ORIGINAL ARTICLE

Safety Profile of Hymenoptera Venom Immunotherapy (VIT) in Monosensitized Patients: Lack of New Sensitization to Nontreated Insect Venom

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■ Abstract

Background: Venom immunotherapy (VIT) has proven to be efficacious in reducing the severity of anaphylactic reactions following field stings in patients with Hymenoptera venom allergy. Due to sequence homologies in the allergens used in Hymenoptera vaccines, there is concern that immunotherapy could lead to sensitization to allergens to which patients were not previously sensitized. The relevance of such an undesired phenomenon is unclear.

Objectives: To investigate the incidence of sensitization to Hymenoptera venoms other than those to which the patients were already sensitized and to assess the overall safety profile of VIT in order to compare the risk-benefit ratio in a subpopulation of monosensitized individuals.

Methods: We performed a retrospective analysis of specific immunoglobulin E (sIgE) levels in patients with no prior detectable sIgE to Hymenoptera venom other than the one for which they received VIT. We assessed the safety profile of VIT using serological and clinical parameters.

Results: Of the 56 monosensitized patients who had VIT, 3 (5%) developed sIgE to the other insect with no history of field sting to explain it. This rate was similar to the rate of new sensitization due to field stings during VIT. VIT was well-tolerated and levels of serological markers improved. No patient had a systemic anaphylactic reaction after having been stung by an insect other than the one he/she was desensitized for during follow-up.

Conclusion: VIT seems to be safe with respect to clinically significant new sensitizations.

Key words: Venom immunotherapy. Hymenoptera venom allergy. Specific immunoglobulin E. Tolerance induction.

■ Resumen

Antecedentes: Se ha demostrado que la inmunoterapia con veneno es eficaz en la reducción de la gravedad de las reacciones anafilácticas tras picaduras en la alergia al veneno de himenópteros. Debido a las homologías de secuencia de los alérgenos utilizados en las vacunas frente a himenópteros, existe cierta preocupación de que la inmunoterapia pueda causar sensibilización a alérgenos a los que los pacientes no estaban sensibilizados previamente. Se desconoce la relevancia de este fenómeno no deseado.

Objetivos: Investigar la incidencia de la sensibilización a venenos de himenópteros distintos de aquellos a los que los pacientes ya estaban sensibilizados y evaluar el perfil de seguridad global de la inmunoterapia con veneno a fin de comparar la relación beneficio/riesgo en una subpoblación de pacientes monosensibilizados.

Métodos: Se llevó a cabo un análisis retrospectivo de los niveles de inmunoglobulina E específica (IgEe) en pacientes sin IgEe previamente detectable frente al veneno de himenópteros diferentes de aquel para el que recibieron inmunoterapia con veneno. Se evaluó el perfil de seguridad de la inmunoterapia con veneno utilizando parámetros serológicos y clínicos.

Resultados: De los 56 pacientes monosensibilizados que recibieron inmunoterapia con veneno, 3 (5%) desarrollaron IgEe frente a los otros insectos sin antecedentes de picaduras que lo explicaran. Esta tasa fue similar a la tasa de nuevas sensibilizaciones debidas a picaduras durante la inmunoterapia con veneno. La inmunoterapia con veneno se toleró bien y se mejoraron los niveles de marcadores serológicos. Ningún paciente tuvo una reacción anafiláctica sistémica tras la picadura de un insecto distinto de aquel para el que había sido desensibilizado durante el seguimiento.

Conclusión: La inmunoterapia con veneno parece segura respecto a nuevas sensibilizaciones clínicamente significativas.

Palabras clave: Inmunoterapia con veneno, alergia al veneno de himenópteros, inmunoglobulina E específica, inducción de tolerancia.

Introduction

Hymenoptera stings are the most commonly identified culprits for anaphylaxis in Switzerland [1]. Beekeepers with an increased preseason concentration (>1.0 kU$_A$/L) of bee venom (BV) specific immunoglobulin E (sIgE) have a 12-fold increased risk of systemic reactions [2]. Skin testing and the radioallergosorbent test (RAST) reveal that insect-allergic patients are often sensitized to several insects. This multiple sensitivity can be due to exposure to several different insects, antigenic cross-reactivity between insect venoms, or both [3]. RAST inhibition experiments showed different patterns of antigenic cross-reactivity in most sera from multisensitized patients [4]. IgE against cross-reactive carbohydrate determinants (CCDs, alpha 1,3-fucosylated N-glycans) is the most frequent and often the only cause of multiple reactivity, although they seem to be clinically irrelevant [5]. Venom immunotherapy (VIT) has proven to be efficacious in reducing the severity of anaphylactic reactions following field stings in Hymenoptera venom allergy and seems to be the most efficacious form of specific immunotherapy [6]. Since no recombinant allergens are yet available, standardized vaccines containing various allergens are used in immunotherapy. There is concern that sequence homologies among allergens in Hymenoptera vaccines—BV hyaluronidase has about 55% sequence identity with vespid hyaluronidases—could lead to sensitization to allergens to which patients were not previously sensitized [7,8], although the incidence and relevance of such an undesired phenomenon is unclear. The incidence of 29%-41% in specific immunotherapy reported in the literature [9,10] seems unacceptably high. According to these data, production of new sIgE would put the patient at increased risk of experiencing a systemic reaction. Therefore, development of new sIgE to other venom antigens would be an intolerable side effect of VIT.

The aim of this study was to investigate the incidence of new sensitizations during VIT to Hymenoptera venoms other than those to which the patients were already sensitized.

Methods

We performed a retrospective analysis of sIgE in patients from our clinic with no prior detectable sIgE to Hymenoptera other than the one for which they received VIT. Other parameters of efficacy and adverse effects of VIT, such as the incidence of anaphylactic reactions during ultrarush induction (URI) of desensitization and changes in sIgE and sIgG, were studied in a subanalysis to compare the risk of new sensitization and adverse effects with the benefits of VIT and thus help clinicians to judge the feasibility of this therapy in monosensitized patients.

Study Protocol

Among the patients who underwent URI of desensitization for Hymenoptera venom allergy, we selected those who were monosensitized to 1 insect and had undetectable sIgE to other Hymenoptera venoms before VIT. Since VIT was continued for 5 years in most cases, we selected those who started VIT prior to 2002, thus enabling us to study the records of patients who had already terminated their VIT. Of the 290 patients who started VIT between 1993 and 2002, 150 received wasp VIT, whereas 136 were treated with bee VIT. Four patients who were found to have relevant cosensitization to both Hymenoptera received both VITs.

The records for the last measured sIgE, sIgG, skin tests, as well as reported natural field stings were checked. We only analyzed data collected in our clinic to avoid interlaboratory variations. If data from the final workup after 5 years of VIT were missing, data from a routine examination after 3 years or at termination of VIT were used if available.

The data collected were then studied in a subanalysis to determine the efficacy of VIT by comparing sIgE and sIgG before and after VIT within the bee VIT group and within the wasp VIT group. A further subanalysis compared the efficacy of VIT between the 2 VIT groups.

Tolerance of VIT was studied by evaluating recorded anaphylactic reactions during URI.

Selection Criteria and Diagnostic Tests

Patients who presented at our clinic with a history of anaphylactic reaction to any Hymenoptera sting were routinely investigated by means of intradermal tests with Pharmalgen venom extracts (ALK-Abelló A/S, Hørsholm, Denmark) and sIgE and sIgG (CAP-FEIA, Phadia, Uppsala, Sweden). Intradermal tests were performed with BV and wasp venom (WV) using serial 10-fold dilutions, if necessary, with concentrations ranging from 0.00001 to 1.0 µg/mL. Histamine (0.1 mg/mL; Allergopharma, Reinbek, Germany) and albumin diluent (ALK-Abellò A/S) served as controls. Wheal size compared to the histamine control (0.1 mg/mL) and negative control (albumin diluent 0.3 mg/mL) was used to distinguish between a positive and a negative skin test. A wheal of 5 mm or more in diameter with erythematous flare was considered positive and indicated the endpoint concentration. sIgE to BV (i1, venom from *Apis mellifera*) and WV (i3, a mixture of venoms from *Vespula vulgaris, Vespula germanica*, and *Vespula maculifrons*) were measured using CAP-FEIA based on solid-phase ImmunoCAP technology, according to the manufacturer's instructions. The measurement range of the CAP-FEIA system is 0.35-100 kU$_A$/L. Results >0.35 kU$_A$/L were considered elevated. If results were unclear or incompatible with the patient's history, the basophil sulfidoleukotriene release test (CAST-ELISA, Bühlmann Laboratory AG, Schönenbuch, Switzerland) was used to identify the culprit insect [11]. Initiation of VIT was based on the grade of anaphylactic reaction, comorbidities and medication, profession, patient willingness, and skin test and in vitro results, according to published guidelines [12]. Patients with a grade 1 anaphylactic reaction according to Mueller [13] were not desensitized as a rule.

VIT Protocol

All the patients selected for VIT underwent URI. This was performed with Pharmalgen venom extracts (ALK-Abelló A/S). A cumulative dose of 111.1 µg divided into 6 subcutaneous injections (0.1, 1, 10, 20, 30, and 50 µg) was

administered over 3.5 hours. Further injections were given on days 8 (2×50 000 SQ units with an interval of 30 min) and 22 (1 injection of 100 000 SQ units) using Alutard SQ (ALK-Abelló A/S). Thereafter, this maintenance dose was injected at intervals of 4-6 weeks, usually over 5 years. All injections were on the outside of the upper arm. Anaphylactic reactions during the URI protocol were graded according to Mueller [13] and treated as needed. Once the maintenance dose was reached and well tolerated, most patients continued VIT with their general practitioner. Re-evaluation at our clinic after a 3-year treatment period was always recommended. A final evaluation was suggested after 5 years to decide whether desensitization had to be continued and which emergency medication had to be continued.

Statistical Analysis

sIgE and sIgG values before and after VIT were compared using the paired t test. Since only a few values were above or under the measurement range, statistical significance was set at $P<.05$ (Tables 1 and 2). As the sIgE and sIgG ratio before and after VIT had an asymmetrical distribution (data not shown),

we used the Mann-Whitney test for comparison of values in Figures 2 and 3 ($P<.05$) before logarithmic transformation.

Results

At baseline, 58 of the 150 patients who underwent wasp VIT between 1993 and 2002 had no detectable sIgE to BV and 45 of the 136 patients who underwent bee VIT had no detectable sIgE to WV (Figure 1).

Patient characteristics at presentation and during URI are shown in Table 1.

Follow-up data could not be collected for 27 of the patients desensitized for WV allergy and for 20 of those desensitized for BV allergy: VIT was continued by their general practitioners and the patients were lost to follow-up (16 and 13 patients for wasp and bee VIT, respectively) or they were not tested for sensitization to the other insect at the end of VIT (11 and 7 patients, respectively). The remaining 56 patients of whom data could be collected were followed for a mean of 1631 days (4.4 years) of VIT. Only 1 BV-allergic patient stopped VIT before
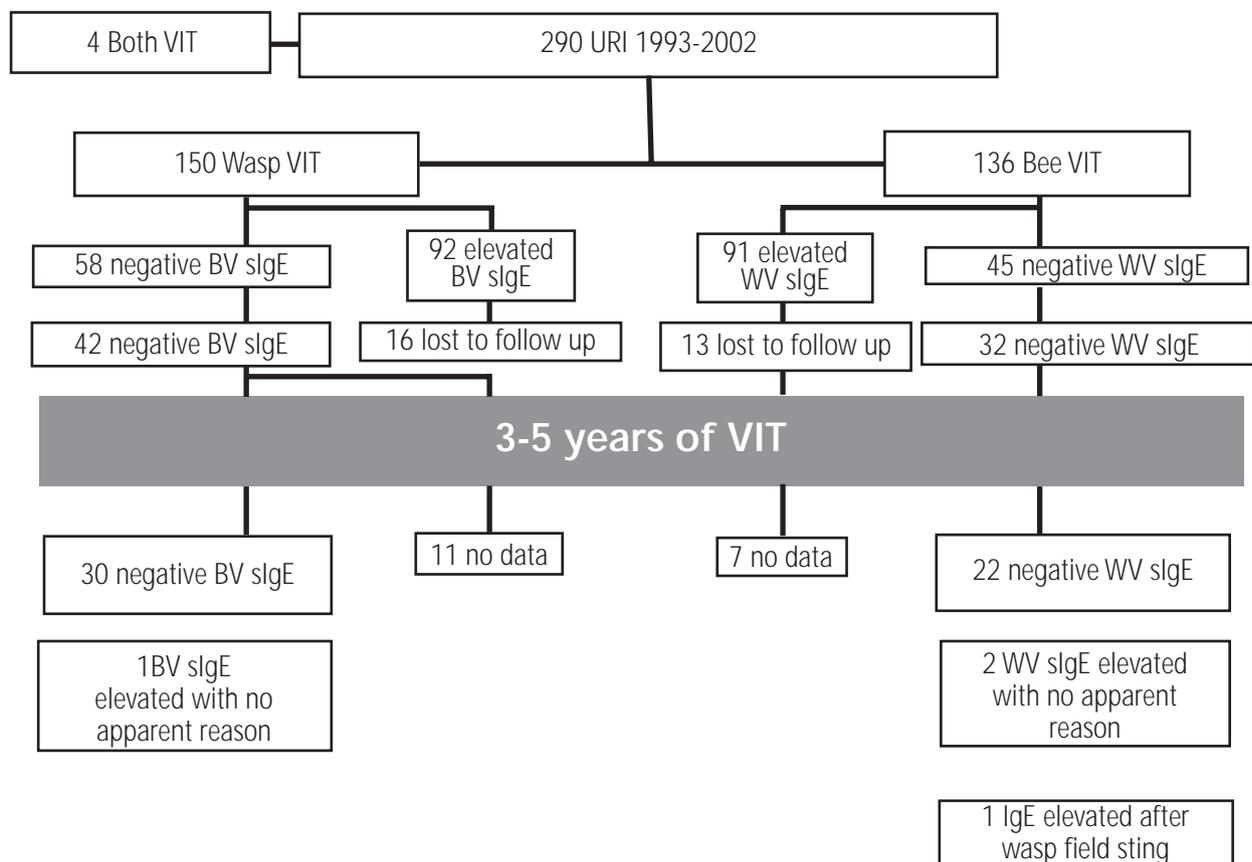

Figure 1. Selection of patients and follow-up. Negative, <0.35 kU$_A$/L; elevated, ≥0.35kU$_A$/L. One patient taking bee VIT did not complete the 3-year treatment (477 d), although his IgE data were included in the statistical analysis. BV indicates bee venom; sIgE, specific immunoglobulin; URI, ultrarush induction; VIT, venom immunotherapy; WV, wasp venom.

Table 1. Characteristics of Monosensitized Patients at Presentation and During URI

	Wasp VIT (n=58)	Bee VIT (n=45)
Mean (range) age at initiation of VIT, y	44 (6-68)	38 (5-70)
Male/Female ratio, %	50.91	60.47
Anaphylactic reaction grade 2, No. %	8 (15%)	8 (19%)
Anaphylactic reaction grade 3, No. %	20 (34%)	24 (53%)
Anaphylactic reaction grade 4, No. %	30 (51%)	13 (28%)
Median concentration for positive ID test with bee venom, μg/mL[a]	1 or no reaction	0.01
Median concentration for positive ID test with wasp venom μg/mL	0.001	1 or no reaction
Median (range) sIgE to wasp venom, kU_A/L	3.1 (<0.35->100)	<0.35
Median (range) sIgE to bee venom, kU_A/L	<0.35	4.8 (<0.35->100)
Median (range) sIgG to wasp venom, mg/L	5.8 (<0.02-32.0)	0.5 (<0.02-20.6)
Median (range) sIgG to bee venom, mg/L	1.4 (0.02-7.51)	5.5 (<0.02-54.4)
Grade 1 anaphylactic reaction during URI, No. %	1 (2%)	9 (20%)
Grade 2 anaphylactic reaction during URI, No. %	1 (2%)	0
Grade 3 anaphylactic reaction during URI, No. %	0	3 (7%)
Grade 4 anaphylactic reaction during URI, No. %	0	1 (2%)

Abbreviations: sIgE, specific immunoglobulin E; sIgG, specific immunoglobulin G; URI, ultrarush induction; VIT, venom immunotherapy
[a]Positive ID tests with 1 μg/mL were considered irritative and therefore nonspecific or negative.

Table 2. Follow-up Data of Patients During and After VIT[a]

	Wasp VIT (n=31)	Bee VIT (n=25)
Mean (range) follow-up, d	1757 (1078-3608)	1594 (477-2356)
Patients stung at least once during follow-up, No. %	23 (74%)	15 (60%)
– by a bee, No. %	0 (0%)	5 (20%)
– by a wasp, No. %	8 (26%)	2 (8%)
– unknown insect, No. %	11 (35%)	7 (28%)
– no data, No. %	3 (10%)	1 (4%)
– both insects, No. %	1 (3%)	0 (0%)
Local reaction after field sting during VIT, No. %	6 (19%)	9 (36%)
No reaction after field sting during VIT, No. %	6 (19%)	3 (12%)
Median sIgE for wasp venom after VIT (range), kU_A/L	1.91 (<0.35-17.2)	<0.35 (<0.35 1.59)
Median sIgE for bee venom after VIT (range), kU_A/L	<0.35 (<0.35-2.44)	2.22 (<0.35-22.2)
Median sIgG for wasp venom after VIT (range), mg/L	22 (4.15-67.6)	2.52 (<0.02-15.0)
Median sIgG for bee venom after VIT (range), mg/L	2.53 (<0.02-32.7)	18.7 (0.78-48.4)
Mean difference of sIgE for bee after bee VIT, kU_A/L	NA	−11.07 ($P=.045$)
Mean difference of sIgG for bee after bee VIT, mg/L	NA	9.31 ($P=.002$)
Mean difference of sIgE for wasp after wasp VIT, kU_A/L	−14.22 ($p=0.015$)	NA
Mean difference of sIgG for wasp after wasp VIT, mg/L	18.02 ($p=0.0001$)	NA

Abbreviations: sIgE, specific immunoglobulin E; sIgG, specific immunoglobulin G; VIT, venom immunotherapy.
[a]One patient in the bee VIT did not complete the 3 years of treatment (477 days), data of IgE at this time were included in the statistical analysis.

the 3 years of follow-up (477 days of treatment), because of a psychiatric disorder; nevertheless, the patient's data were included in the statistical analysis. During VIT, most of the patients were stung at least once by an insect (a few patients could not remember how many times). This was followed mainly by no reaction or a local reaction (Table 2). One WV-allergic patient developed dyspnea after a field sting by a wasp, despite taking emergency corticosteroids and antihistaminics, and a further 2 WV-allergic patients reported tachycardia and vertigo, respectively, the latter after being stung by about 20 wasps. The remaining types of reactions were either not recorded in the charts or the patients could not remember or they were considered not allergic.

The culprit insect was more often a bee in BV-allergic patients and a wasp in WV-allergic patients. Among the remaining 31 patients who received wasp VIT, only 1 developed sIgE to BV, with no apparent explanation. Among the other group of 25 patients who were receiving bee VIT and for whom data were available, 3 developed a new sensitization to WV as demonstrated by elevated sIgE (2 with no apparent reason, 1 reported having been stung by a wasp) (Figure 1). Of the 56 patients who had VIT, 3 (5%) developed previously
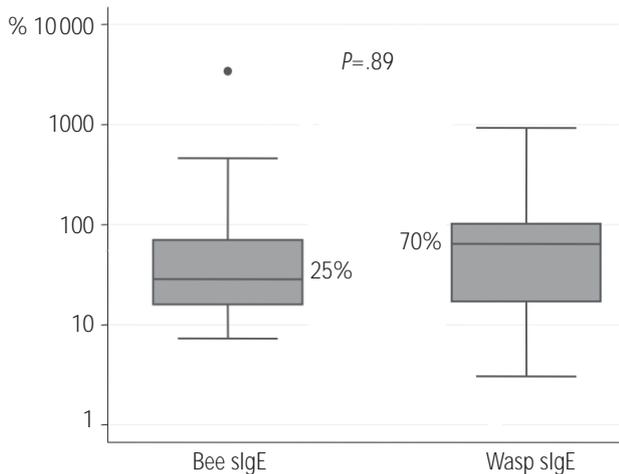
Figure 2. Decrease in specific IgE during VIT for injected venom as a percentage of the baseline value on a logarithmic scale. The difference is not significant (*P*=.89).
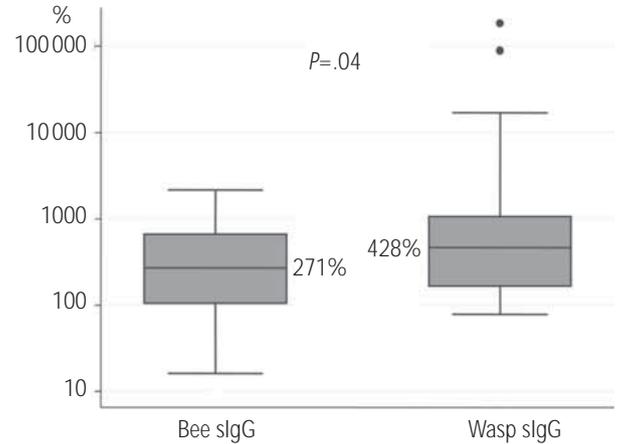

Figure 3. Increase in specific IgG during VIT for injected venom as a percentage of the baseline value on a logarithmic scale. The difference is significant (*P*=.04).

undetectable sIgE to the other insect without a history of field sting to explain it.

Subanalysis Results

Wasp venom URI was better tolerated than bee venom URI, resulting in fewer grade 1 and no grade 3 or 4 anaphylactic reactions (Table 1). During follow-up, sIgE and sIgG to the injected venom changed significantly. sIgE decreased significantly, while sIgG increased significantly (Table 2).

When the 2 VIT regimens were compared, a significant difference was noted between sIgG levels to the injected venom, but not between sIgE levels. The median sIgE of the wasp VIT group decreased to 70% of baseline before VIT. This was not statistically significant compared with the median decrease in sIgE to 25% of baseline in the bee VIT group. The median increase in sIgG among patients desensitized for WV was 428% of baseline, while among those desensitized for BV, it was 271%, the difference being statistically significant (Figures 2 and 3).

Discussion

The characteristics of the patients starting VIT in this study are similar to those reported in the literature [14]. Unfortunately, many of our patients could not be evaluated because of the lack of follow-up data. This was mainly because VIT was continued by the general practitioners after URI, or because only sIgE and sIgG against injected venom were measured and not the specific Ig against the other insect. Since this was the only reason for not including any of the 286 patients who underwent VIT for Hymenoptera venom allergy in the statistical analysis, we believe that this lack of data did not bias our results.

Only 4 out of 56 patients (mean follow-up, 4.4 y) showed an increase in sIgE to the other Hymenoptera venom. During the same period, 38/56 (68%) monosensitized patients were stung by a Hymenoptera insect at least once during the same period.

Therefore, supposing an equal incidence of bee and wasp stings, approximately 19 patients could have been stung by the insect they were not previously sensitized to. This seems comparable to the lifetime incidence of field insect stings in the general population. Prevalence studies carried out in Italy, France, and Turkey showed that 56.6%, 61%-75%, and 94.5%, respectively, of the adult population remember being stung by a Hymenoptera insect at least once in their lives [15,16]. The selection of patients in this study at increased risk for Hymenoptera stings (eg, beekeepers) certainly contributes to the high incidence observed.

It is supposed that about 30% of adults develop detectable allergic sensitization in the first month after a sting and that venom-specific IgE remains positive in 30% of them after 6.8 years [17]. Therefore, only about 10% of Hymenoptera stings cause a sensitization still detectable by sIgE measurement 6.8 years later.

In theory, about 10% of the 19 field stings (ie, 1.9 stings) could have led to measurable sIgE against the untreated venom at the end of VIT. Therefore, half of the new sensitizations that occurred in our patients (2 out of 4) are probably attributable to the field stings.

We did not study serum using immunoblot binding bands, as in other studies [8,9,18], although our results do confirm that few patients develop new sIgE to the other Hymenoptera venom during VIT that is detectable using CAP-FEIA.

Our results show that the risk of new sensitization during VIT to other venom antigens is very low, and probably not higher than the risk of being sensitized by a field sting during VIT. Consequently, if there is no compatible history, additional tests to detect new sensitization during or after VIT are not mandatory. Apart from the fact that these tests serve no purpose without a corresponding clinical reaction, they would not demonstrate whether the newly measured sIgE resulted from a field sting or VIT.

During follow-up, no patient had a systemic anaphylactic reaction after having been stung by an insect other than the one they were desensitized for. Thus, the clinical relevance of such a new sensitization is indeed unknown.

As expected, the subanalysis of sIgE and sIgG to Hymenoptera venom after VIT showed a significant increase in sIgG and decrease in sIgE. In our sample, we found a significant difference in the increase in sIgG during VIT when comparing wasp and bee VIT. Despite similar pretreatment IgG to the venom injected, patients undergoing wasp VIT had a significantly greater increase in sIgG than those undergoing bee VIT. This was consistent with the data in the literature [19]. Since the amount of venom injected in BV and WV immunotherapy is similar, this might be due to a stronger immune response elicited by WV extracts, although the number of anaphylactic reactions during URI was lower in this group, suggesting why bee VIT tends to have a higher frequency of treatment failure than wasp VIT [20], a finding that is consistent with the literature [21,22]. In our study, both VITs seem to lead to good short-term results: only 3 possible anaphylactic reactions were recorded following field stings occurring during VIT.

VIT seems to be safe with respect to clinically significant new sensitizations. Development of new sIgE during VIT is possible, but the risk of this being induced by VIT seems comparable to the risk of it occurring naturally with Hymenoptera stings. Therefore, no additional monitoring for new sensitization due to antigenic cross-reactivity is required during VIT.

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