

# Exclusive Bee Venom Allergy: Risk Factors and Outcome of Immunotherapy

Yossi Rosman<sup>a, b</sup> Fatema Nashef<sup>b</sup> Anat Cohen-Engler<sup>a, b</sup> Keren Meir-Shafir<sup>a</sup>  
Idit Lachover-Roth<sup>a, b</sup> Ronit Confino-Cohen<sup>a, b</sup>

<sup>a</sup>Allergy and Clinical Immunology Unit, Meir Medical Center, Kfar-Saba, Israel; <sup>b</sup>Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

## Keywords

Venom immunotherapy · Bee venom · Venom immunotherapy-induced systemic reactions · c-kit mutation · Tryptase

## Abstract

**Introduction:** Venom immunotherapy (VIT) is considered to be the gold-standard treatment for patients with Hymenoptera venom allergy. Data regarding VIT in bee venom (BV) allergic patients are scarce. **Aim:** The aim of this study was to evaluate the outcome of VIT in patients with exclusive BV allergy and to try to define risk factors for VIT-induced systemic reactions (VIT-ISR) and VIT failure. **Methods:** This is a retrospective study including data from all BV allergic patients that were treated by VIT in the Allergy Unit at the Meir Medical Center in the years 1995–2018. **Results:** Two hundred and forty-seven patients with exclusive BV allergy were included; 206 (83.4%) preferred to undergo rush buildup. Sixty-nine patients (27.9%) had at least 1 reaction during buildup, with the c-kit mutation being the only significant risk factor (100 vs. 28.9%,  $p = 0.02$ ). Female gender (25.4 vs. 13.3%,  $p = 0.04$ ), conventional buildup schedule (26.8 vs. 14.1%,  $p = 0.04$ ), and c-kit mutation (100 vs. 16.8%,  $p < 0.01$ ) but not tryptase level were found to be significantly more frequent in recurrent reactors. Females (20.3 vs. 9%,  $p = 0.03$ ), patients with severe systemic reaction to the index sting (24.3 vs. 9.5%,  $p = 0.004$ ),

and c-kit mutation (66 vs. 12%,  $p = 0.05$ ) but not tryptase level were found to be risk factors for severe systemic reactions.

**Conclusion:** Despite the considerably high rate of VIT-ISR in patients with exclusive BV allergy, VIT can be performed safely and efficiently. C-kit mutation, and not basal serum tryptase level, seems to be a preferable biomarker for VIT-ISR in these patients.

© 2019 S. Karger AG, Basel

## Introduction

Venom immunotherapy (VIT) is considered to be the gold-standard treatment for patients with Hymenoptera venom allergy in general and honeybee venom (BV) allergy in particular [1]. The buildup phase of VIT can be administered either by conventional once-a-week injection or by 3-day rush protocol [2]. This treatment, although well tolerated by most patients, is often complicated by side effects in a significant number of patients [1]. These side effects include local reactions limited to the injection site or systemic reactions (SR), ranging from a benign rash to life-threatening anaphylactic shock [3]. Besides supportive measures, SR to VIT are treated

Edited by: H.-U. Simon, Bern.

by prompt administration of intra-muscular epinephrine, bronchodilators, antihistamines, and systemic corticosteroids. Although considered efficient, in different series, VIT failure is documented in about 5–15% of patients.

BV allergy is considered to be a significant risk factor for VIT-induced systemic reactions (VIT-ISR) and for VIT failure, but data are scarce and extrapolated from series mostly from Europe where BV allergy is rare [4, 5]. Although it seems that VIT to bee and wasp allergy is not the same, no work to date has looked into VIT outcomes in exclusively BV allergic patients.

The aim of this work was to evaluate the outcome of VIT in patients with exclusive BV allergy and to try to define risk factors for VIT-ISR and VIT failure in these patients.

## Methods

This retrospective study was conducted in the Allergy and Clinical Immunology Unit at the Meir Medical Center, Kfar-Saba, Israel. Inclusion criteria were VIT treatment for BV allergy. BV allergy was defined as a history of a SR to bee sting together with positive intra-dermal (ID) skin test to 0.1–1 µg of BV (ALK-Abelló, Denmark) or serum venom-specific IgE to BV (Immulate 2000, Siemens, Germany). Patients with co-sensitization to other venoms and children under the age of 18 years with a reaction limited to the skin – grade 1 according to Brown's grading [6] – were excluded.

### Venom Immunotherapy

After comprehensive explanation about the conventional (CVIT) and rush (RVIT) protocols, patients chose to be treated by either. The detailed protocols of both methods were published elsewhere [2]. Briefly, in the absence of SR to the treatment, the build-up phase lasts 3 days with RVIT and includes 14 injections. The CVIT buildup phase lasts 3–4 months and includes 17 weekly injections (Table 1).

Baseline serum tryptase level and peripheral blood c-kit mutation were measured prior to VIT initiation.

### Systemic Reactions

After each immunotherapy session, all patients were observed for 30 min for SR. SR were diagnosed and treated by a physician specialized in allergy and clinical immunology. Severity of SR was graded according to Brown's criteria [6]. By 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.

### Follow-Up

Follow-up was done during all immunotherapy sessions and once a year after completion of immunotherapy.

**Table 1.** VIT protocols

|                                  | Injection | 1 µg/mL           | 10 µg/mL         | 100 µg/mL      |
|----------------------------------|-----------|-------------------|------------------|----------------|
| <i>Rush VIT protocol*</i>        |           |                   |                  |                |
| Day 1                            | 1         | 0.05 mL (0.05 µg) |                  |                |
|                                  | 2         | 0.1 mL (0.1 µg)   |                  |                |
|                                  | 3         | 0.2 mL (0.2 µg)   |                  |                |
|                                  | 4         | 0.4 mL (0.4 µg)   |                  |                |
|                                  | 5         | 0.8 mL (0.8 µg)   |                  |                |
|                                  | 6         |                   | 0.2 mL (2 µg)    |                |
|                                  | 7         |                   | 0.5 mL (5 µg)    |                |
|                                  | 8         |                   | 1 mL (10 µg)     |                |
|                                  | 9         |                   |                  | 0.2 mL (20 µg) |
|                                  | 10        |                   |                  | 0.2 mL (20 µg) |
| Day 2                            | 11        |                   |                  | 0.2 mL (20 µg) |
|                                  | 12        |                   |                  | 0.3 mL (30 µg) |
|                                  | 13        |                   |                  | 0.5 mL (50 µg) |
| Day 3                            | 14        |                   |                  | 1 mL (100 µg)  |
| <i>Conventional VIT protocol</i> |           |                   |                  |                |
| Week                             | 1         | 0.05 mL (0.05 µg) |                  |                |
|                                  | 2         | 0.1 mL (0.1 µg)   |                  |                |
|                                  | 3         | 0.2 mL (0.2 µg)   |                  |                |
|                                  | 4         | 0.4 mL (0.4 µg)   |                  |                |
|                                  | 5         |                   | 0.05 mL (0.5 µg) |                |
|                                  | 6         |                   | 0.1 mL (1 µg)    |                |
|                                  | 7         |                   | 0.2 mL (2 µg)    |                |
|                                  | 8         |                   | 0.4 mL (4 µg)    |                |
|                                  | 9         |                   |                  | 0.02 mL (2 µg) |
|                                  | 10        |                   |                  | 0.05 mL (5 µg) |
|                                  | 11        |                   |                  | 0.07 mL (7 µg) |
|                                  | 12        |                   |                  | 0.1 mL (10 µg) |
|                                  | 13        |                   |                  | 0.2 mL (20 µg) |
|                                  | 14        |                   |                  | 0.4 mL (40 µg) |
|                                  | 15        |                   |                  | 0.6 mL (60 µg) |
|                                  | 16        |                   |                  | 0.8 mL (80 µg) |
|                                  | 17        |                   |                  | 1 mL (100 µg)  |

\* Doses were administered at 15-min intervals.

### Statistical Analysis

Data were entered and tabulated using Excel 2007. Data are presented as mean and standard error for continuous variables. Comparisons between groups were performed with the Student *t* test for continuous variables and with the Fisher exact test for categorical variables. All tests of hypotheses were considered significant when two-sided probability values were  $p < 0.05$ .

## Results

Two hundred and forty-seven patients with exclusive BV allergy were included in our study. Demographic data are summarized in Table 2. Most of the patients were

**Table 2.** Demographic data

|                                             |             |
|---------------------------------------------|-------------|
| Age, years                                  | 25.9±5.66   |
| <5 years                                    | 17 (6.8%)   |
| >70 years                                   | 6 (2.5%)    |
| Male                                        | 188 (76.1%) |
| Asthma                                      | 8 (3.2%)    |
| Cardiovascular disease                      | 32 (13%)    |
| Beta blocker                                | 14 (5.6%)   |
| ACE-I                                       | 20 (8.1%)   |
| Malignancy                                  | 2 (0.8%)    |
| Autoimmune disease                          | 4 (1.6%)    |
| Baseline tryptase level, mg/dL <sup>a</sup> | 5.7±4       |
| >11.4 mg/dL                                 | 6 (4.5%)    |
| Positive c-kit                              | 3/86 (3.5%) |
| Occupational risk                           | 21 (8.5%)   |
| Severity of the index reaction              |             |
| 1                                           | 39 (15.8%)  |
| 2                                           | 171 (69.2%) |
| 3                                           | 37 (15%)    |
| Rush buildup                                | 206 (83.4%) |

ACE-I, angiotensin-converting enzyme inhibitor. <sup>a</sup> Tryptase level was available for 131 patients.

males (188, 76.1%), and the average age was  $22.9 \pm 5.66$  years (median 18, range 2–75). Twenty-one patients (8.5%) had occupational risk for bee stings. The index reaction was severe (grade 3) in 37 patients (15%) and milder in the rest ( $n = 210$ ).

Most patients (206, 83.4%) preferred to undergo the buildup phase according to the rush protocol. Baseline serum tryptase was available for 131 patients with an average level of  $5.7 \pm 4$  mg/dL. Six patients (4.5%) had a baseline serum tryptase level  $>11.4$  mg/dL. c-kit mutation was evaluated in 86 patients and found positive in 3 (3.5%).

#### *Reactions during the Buildup Phase*

Sixty-nine patients (27.9%) had at least 1 reaction during buildup, most of them (40, 58%) were mild reactions limited to the skin. Twenty-nine patients (11.7%) had severe reactions, and 3 patients had (1.2%) life-threatening reactions.

The differences between patients reacting during the buildup phase are summarized in Table 3. Patients that had a reaction during the buildup were older ( $27.6 \pm 17.1$  vs.  $25.2 \pm 19.3$  years) and with higher baseline tryptase levels ( $6.14 \pm 6$  vs.  $5.5 \pm 2.4$  mg/dL), but both differences did not reach statistical significance ( $p = 0.3$  for both comparisons). The frequency of reactions in women was higher than in men, but this difference did not reach statistical significance (35.6 vs. 25.5%,  $p = 0.09$ ). All patients

with a mutation in c-kit had a reaction in the buildup (100 vs. 28.9%,  $p = 0.02$ ).

No significant difference was noted in the rate of reactions between the two buildup protocols (RVIT 27.1% vs. CVIT 31.7%,  $p = 0.5$ ).

#### *Recurrent Reactions during the Buildup Phase*

Forty patients (16.2%) had more than 1 reaction during buildup and hence were termed recurrent reactors (Table 4). Recurrent reactors tended to be older, but this difference was not significant ( $29.3 \pm 17.3$  vs.  $25.2 \pm 18.9$  years,  $p = 0.2$ ).

Recurrent reactors had a higher baseline tryptase level. This difference almost reached statistical significance ( $7 \pm 7.7$  vs.  $5.4 \pm 2.2$  mg/dL,  $p = 0.07$ ). Female gender (25.4 vs. 13.3%,  $p = 0.04$ ) and conventional buildup schedule (26.8 vs. 14.1%,  $p = 0.04$ ) were found to be significantly more frequent in recurrent reactors (Table 4). All patients with a mutation in c-kit were recurrent reactors (100 vs. 16.8%,  $p < 0.01$ ). High baseline tryptase level was more frequent in recurrent reactors, but this difference did not reach statistical significance (50 vs. 19.2%,  $p = 0.1$ ).

#### *Severe Reactions during the Buildup Phase*

Twenty-nine patients (11.75%) had at least 1 severe reaction during buildup (Table 5). The average age was comparable between patients with severe reactions and the rest ( $26.05 \pm 18.1$  vs.  $25.8 \pm 18.8$  years,  $p = 0.9$ ). Baseline tryptase level was higher in the group with severe reactions as compared to the rest, but this difference did not reach statistical significance ( $7.1 \pm 8.4$  vs.  $5.5 \pm 2.5$  mg/dL,  $p = 0.09$ ). Female patients (20.3 vs. 9%,  $p = 0.03$ ) as well as patients with severe SR to the index sting (24.3 vs. 9.5%,  $p = 0.004$ ) and a mutation in c-kit (66 vs. 12%,  $p = 0.05$ ) were found to be at risk for severe SR during buildup. Patients with high baseline tryptase level and occupational risk had more severe reactions, but these differences did not reach statistical significance (33.3 vs. 14.4 mg/dL,  $p = 0.2$  and 23.8 vs. 10.6%,  $p = 0.08$ , respectively) (Table 4).

#### *Achieving Full Maintenance Dose*

Initially, 16 patients (6.4%) failed to reach the full maintenance dose of 100  $\mu$ g due to recurrent or severe reaction during buildup. The only significant difference found between patients who reached the full maintenance dose and those who failed to do so was the type of buildup protocol: 198 out of 206 (96.1%) in RVIT versus 33 out of 41 (80.5%) in CVIT ( $p < 0.01$ ).

All 16 patients that failed to reach the full maintenance dose were switched to the opposite buildup protocol, eventually reaching a full maintenance dose of 100  $\mu$ g.

**Table 3.** Reactions in the buildup

|                                           | With risk factor | Without risk factor | <i>p</i> |
|-------------------------------------------|------------------|---------------------|----------|
| Age <5 years                              | 2/17 (11.8%)     | 67/230 (29.1%)      | 0.1      |
| Age >70 years                             | 1/6 (16.7%)      | 68/241 (28.2%)      | 1        |
| Male                                      | 48/188 (25.5%)   | 21/59 (35.6%)       | 0.09     |
| Asthma                                    | 3/8 (37.5%)      | 66/239 (27.6%)      | 0.7      |
| Cardiovascular disease                    | 10/32 (31.3%)    | 59/215 (27.4%)      | 0.69     |
| Beta blocker                              | 3/14 (21.4%)     | 66/233 (28.3%)      | 0.7      |
| ACE-I                                     | 7/20 (35%)       | 62/227 (26.4%)      | 0.4      |
| Malignancy                                | 0/2              | 69/245 (16.3%)      | 1        |
| Autoimmune disease                        | 0/4              | 69/243 (16.5%)      | 0.5      |
| High baseline tryptase level <sup>a</sup> | 3/6 (50%)        | 42/125 (33.6%)      | 0.4      |
| Positive c-kit <sup>b</sup>               | 3/3 (100%)       | 24/83 (28.9%)       | 0.02     |
| Occupational risk                         | 9/21 (42.9%)     | 60/226 (26.5%)      | 0.1      |
| Severity of the index reaction – 3        | 13/37 (35.1%)    | 56/210 (26.6%)      | 0.2      |
| Rush buildup                              | 56/206 (27.1%)   | 13/41 (31.7%)       | 0.5      |

ACE-I, angiotensin-converting enzyme inhibitor. <sup>a</sup> Tryptase level was available for 131 patients. <sup>b</sup> c-kit was available for 86 patients.

**Table 4.** Recurrent reactions in the buildup

|                                    | With risk factor | Without risk factor | <i>p</i> |
|------------------------------------|------------------|---------------------|----------|
| Age <5 years                       | 0/17             | 40/230 (17.4%)      | 0.08     |
| Age >70 years                      | 1/6 (16.7%)      | 39/241 (16.2%)      | 1        |
| Male                               | 25/188 (13.3%)   | 15/59 (25.4%)       | 0.04     |
| Asthma                             | 2/8 (25%)        | 38/239 (15.9%)      | 0.6      |
| Cardiovascular disease             | 8/32 (25%)       | 32/215 (14.9%)      | 0.2      |
| Beta blocker                       | 3/14 (21.4%)     | 37/233 (15.8%)      | 0.3      |
| ACE-I                              | 5/20 (25%)       | 35/227 (15.4%)      | 0.7      |
| Malignancy                         | 0/2              | 40/245 (16.3%)      | 1        |
| Autoimmune disease                 | 0/4              | 40/243 (16.5%)      | 1        |
| High baseline tryptase level       | 3/6 (50%)        | 24/125 (19.2%)      | 0.1      |
| Positive c-kit                     | 3/3 (100%)       | 14/83 (16.8%)       | <0.01    |
| Occupational risk                  | 5/21 (23.8%)     | 35/226 (15.4%)      | 0.3      |
| Severity of the index reaction – 3 | 8/37 (21.6%)     | 32/210 (15.2%)      | 0.4      |
| Rush buildup                       | 29/206 (14.1%)   | 11/41 (26.8%)       | 0.04     |

ACE-I, angiotensin-converting enzyme inhibitor.

### Efficacy of VIT

Follow-up was available for an average of 5 years. During the follow-up period, 62 patients, all of them on maintenance dose, were field stung 106 times by bees. Nine patients (14.5%) had 10 reactions (9%) to field stings. Six reactions were mild, limited to the skin, and 4 reactions were systemic and required emergency adrenalin treatment. Patients with cardiovascular disease were significantly more prone to SR by field stings while on maintenance

dose (4/12 stings [33.3%] vs. 6/94 stings [6.4%], *p* = 0.01).

The maintenance dose of all patients that had reacted to field stings was increased to 200 µg of BV. After dose adjustment, subsequent field bee stings that were documented in 5 patients were uneventful.

Baseline tryptase level was available in 16 patients that were stung. The average baseline tryptase level was higher in the group that had reacted to field stings, but this

**Table 5.** Severe reactions in the build-up

|                                    | With risk factor | Without risk factor | <i>p</i> |
|------------------------------------|------------------|---------------------|----------|
| Age <5 years                       | 0/17             | 29/230 (12.6%)      | 0.2      |
| Age >70 years                      | 1/6 (16.7%)      | 28/241 (11.6%)      | 0.5      |
| Male                               | 17/188 (9%)      | 12/59 (20.3%)       | 0.03     |
| Asthma                             | 1/8 (12.5%)      | 28/239 (11.7%)      | 1        |
| Cardiovascular disease             | 6/32 (18.8%)     | 23/215 (10.7%)      | 0.2      |
| Beta blocker                       | 1/14 (7.1%)      | 28/233 (12%)        | 1        |
| ACE-I                              | 3/20 (15%)       | 26/227 (11.5%)      | 0.7      |
| Malignancy                         | 0/2              | 29/245 (11.8%)      | 1        |
| Autoimmune disease                 | 0/4              | 29/243 (11.9%)      | 1        |
| High baseline tryptase level       | 2/6 (33.3%)      | 18/125 (14.4%)      | 0.2      |
| Positive c-kit                     | 2/3 (66%)        | 10/83 (12%)         | 0.05     |
| Occupational risk                  | 5/21 (23.8%)     | 24/226 (10.6%)      | 0.08     |
| Severity of the index reaction – 3 | 9/37 (24.3%)     | 20/210 (9.5%)       | 0.004    |
| Rush buildup                       | 22/206 (10.7%)   | 7/41 (17.1%)        | 0.2      |

ACE-I, angiotensin-converting enzyme inhibitor.

difference did not reach statistical significance ( $7 \pm 4.3$  vs.  $5.2 \pm 1.2$  mg/dL,  $p = 0.4$ ). The only patient with baseline tryptase level  $>11.4$  mg/dL, which had been stung, had a mild reaction to the field sting before increasing his maintenance dose to 200 µg.

## Discussion

In the current study, we aimed to evaluate the outcome of VIT in patients with exclusive BV allergy. The data presented here elucidate the risk factors for VIT-ISR and show that VIT can be performed safely and efficiently in this special group of patients.

BV allergy is a known risk factor for VIT-ISR [5]. In a recent Cochrane collaboration meta-analysis, the incidence of SR during VIT was found to be 3.7–44.8% (average 14.2%) in bee VIT and 0–11.1% (average 2.8%) in wasp VIT [1]. Our data point to a high but expected rate of VIT-ISR in BV allergic patients. Up to 27.9% of the patients had at least 1 reaction during buildup; most of them (58%) were mild. It has to be emphasized that all reactions responded as expected to treatment, including prompt response to the first dose of epinephrine when indicated. This high incidence of VIT-ISR could be explained by the fact that previous data regarding BV allergy are based on small series, mostly not referring to exclusive BV allergy. When both wasp and BV sensitizations were found, it is possible that the BV sensitization was a cross-reaction rather than a true allergy. The data presented here is the

largest collection of exclusively BV allergic patients to date, probably presenting more realistic numbers.

On top of BV allergy per se, previous works have defined additional risk factors for VIT-ISR, including high levels of baseline serum tryptase, cardiovascular disease, antihypertension medication, such as beta blockers or ACE inhibitors, and age extremities [4, 5, 7–11]. These risk factors are based on series where most of the patients were allergic to wasp and only the minority of the patients had BV allergy. In the present work, these classic risk factors for VIT-ISR were not found to be associated with a higher incidence of VIT-ISR.

On the other hand, several risk factors emerged from the data: recurrent and severe VIT-ISR were more prevalent among women. Bee keepers and patients with a severe index reaction were also prone to develop severe VIT-ISR.

Attention needs to be paid to the measurement of baseline serum tryptase levels and c-kit mutation. Baseline tryptase level is regarded as a significant risk factor for VIT-ISR and VIT failure, especially in European patients with wasp allergy [5]. Our work does not support this observation in exclusively BV allergic patient. Although baseline tryptase levels were slightly higher in all the subgroup tested, this difference did not reach statistical significance. Moreover, in our cohort we had only 6 patients (4.5%) with abnormally high ( $>11.4$  mg/dL) baseline tryptase level. This is opposed to previous works suggesting that 10–15% of patients have high baseline tryptase levels in a population with wasp allergy [12–15]. This lower than expected rate is in accordance with our

previous publications pointing out that bee and wasp allergy are probably 2 distinct entities [16]. Among the 6 patients who had baseline serum tryptase levels >11.4 mg/dL, the frequency of VIT-ISR, recurrent reactions, severe reactions, and VIT failure was indeed high. However, the small numbers preclude us from drawing strict conclusions regarding the effect of high baseline tryptase levels on VIT outcome in exclusively BV allergic patients. As opposed to baseline tryptase level, mutation in c-kit correlated with all risk subgroups tested. There are no data to date regarding the use of c-kit as a biomarker for VIT outcome in Hymenoptera allergic patients. Despite the low numbers, our data point out that probably c-kit, and not baseline tryptase level, may provide a more reliable biomarker for VIT-ISR in exclusively BV allergic patients.

Recent studies suggest that VIT may be less effective in patients with high risk for SR, especially in patients allergic to BV [5, 17, 18]. As recently summarized by a Cochrane collaboration meta-analysis, the incidence of recurrent SR to insect stings after VIT is expected to be 2.7% in comparison to 39.8% for all venom allergic patients that were not treated with VIT [1]. The incidence of allergic reactions to field stings during the maintenance dose phase in our study population was higher than expected (14.5% of patients that were stung and 9.5% of all field stings) in other venom allergic treated populations. Nonetheless, it is still considerably lower than the incidence expected in venom allergic patients who do not receive VIT. Doubling the maintenance dose to 200 µg provided complete protection from further stings in these patients.

The current literature is inconsistent regarding the risk of SR when using accelerated buildup protocols. In a multicenter EAACI study, Mosbech et al. [19] found that RVIT was associated with a higher incidence of SR in comparison with a CVIT protocol. Rueff et al. [4, 5] found that 2-day RVIT protocols (referred to as ultra-rush) were associated with a higher risk of SR than more conservative RVIT protocols that took 2 weeks to reach the maintenance dose. Others found that RVIT was as safe as CVIT, especially in wasp allergy [20]. Previous works from our group demonstrated the safety and efficiency of our rush buildup protocol in the general population as well as in children and in high-risk patients, when most of the patients were allergic to BV [2, 16, 21]. Thus, in accordance with our previous findings, the current study found that SR were comparable between both protocols with the advantage of significantly less recurrent reactions and significantly more success in achieving

the full maintenance dose with RVIT in exclusively BV allergic patients. RVIT has more advantages as compared to CVIT, including the significantly shorter time required to reach the maintenance dose, the reduced number of injections required to reach the maintenance dose, and decreased expenses [2]. All these facts make the option of RVIT preferable in cases of exclusively BV allergic patients, as well as in other populations of Hymenoptera allergy.

This study has a few limitations. The first is the retrospective nature of this study. Second, due to the small numbers of patients with high baseline tryptase and positive c-kit mutations in our population, the statistical evaluation of these subgroups should be interpreted with care.

To the best of our knowledge, this is the first study to describe the outcome of a large cohort of patients with exclusive BV allergy. In conclusion, despite the considerably high rate of VIT-ISR in patients with exclusive BV allergy, VIT can be performed safely and efficiently. c-kit mutation, and not basal serum tryptase level, seems to be a preferable biomarker for VIT-ISR in these patients.

## Statement of Ethics

The study protocol has been approved by the research institute's committee on human research.

## Disclosure Statement

The authors declare no conflicts of interest.

## Funding Sources

The authors declare no sources of funding.

## References

- Boyle RJ, Elremeli M, Hockenhull J, Cherry MG, Bulsara MK, Daniels M, et al. Venom immunotherapy for preventing allergic reactions to insect stings. *Cochrane Database Syst Rev*. 2012 Oct;10:CD008838.
- Goldberg A, Yogev A, Confino-Cohen R. Three days rush venom immunotherapy in bee allergy: safe, inexpensive and instantaneously effective. *Int Arch Allergy Immunol*. 2011;156(1):90–8.
- Rüeff F, Przybilla B. Venom immunotherapy: adverse reactions and treatment failure. *Curr Opin Allergy Clin Immunol*. 2004 Aug;4(4):307–11.

- 4 Ruëff F, Przybilla B, Biló MB, Müller U, Scheipl F, Aberer W, 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 Jul;126(1):105–11.e5.
- 5 Ruëff F, Kroth J, Przybilla B. Risk factors in Hymenoptera venom allergy. *Allergol Select*. 2017 Aug;1(1):53–58.
- 6 Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol*. 2004 Aug;114(2):371–6.
- 7 Bernkopf K, Rönsh H, Spornraft-Ragaller P, Neumeister V, Bauer A. Safety and tolerability during build-up phase of a rush venom immunotherapy. *Ann Allergy Asthma Immunol*. 2016 April;116(4):360–5.
- 8 Müller UR, Haerberli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. *J Allergy Clin Immunol*. 2005 Mar;115(3):606–10.
- 9 Stoevesandt J, Hosp C, Kerstan A, Trautmann A. Hymenoptera venom immunotherapy while maintaining cardiovascular medication: safe and effective. *Ann Allergy Asthma Immunol*. 2015 May;114(5):411–6.
- 10 Pitsios C, Demoly P, Biló MB, Gerth van Wijk R, Pfaar O, Sturm GJ, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. *Allergy*. 2015 Aug;70(8):897–909.
- 11 Golden DB, Demain J, Freeman T, Graft D, Tankersley M, Tracy J, et al. Stinging insect hypersensitivity: A practice parameter update 2016. *Ann Allergy Asthma Immunol*. 2017 Jan;118(1):28–54.
- 12 Potier A, Lavigne C, Chappard D, Verret JL, Chevailler A, Nicolie B, et al. Cutaneous manifestations in Hymenoptera and Diptera anaphylaxis: relationship with basal serum tryptase. *Clin Exp Allergy*. 2009 May;39(5):717–25.
- 13 Bonadonna P, Perbellini O, Passalacqua G, Caruso B, Colarossi S, Dal Fior D, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. *J Allergy Clin Immunol*. 2009 Mar;123(3):680–6.
- 14 Bonadonna P, Zanotti R, Pagani M, Caruso B, Perbellini O, Colarossi S, et al. How much specific is the association between hymenoptera venom allergy and mastocytosis? *Allergy*. 2009 Sep;64(9):1379–82.
- 15 Guenova E, Volz T, Eichner M, Hoetzenecker W, Caroli U, Griesinger G, et al. Basal serum tryptase as risk assessment for severe Hymenoptera sting reactions in elderly. *Allergy*. 2010 Jul;65(7):919–23.
- 16 Rosman Y, Confino-Cohen R, Goldberg A. Venom Immunotherapy in High-Risk Patients: The Advantage of the Rush Build-Up Protocol. *Int Arch Allergy Immunol*. 2017;174(1):45–51.
- 17 Ruëff F, Vos B, Oude Elberink J, Bender A, Chatelain R, Dugas-Breit S, et al. Predictors of clinical effectiveness of Hymenoptera venom immunotherapy. *Clin Exp Allergy*. 2014;44(5):736–46.
- 18 Ruëff F, Przybilla B, Biló MB, Müller U, Scheipl F, Seitz MJ, et al. Clinical effectiveness of hymenoptera venom immunotherapy: a prospective observational multicenter study of the European academy of allergology and clinical immunology interest group on insect venom hypersensitivity. *PLoS One*. 2013 May;8(5):e63233.
- 19 Mosbech H, Müller U, Behalf Of The Study Group O; European Academy of Allergology and Clinical Immunology. Side-effects of insect venom immunotherapy: results from an EAACI multicenter study. *Allergy*. 2000 Nov;55(11):1005–10.
- 20 Cox L. Advantages and disadvantages of accelerated immunotherapy schedules. *J Allergy Clin Immunol*. 2008 Aug;122(2):432–4.
- 21 Nachshon L, Goldberg MR, Elizur A, Levy MB, Schwartz N, Katz Y. A Web site-based reporting system for monitoring home treatment during oral immunotherapy for food allergy. *Ann Allergy Asthma Immunol*. 2015 Jun;114(6):510–5.