Clinical Allergology – Original Paper

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2017;174:45–51
DOI: 10.1159/000479692

Received: February 23, 2017
Accepted after revision: July 11, 2017
Published online: September 27, 2017

Venom Immunotherapy in High-Risk Patients: The Advantage of the Rush Build-Up Protocol

Yossi Rosman[a, b] Ronit Confino-Cohen[a, b] Arnon Goldberg[a, b]

[a] Allergy and Clinical Immunology Unit, Meir Medical Center, Kfar Saba, and [b] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Keywords

Venom immunotherapy · Hymenoptera allergy · Bee venom allergy

Abstract

Background: Venom immunotherapy (VIT) is considered to be the gold standard treatment for patients with hymenoptera venom allergy. This treatment induces systemic reactions (SR) in a significant number of patients. ***Objective:*** To evaluate the outcome of VIT in patients with known risk factors for VIT-induced SR and to compare rush VIT (RVIT) and conventional VIT (CVIT). ***Methods:*** All of the patients who received VIT and had at least one of the following risk factors were included: current cardiovascular disease, uncontrolled asthma, high basal serum tryptase, current treatment with β-blockers or angiotensin-converting enzyme inhibitors, and age >70 or <5 years. ***Results:*** Sixty-four patients were included, and most of them (52; 81.5%) were allergic exclusively to bee venom. Thirty-five (54.7%) patients underwent RVIT and 29 CVIT. The incidence of patients who developed SR during the build-up phase was similar for RVIT and CVIT (25.7 and 27.5%, respectively; $p = 1$). However, the incidence of SR per injection was significantly higher in CVIT than in RVIT (5.6 and 2.75%, respectively; $p = 0.01$). Most reactions (79.1%) were mild, limited to the skin. Most of the patients (92.1%) reached the full maintenance dose of 100 μg. This dose was reached by a significantly larger number of patients receiving RVIT compared to CVIT (100 and 82.7%, respectively; $p = 0.01$). None of the patients experienced exacerbation of their concurrent chronic disease during VIT. ***Conclusion:*** VIT can be performed safely and efficiently in patients with risk factors for immunotherapy. In these patients RVIT appears to be safer and more efficient than CVIT.

© 2017 S. Karger AG, Basel

Introduction

Venom immunotherapy (VIT) is considered to be the gold standard treatment for patients with hymenoptera venom allergy. This treatment, though 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 [2]. Beside supportive measures, SR to VIT are treated by prompt administration of intra-

Y.R. and R.C.-C. contributed equally to this work.

KARGER

© 2017 S. Karger AG, Basel

E-Mail karger@karger.com
www.karger.com/iaa

Correspondence to: Dr. Yossi Rosman
Allergy and Clinical Immunology Unit
Meir Medical Center
44261 Kfar Saba (Israel)
E-Mail yossi.rosman@clalit.org.il

Downloaded by: A. Mari - 31298
Universita degli Studi, Bibl. Area Biomed. Tor Vergata
160.80.2.38 - 10/4/2017 6:18:40 AM

muscular (IM) epinephrine, bronchodilators, antihistamines, and systemic corticosteroids. Although data are limited, several risk factors for VIT-induced SR (VIT-ISR) have been proposed over the years. These risk factors include concomitant cardiovascular disease (CVD), high baseline serum tryptase levels, bee venom (BV) allergy, antihypertension medication including β-blockers (BB) and angiotensin-converting enzyme inhibitors (ACE-i), severe uncontrolled asthma, and age <5 or >70 years. Autoimmune disease and malignancy are considered risk factors by some authors, especially due to the risk of exacerbation of these diseases [2–6]. Several studies have also suggested that accelerated build-up protocols (rush VIT; RVIT) are also associated with a higher risk of VIT-ISR [2, 6]. Although the general notion is that the importance of VIT outweighs the risk of SR, there is still concern regarding the appropriate approach in high-risk individuals [5].

The aim of this work was to evaluate the outcome of VIT in patients with hymenoptera allergy and risk factors for VIT-ISR. We also compared the outcome between RVIT and conventional VIT (CVIT) in these patients.

Methods

This was a retrospective study conducted in the Allergy and Clinical Immunology Unit of the Meir Medical Center, Kfar Saba, Israel.

Patient Characteristics

The inclusion criteria were:

(1) VIT treatment for hymenoptera allergy: indication for VIT was defined as a history of a SR to an insect sting together with a positive skin test or serum venom-specific IgE to BV and/or yellow jacket and/or wasp. Children under the age of 18 years with a reaction limited to the skin – grade 1 according to Brown's grading [7] – were excluded.

(2) At least one of the following risk factors: CVD, concurrent treatment with BB or ACE-I, asthma – moderate, with FEV_1 <70% or uncontrolled with at least one hospitalization over the past year or a need for systemic steroid treatment, high base-line serum tryptase, defined as a level >11.4 μg/L, and age >70 or <5 years at the beginning of treatment.

Due to the fact that most venom-allergic patients in Israel are allergic to BV, we decided not to include patients for whom BV allergy was the only risk factor. Patients that autoimmune disease or malignancy as the only risk factor were followed separately for exacerbations of their chronic disease.

Venom Immunotherapy

After a comprehensive explanation about the 2 treatment modalities, the patients chose to be treated either by RVIT or by CVIT. The detailed protocols of both methods have been published elsewhere [8]. Briefly, in the absence of SR to the treatment, the build-up phase lasts 3 days with RVIT and includes 14 injections. The CVIT build-up phase lasts 3–4 months and includes 17 weekly injections (Table 1). Patients who required more than one venom received all venoms simultaneously in the CVIT protocol, whereas those receiving RVIT started the build-up phase of the second venom 1 week after achieving the maintenance dose of the previous venom. After build-up was finished, the injections were administered simultaneously in both groups. In order to overcome the potential bias in the build-up phase, we decided, in this small

Table 1. VIT protocols

Injection number	1 μg/mL	10 μg/mL	100 μg/mL
Rush VIT protocol[1]			
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)
Conventional VIT protocol			
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)

VIT, venom immunotherapy. [1] Doses were administered at 15-min intervals.

Downloaded by: A. Mari - 31.298
Universita degli Studi, Bibl. Area Biomed. Tor Vergata
160.80.2.38 - 10/4/2017 6:18:40 AM

group of patients, to count reactions by sessions of injections in the CVIT group. In the RVIT group we counted injections in the session for which side effects were documented. Consequently, the uneventful injections of probably cross-reacting venoms did not dilute or bias the results. If no side effect was documented, we counted all sessions as one.

The baseline tryptase level was measured in all patients prior to VIT initiation.

Systemic Reactions

After each immunotherapy session all of the patients were observed for 30 min for SR. SR were diagnosed and treated by a physician specialized in allergy and clinical immunology. The severity of SR was graded according to Brown's criteria [7]. 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.

Follow-Up

Follow-up was done during all immunotherapy sessions and once a year after completion of immunotherapy. Some BV allergic patients underwent a live bee sting challenge 1 week after reaching the maintenance dose as part of a previous study [8].

Statistical Analysis

Data were entered and tabulated using Excel 2007. Data are presented as means and standard error (SE) for continuous variables. Comparisons between groups were performed with Student's *t* test for continuous variables and Fisher's exact test for categorical variables. All tests of hypotheses were considered significant when 2-sided probability values were $p < 0.05$.

Results

Patient Characteristics

During the years 2000–2015, 640 patients were treated with specific immunotherapy for hymenoptera allergy at our institution. Seventy patients (10.9%) who had at least one risk factor for VIT-ISR were included in this study. Eight patients had an autoimmune disease or malignancy. Of them, 6 had no other risk factor and hence they were excluded from the VIT-SR study, leaving 64 patients in this analysis. Their characteristics are presented in Table 2. Thirty-five patients (54.7%) underwent RVIT and 29 patients (45.3%) received CVIT. Most of our subjects (75%) were males. The frequencies of the risk factors among the 2 build-up groups were comparable. The most frequent risk factor was CVD (37 patients; 57.8%), followed by ACE-i treatment (25 patients; 39%). Though not regarded as a risk factor for VIT-SR, 7 (10.9%) patients had occupational exposure to bees and hence they had an increased risk of recurrent stings. Over half of the patients ($n = 39$; 60.9%) had multiple risk factors.

Most of the patients ($n = 52$; 81.25%) were allergic exclusively to BV, without a significant difference between RVIT and CVIT (31 [88.5%] and 21 [72.4%], respectively; $p = 0.1$). The initial sting reaction was severe (anaphylactic shock, grade 3) in 23 (35.9%) patients.

Table 2. Patient characteristics

	All ($n = 64$)	RVIT[1] ($n = 35$)	CVIT[1] ($n = 29$)
Age, years	39.1±25	39.8±24.8	38.3±25.7
Males	48 (75)	27 (77.1)	21 (72.4)
CVD	37 (57.8)	20 (57.1)	17 (58.6)
Hypertension	22 (34.3)	14 (40)	8 (27.5)
IHD	13 (20.3)	7 (20)	6 (20.6)
AF	3 (4.6)	2 (5.7)	1 (3.4)
Other[2]	3 (4.6)	0	3 (10.3)
β-Blockers	15 (23.4)	6 (17.1)	9 (31)
ACE inhibitors	25 (39)	15 (42.8)	10 (34.5)
Asthma	4 (6.25)	1 (2.8)	3 (10.3)
High basal serum tryptase level	5 (7.8)	5 (14.3)	0
Age			
>70 years	7 (10.9)	3 (8.5)	4 (13.8)
<5 years	17 (26.5)	9 (25.7)	8 (27.5)
Occupational exposure (beekeepers)	7 (10.9)	6 (17.1)	1 (3.4)
Number of risk factors			
1	25 (39.1)	11 (31.4)	14 (48.2)
>1	39 (60.9)	24 (68.6)	15 (55.5)
Venoms administered			
B	52 (81.25)	31 (88.5)	21 (72.4)
YJ	2 (3.1)	1 (2.8)	1 (3.4)
B+W	1 (1.5)	0	1 (3.4)
B+YJ	5 (7.8)	1 (2.8)	4 (13.7)
W+YJ	1 (1.5)	1 (2.8)	0
B+W+YJ	3 (4.6)	1 (2.8)	2 (6.8)
Severity of the initial reaction			
1	4 (6.25)	0	4 (11.1)
2	37 (57.8)	23 (65.7)	14 (48.2)
3	23 (35.9)	12 (34.2)	11 (40.7)

Values are presented as numbers (%) or means ± SE. RVIT, rush venom immunotherapy; CVIT, conventional venom immunotherapy; AF, atrial fibrillation; ACE, angiotensin-converting enzyme; B, bee; CVD, cardiovascular disease; IHD, ischemic heart disease; W, wasp; YJ, yellow jacket. [1] All comparisons between RVIT and CVID were nonsignificant. [2] Peripheral vascular disease, mitral regurgitation, and myocarditis.

Downloaded by: A. Mari - 31.298
Universita degli Studi, Bibl. Area Biomed. Tor Vergata
160.80.2.38 - 10/4/2017 6:18:40 AM

Table 3. Characteristics of venom immunotherapy build-up

	All (n = 64)	RVIT (n = 35)	CVIT (n = 29)	p
Number of injections until the maintenance dose was reached	19.1±9	16.6±6.5	23.7±10.1	<0.01
Time required to reach the maintenance dose, days	46.1±68.7	3.8±2.4	147.5±71.6	<0.01
Patients with systemic reactions	17 (26.5)	9 (25.7)	8 (27.5)	1
Systemic reactions/all injections	48/1,199 (4)	16/582 (2.75)	32/568 (5.6)	0.01
Grade 1	38 (79.1)	13 (81.25)	25 (78.1)	1
Grade 2	6 (12.5)	2 (12.5)	4 (12.5)	
Grade 3	4 (10.5)	1 (6.25)	3 (9.4)	
Treatment				
Antihistamine	17 (26.5)	9 (25.7)	8 (27.5)	1
Inhalation	3 (4.6)	2 (5.7)	1 (3.4)	1
Epinephrine	4 (6.25)	1 (2.8)	3 (10.3)	0.3
Corticosteroids	1 (1.5)	1 (2.8)	0	1
Patients achieving the full maintenance dose	59 (92.1)	35 (100)	24 (82.7)	0.01

Values are presented as means ± SD or n (%) unless otherwise stated. RVIT, rush venom immunotherapy; CVIT, conventional venom immunotherapy.

VIT-Induced SR

During the build-up phase, 17 (26.5%) patients suffered from at least one SR, with no difference between RVIT and CVIT (9 [25.7%] and 8 [27.5%], respectively; $p = 1$) (Table 3). The incidence of SR per injection during the build-up phase was 4% (1 reaction for every 25 injections). The highest incidence was found in patients with elevated baseline tryptase levels (7.1%) and the lowest was in patients under the age of 5 years (0.6%). The incidence of SR per injection was significantly higher in the CVIT group compared to RVIT (5.6 and 2.75% respectively; $p = 0.01$). This difference between RVIT and CVIT was even more striking in patients with CVD (1.8 and 6.1%, respectively; $p < 0.01$), patients on ACE-i treatment (2.3 and 6.3%, respectively; $p = 0.05$), and patients with multiple risk factors (2.7 and 5.9%, respectively; $p = 0.03$) (Table 4). Most of the reactions ($n = 38$; 79.1%) were confined to the skin (grade 1) and IM epinephrine was required only in 4 (6.25%) severe SR. All reactions responded as expected to treatment, including a prompt response to the first dose of epinephrine when indicated. In the subgroups of patients on concurrent treatment with BB or ACE-i, our findings were similar. Thus, 5 out of 6 (83.3%) SR in patients who received BB treatment were mild and the sixth reaction was a grade 3 reaction that responded promptly to a single dose of IM epinephrine. In patients treated with ACE-i, 14 out of 18 (77%) reactions were mild, 3 reactions were moderate (grade 2), and 1 reaction was a severe, grade 3 reaction. A single dose of epinephrine was administered to 2 patients with immediate resolution of symptoms. All of the other patients were managed with oral antihistamines and occasionally with bronchodilators.

Achieving the Maintenance Dose

At the end of the build-up phase, 59 patients (92.1%) reached the full maintenance dose of 100 μg. This rate was significantly higher in the RVIT group compared to the CVIT group (35 [100%] and 24 patients [82.7%], respectively; $p = 0.01$). We were not able to reach the full maintenance dose in 5 patients of the CVIT group due to recurrent SR. As previously described [8, 9], all of the patients who failed to reach the maintenance dose by CVIT were offered RVIT. Four patients who consented underwent a recurrent build-up phase with RVIT and reached the 100-μg maintenance dose uneventfully. The fifth patient was a 4-year-old child who underwent CVIT and suffered from a single mild SR following administration of 50 μg of BV. After receiving an explanation about the possible treatment options, her parents decided to keep her on a lower maintenance dose of 50 μg.

Long-Term Follow-Up

Follow-up during maintenance immunotherapy was available for an average of 5.1 ± 5.2 years. During this time, 9 (14%) patients had SR to VIT. The incidence of SR

Downloaded by: A. Mari - 31.298
Universita degli Studi, Bibl. Area Biomed. Tor Vergata
160.80.2.38 - 10/4/2017 6:18:40 AM

Table 4. Venom immunotherapy-induced systemic reactions during the build-up phase, by risk factor

Risk factor	All SR (SR/total injections)	RVIT SR (SR/total injections)	CVIT SR (SR/total injections)	*p*
CVD	27/664 (4)	6/325 (1.8)	21/339 (6.1)	<0.01
BB	6/249 (2.4)	4/126 (3.1)	2/123 (1.6)	0.6
ACE-i	18/446 (4)	6/255 (2.3)	12/191 (6.3)	0.05
Age >70 years	7/130 (5.4)	7/88 (8)	0/42	0.1
Age <5 years	2/275 (0.7)	2/128 (1.5)	0/147	0.2
High basal serum tryptase	10/141 (7.1)	10/141 (7.1)	–	NA
Asthma	4/96 (4.1)	0/14	4/82 (4.8)	1
One risk factor	18/476 (3.7)	5/177 (2.8)	13/299 (4.3)	0.4
Multiple risk factors	30/723 (4.1)	11/405 (2.7)	19/318 (5.9)	0.03

Values in parentheses are percentages. SR, systemic reactions; RVIT, rush venom immunotherapy; CVIT, conventional venom immunotherapy; CVD, cardiovascular disease; BB, β-blockers; ACE-i, angiotensin-converting enzyme inhibitors; NA, not applicable.

during the maintenance period was 1.6% of all injections (1/60 injections). Most of these reactions (64.7%) were limited to the skin (grade 1) and none was graded as severe (grade 3). There was no difference between RVIT and CVIT in the incidence of SR during maintenance (1/70 vs. 1/50 injections, respectively; $p = 0.3$). Epinephrine was administered only once during the maintenance phase.

Forty-seven insect stings (33 field stings and 11 controlled sting challenges) in 23 patients were documented during follow-up. Most stings ($n = 40$; 85.1%) were well tolerated. Six patients (26%, i.e., 3 from the RVIT group and 3 from the CVIT group) had 7 documented reactions to insect stings (5 reactions to field stings and 2 to a controlled sting challenge). All patients had their maintenance dose increased to 200 μg. Subsequently, 4 insect stings (1 controlled sting challenge and 3 field stings) recorded in 3 patients (2 in the CVIT group and 1 in the RVIT group) were well tolerated. Fifteen stings in 6 patients were documented in the subgroup of patients receiving ACE-i (all of them during the maintenance period), with 2 SR (13.3%) to a field sting that responded well to autoinjection of epinephrine.

Two patients had an active malignant disease (thyroid papillary carcinoma and an adrenal neoplasm) and 6 patients had a concurrent autoimmune disease (3 patients with Crohn disease, 2 with rheumatic arthritis, and 1 with antiphospholipid syndrome). These 8 patients were followed for an average of 4.5 years (range 1–9), with no evidence of exacerbation of their chronic disease.

Discussion

In the current study we aimed to evaluate the outcome of VIT in patients with risk factors for VIT-ISR. The data presented show that VIT can be performed safely and efficiently in such patients and that the outcome of RVIT is favorable compared to CVIT.

Data regarding risk factors for VIT-ISR are limited. Ruëff et al. [6] found that bee VIT, high levels of baseline tryptase, CVD, antihypertension medication, and older age were risk factors for SR. Data regarding the risk of concurrent BB or ACE-i treatment are based mostly on expert opinions and on a few case reports from the 1980s [10–12]. Bernkopf et al. [13] found that concurrent ACE-i treatment, but not BB treatment, was a risk factor for VIT-ISR in a cohort of wasp-allergic patients undergoing RVIT. Müller and Haeberli [14] failed to demonstrate an increased risk of systemic adverse effects in patients receiving concurrent BB treatment during VIT, but their cohort consisted of only 4 patients during the build-up phase. Stoevesandt et al. [15] concluded that cardiovascular medications, including BB and ACE-i, did not impair the safety of VIT, but most of their patients received wasp VIT and BB treatment was stopped during build-up unless considered necessary. Disregarding the controversy, it is still recommended to stop BB and ACE-i treatment before VIT if feasible [4].

A recent EAACI position paper stated that caution should be exercised before prescribing VIT to patients with asthma, under the age of 5 years, with concurrent CVD, on BB or ACE-i treatment, or suffering from an active autoimmune disease or malignancy. Most of these

Downloaded by: A. Mari - 31.298
Universita degli Studi, Bibl. Area Biomed. Tor Vergata
160.80.2.38 - 10/4/2017 6:18:40 AM

recommendations are based on expert opinions and are not evidence based [5].

In a recent Cochrane collaboration meta-analysis, the incidence of SR during VIT in the general population was found to be 3.7–44.8% (14.2%) in bee VIT and 0–11.1% (2.8%) in wasp VIT. One systemic side effect was reported for every 52 injections (1.9%) of bee VIT. Considering the fact that the vast majority of our patients were allergic to BV, the incidence found in our patients was higher. Thus, 26.5% of our patients had at least one SR during the build-up phase and the incidence of SR per injection was 4% (1 in every 25 injections). Similarly, the incidence of SR per injection was significantly higher for each risk factor if examined separately. The only exceptions were children younger than 5 years, who demonstrated a surprisingly low rate of SR (i.e., 2 patients [11.7%], with an incidence of 1 SR for every 137 injections [0.7%] during build-up; Table 4).

Concern has been raised regarding not only the incidence of SR but also their severity and whether they respond well to IM epinephrine, especially in patients on concurrent BB or ACE-i treatment [10, 12, 16–20]. Our data do not support this apprehension. First, most SR (38, 79.1%) were mild. Second, all of the reactions responded as expected to treatment, including a prompt response to the first dose of epinephrine when indicated. Similar results were also obtained for patients on concurrent treatment with BB or ACE-i.

A recent study suggested that VIT may be less effective in patients with a high risk of SR, especially in patients on concurrent ACE-i treatment [21]. As recently summarized by a Cochrane's collaboration meta-analysis, the incidence of recurrent SR to insect stings after VIT is expected to be 2.7%, compared to 39.8% for venom allergic patients who were not treated with VIT [1]. Although the incidence of reactions to future insect stings in our study population was slightly higher than expected in the general population, it was 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.

Several authors have expressed concern regarding the harmful effect of VIT on concurrent chronic illness, especially malignancy or autoimmune disease [5]. Accordingly, these medical situations are considered complete or relative contraindications for immunotherapy in some guidelines [5]. This recommendation is based mainly on case reports and expert opinion and it is not evidence-based [5]. Although this study population included only 8 patients with such chronic disease, our results indicate otherwise.

The current literature is inconsistent regarding the risk of SR when using accelerated build-up protocols. Ruëff and Przybilla [6] found that 2 days of the RVIT protocols (referred to as ultra-rush) were associated with a higher risk of SR compared to more conservative RVIT protocols that took 2 weeks to reach the maintenance dose. Others found that RVIT was as safe as CVIT, especially in vespid venom allergy [22]. We have demonstrated in the past the safety and efficiency of our rush build-up protocol in the general population as well as in children, including very young children, when most of the patients were allergic to BV [8, 23]. Thus, in accordance with our previous findings, the current study also found a lower incidence of SR per injection in patients receiving RVIT compared to CVIT despite the fact that all of the patients with a high baseline tryptase level, which is known to be a major risk factor for VIT- ISR, were in the RVIT group. This finding was most noteworthy in patients with CVD and in patients with multiple risk factors. The statistically significant difference found between RVIT and CVIT only regarding the incidence of SR per injection and not per patient may be explained by 2 factors. First, it may be attributed to the relatively smaller number of patients compared to the number of injections, which diminished the statistical power of the later comparison. Second, it might be another indication of the better efficacy of RVIT, meaning that a patient who suffered from a single SR "overcame" it better with RVIT than with CVIT, suffering from significantly fewer subsequent SR.

RVIT has several advantages compared to CVIT. Obviously, the significantly shorter time required to reach the maintenance dose provides quick protection from further stings. This is especially important when imminent stings are expected due to occupational exposure. The second advantage is the reduced number of injections required to reach the maintenance dose in RVIT compared to CVIT, as shown here. This consequently decreased expenses, as shown previously by us [8]. Another advantage of RVIT over CVIT is its efficacy, as reflected here in the significantly larger rate of patients who achieved the full 100-μg maintenance dose.

This study has a few limitations. First is the retrospective nature of this study. Second, due to the small number of patients and anaphylactic events, the statistic evaluation of subgroups should be interpreted with care. Third, there was an uneven distribution of risk factors between the 2 study groups. Nevertheless, in the CVIT group there

Downloaded by: A. Mari - 31298
Universita degli Studi, Bibl. Area Biomed. Tor Vergata
160.80.2.38 - 10/4/2017 6:18:40 AM

were no patients with high tryptase levels, less BV allergy, and fewer patients with multiple risk factors, hence strengthening our findings even more.

To the best of our knowledge this is the first study to describe the outcome of a large cohort of patients with multiple risk factors to VIT-ISR when most of them also had a BV allergy, which is known apriori as a significant risk factor. Moreover, this is the first study to compared RVIT and CVIT in this group of patients.

In conclusion, VIT can be performed safely and efficiently in patients with risk factors to immunotherapy. In this group of patients, RVIT seems safer and more efficient than CVIT.

Disclosure Statement

The authors declare no conflict of interests.

Funding Sources

The authors declare no sources of funding.

References

1 Boyle RJ, Elremeli M, Hockenhull J, Cherry MG, Bulsara MK, Daniels M, Oude Elberink JN: Venom immunotherapy for preventing allergic reactions to insect stings. Cochrane Database Syst Rev 2012;10:CD008838.

2 Ruëff F, Przybilla B: Venom immunotherapy: adverse reactions and treatment failure. Curr Opin Allergy Clin Immunol 2004;4:307–311.

3 Cichocka-Jarosz E, Sanak M, Szczeklik A, Brzyski P, Gielicz A, Pietrzyk JJ: Serum tryptase level is a better predictor of systemic side effects than prostaglandin D_2 metabolites during venom immunotherapy in children. J Investig Allergol Clin Immunol 2011;21:260–269.

4 Golden DB, Demain J, Freeman T, Graft D, Tankersley M, Tracy J, Blessing-Moore J, Bernstein D, Dinakar C, Greenhawt M, et al: Stinging insect hypersensitivity: a practice parameter update 2016. Ann Allergy Asthma Immunol 2017;118:28–54.

5 Pitsios C, Demoly P, Bilò MB, Gerth van Wijk R, Pfaar O, Sturm GJ, Rodriguez del Rio P, Tsoumani M, Gawlik R, Paraskevopoulos G, et al: Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy 2015, 70:897–909.

6 Ruëff F, Przybilla B, Bilò MB, Müller U, Scheipl F, Aberer W, Birnbaum J, Bodzenta-Lukaszyk A, Bonifazi F, Bucher C, 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;126:105–111.e5.

7 Brown SG: Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004;114:371–376.

8 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;156:90–98.

9 Goldberg A, Confino-Cohen R: Rush venom immunotherapy in patients experiencing recurrent systemic reactions to conventional venom immunotherapy. Ann Allergy Asthma Immunol 2003;91:405–410.

10 Awai LE, Mekori YA: Insect sting anaphylaxis and beta-adrenergic blockade: a relative contraindication. Ann Allergy 1984;53:48–49.

11 Ingall M, Goldman G, Page LB: Beta-blockade in stinging insect anaphylaxis. JAMA 1984; 251:1432.

12 Kivity S, Yarchovsky J: Relapsing anaphylaxis to bee sting in a patient treated with beta-blocker and Ca blocker. J Allergy Clin Immunol 1990;85:669–670.

13 Bernkopf K, Rönsch 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;116:360–365.

14 Müller UR, Haeberli G: Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. J Allergy Clin Immunol 2005; 115:606–610.

15 Stoevesandt J, Hosp C, Kerstan A, Trautmann A: Hymenoptera venom immunotherapy while maintaining cardiovascular medication: safe and effective. Ann Allergy Asthma Immunol 2015;114:411–416.

16 Hiatt WR, Stoll S, Nies AS: Effect of beta-adrenergic blockers on the peripheral circulation in patients with peripheral vascular disease. Circulation 1985;72:1226–1231.

17 Jacobs RL, Rake GW Jr, Fournier DC, Chilton RJ, Culver WG, Beckmann CH: Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. J Allergy Clin Immunol 1981;68:125–127.

18 Newman BR, Schultz LK: Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. Ann Allergy 1981;47:35–37.

19 Hermann K, Ring J: The renin-angiotensin system in patients with repeated anaphylactic reactions during hymenoptera venom hyposensitization and sting challenge. Int Arch Allergy Immunol 1997;112:251–256.

20 Hermann K, von Tschirschnitz M, Ebner von Eschenbach C, Ring J: Histamine, tryptase, norepinephrine, angiotensinogen, angiotensin-converting enzyme, angiotensin I and II in plasma of patients with hymenoptera venom anaphylaxis. Int Arch Allergy Immunol 1994;104:379–384.

21 Ruëff F, Vos B, Oude Elberink J, Bender A, Chatelain R, Dugas-Breit S, Horny HP, Küchenhoff H, Linhardt A, Mastnik S, et al: Predictors of clinical effectiveness of Hymenoptera venom immunotherapy. Clin Exp Allergy 2014;44:736–746.

22 Cox L: Advantages and disadvantages of accelerated immunotherapy schedules. J Allergy Clin Immunol 2008;122:432–434.

23 Confino-Cohen R, Rosman Y, Goldberg A: Rush venom immunotherapy in children. J Allergy Clin Immunol Pract 2017;5:799–803.

Downloaded by: A. Mari - 31298
Universita degli Studi, Bibl. Area Biomed. Tor Vergata
160.80.2.38 - 10/4/2017 6:18:40 AM