VIT pro-

ocols have demonstrated both efficacy and safety comparable or superior to that of conventional schedules. Nevertheless, these studies concentrated mainly on vespid venom-allergic patients. Since systemic reactions due to VIT have been shown to be more prevalent with BV than with vespid venom administration [10], the safety and efficacy of BV rush VIT deserve better substantiation. The number of patients treated with vespid rush VIT exceeded 150 in 3 studies [5–7] and reached 587 in the fourth [8], whereas the largest study on BV rush VIT comprised 65 patients [8] and the largest study on BV ultra-rush VIT comprised 90 patients [7]. In the present study, 132 BV-allergic patients received rush VIT, which makes it the largest study to date focusing on this specific group of patients.

The primary objective of VIT is to reach the maintenance dose. In the present study, 3.4% of the patients did not reach the maintenance dose due to poor compliance or because of systemic reactions to the rush VIT. This rate is smaller than the 8% reported in a study on conventional VIT [19]. In a previous study on allergen immunotherapy which included patients who were allergic to various allergens and continued to follow them after maintenance dose was reached, the overall compliance rate was 77.4% [20]. It was higher in patients on conventional schedule (80%) compared with those on a rush schedule (48.4%). Although we cannot compare this study with our study, which followed venom-allergic patients during their build-up phase only, the 98% compliance rate observed in our patients is still notably higher.

The safety of rush VIT is reflected by the incidence and severity of systemic reactions. The overall incidence of systemic reactions in our BV-allergic patients was 31%, but after excluding the hyperreactive subgroup that, unsurprisingly, had an extremely high incidence of systemic reactions (75%), the incidence was only 24%. It is lower than the incidence described by most studies on BV rush VIT, which varied from 31 to 46% [5, 8, 9, 12], although in a single study it was 12% [11]. In the vast majority of our patients, these systemic reactions failed to interfere with the treatment objective of achieving the maintenance dose. Thus, none of the ordinary patients and only 10.5% of the hyperreactive patients failed to reach the maintenance dose. The absence of grade 3 systemic reactions and the infrequent epinephrine administration in the ordinary group are other indicators of the safety of BV rush VIT.

A previous report found systemic reactions to be more prevalent among honeybee compared with YJ-allergic patients [10]. However, most participants in this study re-

ceived conventional VIT and only about one third (77 of 205) received rush VIT. In addition, patients were followed and systemic reactions were recorded for extended periods of time, both during the build-up and the maintenance periods. A more recent study that examined 4-hour ultra-rush VIT did not show any safety differences between wasp and bee VIT [14]. In our control patients receiving conventional VIT, we also observed a higher incidence of systemic reactions in BV compared with vespid venom-allergic patients. However, the present study is the first to specifically examine treatment safety only during the build-up period of rush VIT in patients receiving different venoms. Indeed, although the overall incidence of systemic reactions was greater among BV compared to vespid venom allergic patients, this difference originated from the high incidence of systemic reactions in hyperreactive patients with previous systemic reactions to conventional VIT. After excluding these unique patients, there was no difference between 'ordinary' patients receiving different venoms during the build-up period of rush VIT. Thus, whereas conventional VIT is associated with higher systemic reaction rate in published literature, rush VIT seems to ameliorate this difference, giving this treatment modality a new, previously unknown, advantage over conventional VIT in BV-allergic patients.

The efficacy of rush VIT was assessed by a honeybee sting challenge performed within 1 week after maintenance dose was reached. None of the challenges resulted in a life-threatening systemic reaction and the overall incidence of grade 1 or 2 systemic reactions was 10.9%. It should be noted that the incidence in the ordinary group (4.3%) was significantly lower than that of the hyperreactive subgroup (50%). The incidence of systemic reactions to the sting challenge in our ordinary BV-allergic patients is within the 6–23% rate observed by other large studies on sting challenges in BV-allergic patients, as previously reviewed by Ruëff et al. [21]. Moreover, when employed to increase the regular maintenance dose in patients who had developed systemic reaction to the first sting challenge, rush VIT was well tolerated. Similar to a previous study [22], we also did not observe systemic reactions to the repeat sting challenge in our patients who had reached the increased maintenance dose. Thus, achieving the maintenance dose in all our ordinary patients, as well as the lack of systemic reactions to the sting challenge in these patients, indicate the very high efficacy of rush VIT in BV allergic patients.

The hyperreactive subgroup, which consisted of patients who failed to achieve the maintenance dose with

conventional VIT, represents a unique challenge. Therefore, overcoming the recurrent systemic reactions experienced by these patients should be considered a significant accomplishment in any number of patients. We were able to demonstrate a relatively low rate of failure to reach the maintenance dose (10.5%) in these patients. Although half of the challenged patients developed a systemic reaction after the sting, it was either very mild and transient in some of them or did not recur after increasing the maintenance dose in the other patients. Thus, overall, even in this highly challenging group, the rush VIT protocol proved to be effective for almost 90% of patients.

The cost associated with the build-up phase of conventional VIT was twice that of rush VIT. Because of large national differences in reimbursement for in-hospital and outpatient treatment, the results of the present study cannot be generalized and studies focusing on this subject in other countries are required. The net time required to accomplish the maintenance dose was 3 times longer in conventional VIT. Thus, rush VIT is significantly less time-consuming compared with conventional VIT, regarding both the duration required to reach the maintenance dose as well as the net time spent by the patient to reach it. Taken together, rush VIT might have an economic advantage over conventional VIT, as well. Ultra-rush VIT is faster than the protocol used by us and has also been shown to be safe. Having had an extensive experience with the 3-day rush VIT we elected to adhere to our familiar protocol, but ultra-rush VIT might be even more cost-effective than the 3-day protocol.

In summary, besides quickly gaining protection from restings by rush VIT, the present study demonstrates that the safety, efficacy and economic burden of this protocol in BV-allergic patients are at least as good as, and arguably better than, those of conventional VIT. In addition, rush VIT has been shown to be remarkably successful in overcoming previous multiple failures of conventional VIT. Therefore, in the appropriate setting, rush VIT might be considered the preferred mode of treatment in BV-allergic patients.

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