

Maintenance Venom Immunotherapy Administered at a 3-Month Interval Preserves Safety and Efficacy and Improves Adherence

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■ Abstract

Background: Hymenoptera venom immunotherapy (VIT) is a safe and effective approach to insect sting allergy. However, after discontinuation, relapses can occur in some patients, especially those with a high occupational risk, and they may need to prolong VIT indefinitely. In order to improve adherence, we propose extending the interval between injections of maintenance VIT (MVIT).

Objective: To evaluate the safety, efficacy, and patient acceptance of a 3-month interval between MVIT injections in a group of Hymenoptera-allergic patients who are occupationally exposed to insect stings.

Patients and Methods: We included 72 patients with severe systemic reactions to Hymenoptera stings. MVIT was administered for 4 years at intervals increasing up to 3 months and then continued for a further 2 years. Patients were informed of the risk of relapse after discontinuation and of the need for indefinite treatment at 3-month intervals.

Results: During the 3-month interval maintenance phase, only 235 local reactions (17.8%) were observed in 17 patients. Sixty patients experienced 125 field re-stings and only 1 experienced a systemic reaction with generalized urticaria.

Conclusions: The study confirms that the conventional MVIT interval of 4 to 6 weeks can be extended to 3 months in most patients with no adverse events, while maintaining safety and efficacy, improving adherence, and guaranteeing safe continuation of professional activity.

Key words: Venom immunotherapy. Patient acceptance. Safety. Efficacy. 3-month interval. Maintenance.

■ Resumen

Antecedentes: La inmunoterapia con veneno de himenópteros es una manera segura y eficaz de abordar la alergia a la picadura de insectos. Sin embargo, tras su interrupción, algunos pacientes pueden experimentar recaídas, sobre todo aquellos con un alto riesgo profesional, por lo que puede que deban prolongar el tratamiento indefinidamente. Con el fin de mejorar el cumplimiento, se propone ampliar el intervalo entre inyecciones de la inmunoterapia de mantenimiento con veneno (ITMV).

Objetivo: Evaluar la seguridad, la eficacia y la aceptación por parte del paciente de un intervalo de 3 meses entre inyecciones de ITMV en un grupo de pacientes alérgicos al veneno de himenópteros que, debido a su profesión, se hallan expuestos a la picadura de insectos.

Pacientes y métodos: En el estudio participaron 72 pacientes con reacciones sistemáticas graves a la picadura de himenópteros. Se administró la ITMV durante 4 años a intervalos que aumentaron progresivamente hasta los 3 meses y, a continuación, se prolongó 2 años más. Se informó a los pacientes del riesgo de recaída después de la interrupción, así como de la necesidad de recibir tratamiento indefinido a intervalos de 3 meses.

Resultados: Durante la fase de mantenimiento a intervalos de 3 meses, sólo se observaron 235 reacciones locales (17,8%) en 17 pacientes. Sesenta pacientes experimentaron 125 nuevas picaduras y sólo un paciente refirió una reacción sistemática con urticaria generalizada.

Conclusiones: El estudio confirma que el intervalo habitual de 4 a 6 semanas de la ITMV puede ampliarse a 3 meses en la mayoría de los pacientes que no presentan acontecimientos adversos, a la vez que se mantiene la seguridad y la eficacia, mejora el cumplimiento y se garantiza la continuación segura de la actividad profesional.

Palabras clave: Inmunoterapia con veneno. Aceptación del paciente. Seguridad. Eficacia. Intervalo de 3 meses. Mantenimiento.

Introduction

Venom immunotherapy (VIT) is the treatment of choice in Hymenoptera-allergic patients [1-3], and several studies have shown it to be safe and highly effective [4-7]. Approximately 98% of desensitized patients with a history of systemic reaction to Hymenoptera venom are protected from severe reactions to subsequent stings [8]. The inclusion criteria for VIT and treatment protocols are now well standardized. The incidence of side effects reported in the literature varies widely depending on the treatment administered and the systems used to classify the severity of adverse reactions [9-11]. The duration of VIT and the criteria for discontinuation remain controversial [12]. A 5-year treatment schedule usually guarantees complete protection during the maintenance interval (4 to 6 weeks) and could be considered adequate to prevent future life-threatening allergic reactions. However, cases of systemic reaction and, rarely, death have been reported after the interruption of VIT [13,14]. In particular, the protection rate for subsequent stings tends to decrease gradually after discontinuation [15], although the vast majority of patients—80% or more—remain protected when re-stung up to 7 years after discontinuation [16-18]. In patients allergic to bee venom who stopped VIT after achieving low or unmeasurable levels of venom-specific immunoglobulin (Ig) E, a challenge with bee sting induced a systemic reaction in 3% after 1 year and in 14% after 2 years [15].

Muller et al [19] studied 86 patients who had received treatment for bee venom allergy over a mean period of 54.4 months: all patients tolerated a field bee sting or a sting challenge while receiving VIT. Thirteen months after discontinuation, 15 patients (17%) experienced a mild systemic reaction after a sting challenge. These data led us to conclude that anaphylaxis never occurs during the first year of discontinuation, but that the risk of recurrence increases by up to 20% after a few years [17]. Some authors reported that a negative skin test result appears to be an indication for cessation of VIT [15,20]; however, it has recently been reported that negative venom skin test results are not a guarantee of safety, because almost 10% of patients who appear to have lost sensitivity experience a reaction [12].

Recurrence of systemic reaction to Hymenoptera stings depends on several factors: the severity of the reaction before desensitization, persistence of positive skin test results, occurrence of the reaction during VIT due to treatment injections or re-stings, frequency of further exposures to venom due to occupation or living environment, role of honeybee venom rather than vespine venom, and elevated basal serum tryptase levels. These factors increase the risk of relapse of anaphylaxis to re-sting after discontinuation of VIT [12,21,22],

and the presence of concomitant cardiovascular and respiratory diseases indicates a poor prognosis.

Patients at a high risk of relapse should continue VIT indefinitely; however, prolongation increases workload and costs and may lead some patients to withdraw. Therefore, we sought to evaluate the effects of treating patients at risk of relapse with a maintenance VIT (MVIT) regimen requiring fewer yearly injections in the maintenance phase. Such an approach would improve adherence, reduce treatment costs, and increase effectiveness and tolerability.

The concept of prolonged MVIT dates back to 1988 [23], and experience since then [22,23] has shown favorable results when treatment is administered at 3-month intervals. We present our experience of treating venom-allergic patients with MVIT over a long period.

Patients and Methods

We selected 72 patients (age range, 18-75 years; male-to-female ratio, 2:1) who were allergic to Hymenoptera venom (37 to *Vespula*, 16 to *Polistes*, and 19 to *Apis*) and matched for degree of systemic reaction to insect stings (grade III-IV, according to Mueller's classification [24]). Fifty-two patients presented a grade III reaction and 20 patients presented a grade IV reaction (maximum severity). All had a high risk of re-sting due to their occupation (beekeepers, farmers, firemen). Sixty-four patients had a history of severe systemic reaction requiring admission to the intensive care unit, and 23 were at high risk of life-threatening allergic reactions due to the presence of concomitant cardiac and/or respiratory chronic diseases. Seventeen patients were asthmatic, 7 allergic to pollen, 6 allergic to mites, and 3 to several allergens. Eleven patients had elevated serum tryptase levels, with no clinical evidence of mastocytosis. Fifteen patients were treated with β -blockers (8 for arrhythmia and 7 for myocardial ischemia) on admission to our outpatient clinic, and all treatments were replaced with drugs that were suitable for patients at risk of anaphylaxis.

Hymenoptera venom allergy was diagnosed by skin testing with the venom extract (prick and intradermal testing) and radioallergosorbent assay (CAP, Pharmacia, Uppsala, Sweden) for venom-specific IgE.

All patients started a semirush regimen with aqueous venom allergen extracts (DHS-Stallergènes, Antony, France), reaching the maintenance dose of 100 μ g (MVIT) within 3 weeks.

MVIT was then administered every 5 weeks during the first year, and every 6 and 8 weeks during the second and the third years, respectively. Starting from the fourth year of treatment

and for the following 2 years, the maintenance dose was administered every 12 weeks (Table 1). At the end of the fifth year, all patients underwent skin prick tests. Eleven patients, all of whom had experienced grade III reactions, showed negative results. Patients who continued to show positive results were informed that they still had a 10% risk of reaction if re-stung. They all chose to continue MVIT indefinitely.

At the end of the fifth year, patients were informed about the risk of presenting a new systemic reaction after discontinuing VIT, according to their individual risk profile. Due to the presence of risk factors we proposed prolonging VIT indefinitely, and all the patients included in the study have been taking 3-month MVIT for the last 5 to 9 years (Table 2).

During treatment, all adverse reactions were classified according to the degree of severity and reported in the patient's history to evaluate the tolerability of treatment.

All patients were informed about possible reactions in the case of a re-sting and about the medications they could use before reaching our allergy unit to complete their treatment, if necessary. All reactions were classified, and the maximum and minimum diameters of local reactions and the time elapsed from the last VIT injection were reported.

Sample Size

Data from the literature and the clinical experience of the investigators indicated that approximately 0.5% of

patients would experience an adverse systemic reaction to the injection. We used one of our objectives—evaluation of the equivalence of the experimental therapy (MVIT) and the currently used VIT in terms of adverse systemic reactions after injections—to determine the total number of injections that had to be performed. Assuming a Δ value of 0.3% (limit set for equivalence of the 2 therapies), an α of 0.05, and a power of 80%, the required sample size was calculated to be 4200 injections. Assuming a dropout rate of approximately 5%, at least 4410 injections would have to be administered. Therefore, if each patient was expected to receive approximately 55 injections, at least 70 patients had to be enrolled.

Statistical Analysis

All data relative to local and systemic reactions were expressed as frequencies and percentages.

Analysis of the differences between the patients who received MVIT and expected values in terms of reaction to injection and reaction to field stings was based on the χ^2 test or Fisher exact test, where appropriate. A *P* value equal to or less than .05 was considered statistically significant.

Analysis of sample size and power was performed with NCSS-PASS (NCSS, Kaysville, Utah, USA). All other statistical analyses were carried out using SPSS 15.0 (SPSS Inc., Chicago, Illinois, USA).

Table 1. Venom Immunotherapy Protocol

Induction phase	First visit (day 1)	0.01 μ g, 0.1 μ g, 1 μ g, 10 μ g (within 6 h)	10.11 μ g/d
	Second visit (day 8)	10 μ g, 20 μ g, 30 μ g (within 6 h)	60 μ g/d
	Third visit (day 15)	50 μ g, 50 μ g (within 2 h)	100 μ g/d
	Fourth visit (day 30)	50 μ g, 50 μ g (within 1 h)	100 μ g/d
MVIT	First year	100 μ g once every 5 wk	1040 μ g/y
	Second year	100 μ g once every 6 wk	866 μ g/y
	Third year	100 μ g once every 8 wk	650 μ g/y
	Fourth year and subsequent years	100 μ g once every 12 wk	430 μ g/y

Abbreviations: MVIT, maintenance venom immunotherapy.

Table 2. Years of 3-Monthly Maintenance Venom Immunotherapy

	Yellow Jacket (n=36)	Honeybee (n=19)	Wasp (n=17)
MVIT 1-3 y	13	5	4
MVIT 3-5 y	7	8	8
MVIT 5-9 y	16	6	5

Abbreviation: MVIT, maintenance venom immunotherapy.

Results

During the dose-increase phase of VIT, we carried out a total of 867 injections, and observed 11 systemic reactions (1.26%) and 335 local reactions (38.6%). The systemic reactions occurred in 9 patients (12.5%), 4 of whom were allergic to honeybee venom, 4 to yellow jacket venom, and 1 to wasp venom.

Of the 11 systemic reactions, 7 were grade I (diffuse itching in 3 cases) and 4 were grade II. All were successfully treated with parenteral corticosteroids. A honeybee-allergic patient had a grade III systemic reaction with generalized urticaria and intense dyspnea requiring corticosteroids, β -agonists, and antihistamines. Immediate pharmacological treatment was essential in all cases, particularly in grade I reactions that did not progress (ie, most of the systemic reactions). All patients who experienced a systemic reaction in the induction phase reached the maintenance phase, with appropriate dose adjustments in the injection schedule. There were 335 local reactions (38.6% of all injections) in 23 patients (44.4%): 13 were allergic to honeybee, 7 to yellow jacket, and 3 to wasp. The reactions were not severe enough to impose changes in the injection schedule or interruption of immunotherapy.

During the first 3 years of MVIT (extension phase), we administered 1703 injections and reported 4 grade I systemic

reactions (0.2%) in 2 honeybee-allergic patients, 1 yellow jacket-allergic patient, and 1 wasp-allergic patient. The reactions were characterized by diffuse itching that resolved promptly with parenteral antihistamines and corticosteroids. There were 330 (19.4%) local reactions in 18 patients (25%): 8 were allergic to honeybee, 7 to yellow jacket, and 3 to wasp.

All patients gave their informed consent to continue VIT indefinitely. During the 3-month maintenance phase, we administered 1318 injections with no systemic reaction and 235 (17.8%) local reactions in 17 patients (23.6%): 7 were allergic to honeybee, 7 to yellow jacket, and 3 to wasp.

Tables 3 and 4 compare the reactions observed at the 3 different stages of treatment (dose-increase phase, extension MVIT phase, and 12-week MVIT phase) in relation to the number of injections, patients, and venom sensitivity.

During the extension phase, 63 patients experienced a total of 115 field re-stings (individually from 1 to 4 stings), although only 1 experienced a systemic reaction, characterized by generalized urticaria and diffuse itching that resolved promptly with sublingual antihistamines. Before immunotherapy, the patient, who was allergic to yellow jacket, had suffered a life-threatening anaphylactic reaction requiring admission to the intensive care unit. Interestingly, this patient showed the highest serum tryptase values of all our patients (84.3 ng/L). All but 2 patients continued treatment: one died in a car accident, the other developed gastric cancer.

Table 3. Patients With Allergic Reactions Observed During the 3 Different Phases of Treatment

Venom Sensitivity		Honeybee	Yellow Jacket	Wasp	Total (N=71)
Induction phase	SR	4	4	1	9 (12.5%)
	LR	13	7	5	23 (44.4%)
Extension MVIT phase	SR	2	1	1	4 (5.5%)
	LR	8	7	3	18 (25%)
12-week MVIT phase	SR	0	0	0	0 (0%)
	LR	7	7	3	17 (23.6%)

Abbreviation: LR, local reaction; MVIT, maintenance venom immunotherapy; SR, systemic reaction.

Table 4. Reactions Observed During the 3 Different Phases of Treatment

Venom Sensitivity		Honeybee	Yellow Jacket	Wasp	Overall
Induction phase (86 injections)	SR	6	4	1	11 (1.2%)
	LR	137	136	62	335 (38.6%)
Extension MVIT phase (170 injections)	SR	2	1	1	4 (0.2%)
	LR	111	167	52	330 (19.3%)
12-week MVIT phase (131 injections)	SR	0	0	0	0 (0%)
	LR	80	127	28	235 (17.8%)

Abbreviation: LR, local reaction; MVIT, maintenance venom immunotherapy; SR, systemic reaction.

Except for the patient with generalized urticaria after re-sting during the extension phase, no correlations were found between serum tryptase level and the possibility of suffering from reactions to immunotherapy.

Discussion

This study shows that prolonging the interval between maintenance VIT injections (4 injections yearly) is well accepted by patients. No patients withdrew from the present study, whereas in the past almost 5% of patients receiving monthly VIT abandoned treatment in the third year, with important consequences for occupational safety.

The regimen was reserved for those patients at risk of anaphylaxis after re-sting, especially occupationally exposed patients, for whom desensitization should be prolonged indefinitely. A 3-5-year VIT regimen usually guarantees long-term protection, although it cannot be safely discontinued in all patients. Severe re-sting reactions, although uncommon, can still occur, especially after repeated stings. Several prospective studies analyze the duration of VIT required for long-term protection [13,15,19]. While most patients are still fully protected 1 year after discontinuation of therapy, relapses of anaphylaxis due to a re-sting can occur in up to 20% of patients re-exposed many years after treatment.

Recurrence of anaphylaxis due to re-sting after discontinuation of VIT depends on several risk factors: severity of the first allergic reaction, persistence of a positive skin test result despite treatment, occurrence of systemic reactions during VIT, frequency of further exposures to venom (beekeepers and their immediate family members), role of honeybee venom allergy rather than vespid allergy, high serum tryptase level, very high risk for severe sting reactions (eg, older age, history of very severe previous sting reactions, elevated basal serum tryptase or mastocytosis, use of β -blockers), and generalized allergic reactions to immunotherapy injections or stings during immunotherapy [14,21,22]. Such patients could benefit from longer treatment (or lifelong treatment). Prolongation of treatment could also be suggested to patients with negative venom skin test results after classic VIT, because they still have a 10% frequency of systemic reactions, even if they appear to lose sensitivity [12,14], although this indication remains controversial.

When an indefinite duration is advisable, more convenient regimens may favor adherence. A 3-month interval was first proposed when risk factors for relapse had not yet been identified [23,25] and later applied by other authors, who reported excellent efficacy and safety, as assessed by sting challenges performed in bee venom-allergic patients while on MVIT [26]. Other authors proposed an even longer interval—6 months—although they also observed a reaction rate of about 5% to re-stings and side effects to maintenance doses [27].

Our results confirm that VIT at 3-month intervals maintains its effectiveness and has excellent tolerability. We evaluated tolerability by comparing the number of local and systemic reactions with the total number of injections administered and the number of patients experiencing adverse reactions with

those undergoing immunotherapy. The 100- μ g maintenance dose was maintained throughout follow-up. During the 3-month MVIT we observed a similar rate of local and systemic reactions compared with the previous regimen. A similar decrease was detected in the percentage of patients who experienced adverse reactions, possibly resulting from the longer period of VIT rather than the prolonged interval between injections.

However, most local and systemic reactions occurred during induction rather than maintenance. Irrespective of the stage of treatment, most of these reactions were associated with honeybee.

The number of patients who were exposed to the culprit venom through accidental re-sting during MVIT and did not suffer allergic reactions was relevant, thus demonstrating the ability of the regimen to maintain desensitization as effectively as conventional regimens.

Our results and those of other authors show that the safety of MVIT administered at 3-month intervals—as assessed by the incidence of adverse reactions to the venom injections—and its efficacy—as assessed by the incidence of systemic reactions caused by field and challenge stings—is equal to or better than that achieved with conventional MVIT.

Our data confirm that the conventional MVIT interval (4 to 6 weeks) can easily be extended to 3 months with no adverse events in most patients and that MVIT administered at 3-month intervals is both safe and efficacious. Further clinical evaluations will enable us to determine whether this regimen can be extended to all patients. The regimen we studied was very well accepted by patients, and favors indefinite continuation of VIT until the allergy has disappeared (negative venom skin test result), thus preventing the relapse of anaphylaxis, especially in patients occupationally exposed to Hymenoptera sting.

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■ *Manuscript received February 27, 2009; accepted for publication June 9, 2009.*

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