Continuous immunotherapy for hymenoptera venom allergy using six month intervals

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ABSTRACT

Background: Specific immunotherapy for hymenoptera venom allergy (venom immunotherapy [VIT]) is safe and effective. The duration of treatment is still open for discussion because there is no reliable routine test to determine the real risk of serious anaphylactic reactions. This prospective study, which spans more than 25 years, was conducted to ensure unlimited protection through continuous VIT. To reduce workload and cost, the maintenance interval was increased to 6 months without increasing the rate of adverse events. Only patients with continuous follow-up by our service were included in this study.

Patients and methods: VIT was conducted in 176 patients (125 allergic to wasp venom, 20 to bee venom, 31 to both) over a mean of 7.14 years (1.16-25.49). Total and specific IgE were determined on a regular basis.

Results: A total of 162 re-stings were reported. Of these, 154 produced a strictly local reaction, seven produced non-serious reactions and one produced a systemic reaction similar to that produced by the initial sting before VIT. Total and specific IgE diminished during VIT.

Substantial adverse effects were rare and never life-threatening. The effects occurred during observation in the ward and were controlled according to the treatment protocol recommended by a German expert consensus meeting on the treatment of anaphylactoid reactions. VIT was terminated in only one patient due to recurrent adverse effects.

Conclusion: Continuous VIT at 6-monthly maintenance intervals conferred permanent protection in patients allergic to bee and wasp venoms and was found to be a safe and effective alternative to current standard protocols.

Key words: Venom immunotherapy. VIT. Wasp. Bee. 6-month maintenance interval

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RESUMEN

Antecedentes: La inmunoterapia al veneno de hymenopteros (ITVH) se considera segura y eficaz. La discusión sobre la duración del tratamiento está todavía abierta dado que no existe un método fiable para determinar el riesgo real de reacción anafiláctica grave. Este estudio prospectivo que abarca un periodo de 25 años, se llevó a cabo para asegurar la protección ilimitada de la ITVH con el intervalo entre dosis ampliado a 6 meses, que disminuía costes y esfuerzos y sin incremento del índice de reacciones adversas. Únicamente se incluyeron en el estudio a pacientes de nuestro servicio en fase de seguimiento.

Pacientes y métodos: La inmunoterapia frente a venenos se llevó a cabo en 176 pacientes (125 alérgicos al veneno de avispa, 20 al veneno de abeja y 31 a ambos) durante una media de 7,14 años (1,16-25,49). La IgE, total y específica, se determinó de forma habitual.

Resultados: Se comunicaron un total de 162 re-picaduras, 154 de ellas con reacciones estrictamente locales, 7 con reacciones menos que intensas y sólo 1 con una reacción comparable a la primera picadura antes de la ITVH. Tanto la IgE total como específica disminuyeron durante la ITVH.

Lo importante sobre los efectos secundarios es que fueron poco habituales y nunca amenazaron la vida de los pacientes. Las reacciones se presentaron durante el periodo de observación en el servicio y se trataron según el protocolo recomendado por un grupo de expertos de Alemania tras una reunión de consenso sobre reacciones anafilácticas. Sólo 1 paciente abandonó el tratamiento con ITVH por repetidos efectos adversos.

Conclusión: Se demostró una protección permanente en pacientes alérgicos al veneno de abeja y/o avispa con una inmunoterapia de continuación frente a venenos, administrada a intervalos de 6 meses que se consideró una alternativa segura y eficaz a los actuales protocolos utilizados de forma estándar.

Palabras clave: Inmunoterapia frente a venosos. VIT. Abeja. Avispa. Intervalo entre dosis de mantenimiento de 6 meses.

INTRODUCTION

Specific immunotherapy using purified venom (venom immunotherapy) (VIT) is indicated in individuals who have experienced a hypersensitive systemic hymenoptera sting reaction[1-3] (table I).

A typical VIT schedule comprises two steps. The first is to increase doses reaching the maximum dose (usually 100 μg of purified venom) over a number of days to several weeks. The second is to maintain the maximum dose and to extend the injection intervals (usually 4 to 6 weeks[1,4]). A few groups have prolonged these intervals up to 12 weeks[5-8]. Termination of VIT is generally proposed after 3-5 years. There is no routine test available to prove the effect of VIT or a resensitization.

Relying on the observation that a wide variation with regard to the schedule provides safe protection we prolonged the intervals between maintenance VIT up to 6 months without temporary limitation. This design was to demonstrate safety, efficacy and tolerance to be comparable to that found with existing VIT protocols. In addition, this modified schedule was to achieve ongoing protection by continuation of maintenance therapy as well as to alleviate efforts and costs by widening the VIT intervals up to 6 months. This was conducted in a prospective study.

MATERIALS AND METHODS

Patients

The study involved a total of 176 patients (96 females, 80 males; mean age, 52.5 years, age range 18-84 years). VIT indication criteria were a significant medical history of anaphylactic reaction in context with a positive skin test result and/or detection of venom specific IgE. All patients had experienced systemic reactions of different severities (table II). In cases of sensitization to both bee and wasp allergen

Table I

Classification of severity of anaphylactic reactions[20]

Anaphylactic grade	Emergency situation	Symptoms
0	Local reaction of allergic origin	Localised erythema and swelling
0/I	Non objective anaphylaxis-associated generalized symptoms	Itching, paraesthesia, alteration of sensoric perception, e.g. visual, acoustic, olfactory
I	Generalized reaction of the skin and/or oral, nasal or conjunctival membranes	Generalized erythema, urticaria, subcutanous edema
II	Pulmonary, cardiovascular and gastrointestinal reaction of minor severity	Bronchospasm, alteration of pulse and/or tension e.g. dyspnoea, tachycardia, hypotension, nausea, abdominal spasms
III	Pulmonary, cardiovascular and gastrointestinal reaction of major severity	Insufficiency of respiration and/or circulation, shock, cyanosis, vomiting, diarrhoea, loss of consciousness
IV	Respiratory or circulatory arrest	Absence of respiration and/or circulation

Table II

Grading of initial systemic reactions according to treatment groups

Grade of severity	Wasp venom (n = 125)	Bee venom (n = 20)	Wasp and bee venom (n = 31)	Pooled patients (n = 176)
I	25	3	10	38
II	75	15	16	106
III	25	2	5	32
on ACE-inhibitor	6 (3 × II, 3 × III)	1 (1 × III)	3 (3 × II)	10 (6 × II, 4 × III)

we started a combined treatment schedule of wasp and bee venom. All patients gave their informed consent.

Honey bee venom (HBV) was given to 20 patients, wasp venom (WV) to 125 patients and both venoms to 31 patients. This comprised 176 treatments and 1256 treatment years. Six months maintenance phase in total is 1125 treatment years. The mean duration of treatment was 7.14 years (range 1.16-25.49 years) as shown in table III.

Many patients dropped out of the study during the maintenance phase because they could not continue over several years. The majority moved away from our area or developed a non-related disease (e.g. chemotherapy treatment) resulting in their exclusion. Controls to compare to conventional VIT schedules could not be recruited because of non-compliance over years following these schedules and the desire to be included in our special schedule.

Treatment

Treatment was initiated in accordance with standard criteria. The protocol (table IV) provided an increasing dose from 0.01 μg up to 100 μg within a maximum time range of 6 weeks (typical injection intervals of 3 to 4 days). After reaching the maximum dose of 100 μg the injection intervals were gradually extended up to 6 months, as shown in table IV, by maintaining the dose of 100 μg venom per injection. Treatment was continued unless the patient wished to withdraw.

Consent was given after a statement of advantages and disadvantages concerning our treatment protocol compared to protocols applied in other centres. This was documented in the dossiers.

Aqueous solutions of HBV or WV were injected (Venomil®, Bencard Allergy (ATL), Munich, Germany, or Reless®, Scherax, Hamburg, Germany). Maintenance therapy was performed strictly every 6 months.

Table III

Mean duration of VIT and field sting data

a: wasp venom

Duration of treatment (mean = 7.17 years)	Number of patients (total = 125)	Re-stings/events/patients
Up to 3 years	32	4/4/3
3 to 5 years	21	12/12/6
5 to 10 years	40	40/39/20
> 10 years	32	57/50/23

b: bee venom

Duration of treatment (mean = 8.17 years)	Number of patients (total = 20)	Re-stings/events/patients
Up to 3 years	4	0/0/0
3 to 5 years	4	2/2/1
5 to 10 years	5	2/2/2
> 10 years	7	9/9/4

c: wasp and bee venom

Duration of treatment (mean = 6.36 years)	Number of patients (total = 31)	Re-stings/events/patients
Up to 3 years	7	3/2/1
3 to 5 years	9	11/11/5
5 to 10 years	8	12/12/5
> 10 years	7	10/10/4

d: all treatments (wasp, bee, bee and wasp)

Duration of treatment (mean = 7.14 years)	Number of patients (total = 176)	Re-stings/events/patients
Up to 3 years	43	7/6/4
3 to 5 years	34	25/25/12
5 to 10 years	53	54/53/27
> 10 years	46	76/69/31

Table IV

Venom immunotherapy (VIT) regimen

Injection number/ interval to last dose	Concentration (μg/ml)	Volume (ml)	Venom dose (μg)	Treatment characteristics
1	0.1	0.1	0.01	Increase of dosage at stable intervals (3 to 4 days) In total 6 weeks
2/3-4 d	1.0	0.1	0.1	
3/3-4 d	10	0.1	1.0	
4/3-4 d	10	0.5	5.0	
5/3-4 d	100	0.1	10.0	
6/3-4 d	100	0.2	20.0	
7/3-4 d	100	0.3	30.0	
8/3-4 d	100	0.5	50.0	
9/3-4 d	100	0.6	60.0	
10/3-4 d	100	0.7	70.0	
11/3-4 d	100	0.8	80.0	
12/3-4 d	100	1.0	100.0	
13/1 week	100	1.0	100.0	Increase of intervals at stable maintenance doses In total 9 months
14/1 week	100	1.0	100.0	
15/2 weeks	100	1.0	100.0	
16/2 weeks	100	1.0	100.0	
17/4 weeks	100	1.0	100.0	
18/4 weeks	100	1.0	100.0	
19/3 months	100	1.0	100.0	
20/3 months	100	1.0	100.0	
All further injections in 6-months intervals	100	1.0	100.0	Maintenance Therapy Years

Deviations of several days were permitted for urgent reasons such as fever or holidays. Following an injection and a 30-minute observation period of the patient, the local reaction was measured and documented in the ward. In response to any complaint the observation was extended. In a few cases pharmacological intervention was necessary to counteract systemic side effects of venom injection.

Documentation of tolerance to therapy and sting reactions

Every venom injection was preceeded by a medical interview for current medication, new complaints, acute infectious or allergic signs, tolerance of last VIT injection, occurrence and course of any new hymenoptera stings. Reactions resulting from VIT or field stings were documented in the patient's report.

Serological evaluation

Sequential measurements of serum IgE (total IgE) and venom specific IgE were made before starting VIT and repeated regularly during long term treatment. For determination of venom specific antibodies over the last 25 years we specifically used standardized assay procedures (RAST, CAP) available from Pharmacia (Uppsala, Sweden). Results were expressed in U/ml and according to the manufacturer's scoring system and documented in the patient's dossier. From the start of our study only RAST scores (and not discrete units of specific IgE) were available. Thus for these cases we created a mean value from the RAST class as a surrogate parameter.

RESULTS

Tolerance and safety

Generally, VIT was tolerated very well. All of the patients in this study had reached the stage of maintenance treatment in the 6 months treatment interval. Patients experienced local reactions such as itching and swelling around injection site, which disappeared spontaneously within 24 hours post-injection. Patients who complained were allowed to

Table V

Side-effects (systemic reactions) during build-up phase and 6 months maintenance therapy

Therapy	Number of patients with reactions during build-up phase, severity grade (according to table I)	Number of patients with reactions during 6 months maintenance phase, severity grade (according to table I)	Consequence	Number of injections during maintenance phase
Wasp venom (125 patients)	7 patients 4 × 0/I, 1 × 0/I (ACE), 1 × I, 1 × II	3 patients 2 × 0/I 1 × I	Continuation of therapy, no further reactions	1,605
Bee venom (20 patients)	4 patients 3 × 0/I, 1 × I*	5 patients 3 × 0/I, 1 × I*, 1 × II,	Continuation in 4 patients, no further reactions, stopped in this patient with grade I*	297
Bee and wasp venom (31 patients)	3 patients 2 × 0/I, 1 × II (ACE)	3 patients 3 × 0/I	Continuation of therapy, no further reactions	307 × 2 (bee and wasp every visit)

ACE: inadverdent medication with ACE-inhibitor.

take antihistamines at the evening before treatment day. Local reactions never exceeded 10 cm in diameter. The risk of development of systemic reactions to venom injection, which occurred rarely in this study, did not correspond with the size of local reactions.

Systemic reactions to a single or a few injections were observed in 11 patients (6.3 %) (3 treated with wasp venom, 5 treated with bee venom, 3 with combined treatment) during maintenance therapy, whereas during the build-up phase a total of 14 patients (8.0 %) had systemic reactions. These side effects mostly appeared within 15 minutes following subcutaneous injections and were usually mild, i.e. maximum grade I (table V). In one case (bee venom) after 6 years of maintenance injections with the maximum dose without any systemic side effect, an anaphylactic reaction of grade II developed after injection. This reaction did not recur after further injections that were given without change of protocol. Another patient that showed a grade II reaction during the build up phase was without reactions in all subsequent Injections that included even higher dosages. Because of an inadvertent comedication with ACE-inhibitor for hypertension that was taken in spite of better knowledge, two patients reacted during the build-up phase (1 × grade 0/1, 1 × grade II). After discontinuation of this medication treatment was well tolerated. In only one patient treatment was stopped because of ongoing grade I reactions to the maintenance dose (bee venom). In this patient already during build-up phase the maximum dose provoked the same extent of reaction.

Determination of efficacy by re-sting reactions

In 74 patients (42 %) under maintenance therapy, a total of 153 hymenoptera attacks occurred (events), comprising a total of 162 field stings. For wasp venom VIT, there were 113 wasp stings in 105 events in 52 patients. For bee venom VIT, there were 13 bee stings in 13 events in 7 patients. For combined VIT, there were 36 hymenoptera stings in 35 events in 15 patients. Systemic reactions re-occurred in 8 events (8 stings, 8 patients) during 6 months maintenance therapy (10.8 % of patients stung, 4.5 % of all patients). In 7 out of the 8 patients with persistent anaphylactic reactivity (in spite of therapy) re-sting reaction was of lower intensity compared to the initial reaction (1 × grade III → grade I, 1 × grade III → grade 0/1, 2 × grade II → grade I, 3 × grade II → grade 0/I) whereas in one patient re-sting reaction remained a grade II reaction (table VI). This patient was judged as a therapy failure, whereas in all other re-sting reactions the initial life-threatening situation was eliminated. Thus patients were stable after the field sting and pharmacological intervention was not regarded as necessary.

Efficacy of venom treatment with 6 months maintenance intervals was 98.6 % (73 of 74 patients restung showed minor or no reactions) or 99.4 % regarding the number of total stings received during maintenance therapy. There was no correlation between duration of the maintenance therapy at the time of the re-sting and the severity of the reaction. Neither could we find a connection between the reaction severity after the re-sting and the reaction severity after the initial sting (table VI).

Table VI

Severity grade of reactions following re-sting during maintenance VIT

Initial grade of severity	Wasp venom (n = 125)	Patients with re-stings/reaction	Grade of severity
I	25	8/0	–
II	75	31/4	II, I, 0/I, 0/I
III	25	13/2	I, 0/I
ACE-inhibitor co-medication	6 (3 × II, 3 × III)	1/0	–
Initial grade of Severity	**Bee venom (n = 20)**	**Patients with re-stings/reaction**	**Grade of severity**
I	3	0/0	–
II	15	7/2	I, 0/I
III	2	0/0	–
ACE-inhibitor co-medication	1 (1 × III)	0/0	–
Initial grade of Severity	**Wasp and bee venom (n = 31)**	**Patients with re-stings/reaction**	**Grade of severity**
I	10	4/0	–
II	16	8/0	–
III	5	3/0	–
ACE-inhibitor co-medication	3 (3 × II)	1/0	–

Serological results

Before and during treatment total IgE and allergen-specific IgE was monitored. Total IgE and specific IgE was expressed in U/ml. Additionally the RAST and CAP scoring system was used, according to the laboratory test provider. The mean value (arithmetic mean) of total IgE from 125 patients on wasp venom therapy decreased from 159.2 U/ml before start of therapy to a mean value of 105.4 U/ml. This was paralleled by a decrease of the arithmetic mean of wasp specific IgE, i.e. 9.9 U/ml before treatment and 5.2 U/ml after treatment. This decrease was not observed when comparing the median of the manufacturer's scoring system (RAST/CAP class 2 before and after treatment). The corresponding values in the bee venom group and the combined treatment group are listed in table VII.

DISCUSSION

For over 25 years VIT has been demonstrated as an efficacious treatment for hypersensitivity to hymenoptera venom[9-11]. However, the criteria for the maintenance therapy protocol still remain debatable. In particular, the optimal duration is still not known but is suggested between 3 and 5 years according to different authors[1,4,12,13] and based on results from sting challenge[14-18].

Our therapeutic modification extended VIT maintenance dose intervals gradually to 6 months. A control group was not recruitable over the same time period. Incidence and severity of side-effects in our group did not differ from those observed in other studies with shorter intervals (table VIII)[9,10].

Side-effects were calculated as a percentage, comparing the number of patients with reactions to the total number of treated patients. The number of patients with mild systemic reactions was lower during the 6 months maintenance phase (6.3 %) than during the initial build-up phase (8.0 %). However, comparability is not exact, because of the different settings in both treatment phases and also because there have been more injections in the build-up phase than in the maintenance phase (20 versus 13 injections calculated on the average duration of treatment). The frequency of systemic side-effects compares well to the results obtained from conventional protocols using standard maintenance intervals. As reported in other studies[10], most of subjects showing systemic side effects suffered from allergy to bee venom or had a combination treatment. One female patient treated with bee venom finally stopped treatment because of ongoing grade I reactions, during both the build-up phase and the six months maintenance phase.

The efficacy of the presented regimen was assessed by the effects of 162 re-stings with the culprit insect attacking 74 patients during maintenance therapy (details in table III). Mild systemic reactions (non objective anaphylactic symptoms: grade 0/I) were developed in 4 patients. In 3 patients re-sting reactions were grade I and thus significantly less pronounced than before commencing VIT (2 of them experienced a grade II and 1 patient a grade III initial sting reaction, see table VI). In only one patient the initial and re-sting reactions remained unchanged. In total, 4/74 (5.4 %) patients expressed objective anaphylactic symptoms (3x generalized skin reaction, 1x cardiovascular reaction of grade II) in the re-sting situation and 4/74 (5.4 %) patients showed non-objective systemic reactions after re-sting. Other groups have reported systemic reactions after re-sting in 3-23 % of patients receiving one dose a month[19].

We paid particular attention to patients taking ACE-inhibitors which may enhance anaphylactic reactions. In 10 patients an anaphylactic sting reaction occurred whilst under medication with an ACE-in-

Table VII

Serological study

a: wasp venom

Duration of treatment (mean = 7.17 years)	Number of patients (total = 125)	Total IgE before (U/ml)	Total IgE actual (U/ml)	Wasp specific IgE before (U/ml)	Wasp specific IgE actual (U/ml)
Up to 3 years	32	191.7	125.4	15.0	11.3
3 to 5 years	21	133.7	87.8	9.2	5.5
5 to 10 years	40	162.2	90.9	9.7	2.3
> 10 years	32	138.4	115.2	5.5	2.3
Patients pooled	125	159.2	105.4	9.9	5.2

b: bee venom

Duration of treatment (mean = 8.17 years)	Number of patients (total n = 20)	Total IgE before (U/ml)	Total IgE actual (U/ml)	Bee specific IgE before (U/ml)	Bee specific IgE actual (U/ml)
Up to 3 years	4	61.3	36.0	11.0	2.9
3 to 5 years	4	47.5	32.0	2.3	1.1
5 to 10 years	5	67.8	40.8	13.6	1.5
> 10 years	7	81.6	77.9	9.9	2.3
Patients pooled	20	67.3	51.1	9.5	2.0

c: wasp and bee venom

Duration of treatment (mean = 6.36 years)	Number of patients (total = 31)	Total IgE before (U/ml)	Total IgE actual (U/ml)	Wasp specific IgE before (U/ml)	Wasp specific IgE actual (U/ml)	Bee specific IgE before (U/ml)	Bee specific IgE actual (U/ml)
Up to 3 years	7	295.5	196.0	3.5	2.6	13.0	5.6
3 to 5 years	9	265.5	133.8	9.1	2.9	9.6	3.4
5 to 10 years	8	276.6	264.5	13.5	3.7	16.0	4.0
> 10 years	7	442.7	178.0	20.2	4.8	23.8	7.1
Patients pooled	31	315.1	191.6	11.5	3.4	15.2	4.9

hibitor. After discontinuing the medication, VIT did not result in any pronounced side-effects. Two re-stings were reported in this small group without a following reaction.

Analysis of specific IgE from serum samples showed a mean decrease of about 50 %. As specific IgE only rarely disappears following VIT these results are congruent to IgE monitoring in other insect allergen treatment schedules[2,9,10]. There was no substantial correlation to the side-effects or the reactions following re-sting. The same holds true for the skin-test data (not shown), rendering a reduction in the mean diameter without observation of negative tests. Thus, the measurement of specific IgE and

Table VIII

Other studies with prolonged maintenance intervals

Study	Maintenance interval	Number of patients	Re-stings (+ systemic reaction)	Side-effects	Sting challenge (+ systemic reaction)
Golden et al (1981)[8]	6 weeks	30	0	0	29[1]
Goldberg et al (1988)[5]	6, 8, 12 weeks	26 (13,10,3)	17 (0)	0	0
Kochuyt et al (1994)[7]	12 weeks	152	290 (1)	0	0
Goldberg et al (1994)[6]	12 weeks	28	4 (0)	0	0

skin-testing in our study was appropriate for diagnosis but not for monitoring.

In conclusion, this study has demonstrated the efficacy and safety of long-term VIT incorporating 6-month maintenance therapy intervals. Results are comparable to that found following the standard protocols used by other groups, particularly with regard to success following re-sting. Regarding side-effects, local reactions during six months intervals did not differ from local reactions in the short intervals after reaching the maximum dose (100 μg). The occurrence of systemic reactions to therapy was not higher than in the protocols reported in the literature and have been easily controlled by an adapted antiallergic treatment[20]. No patient had to be hospitalized for a systemic reaction to VIT.

It is established that long-term VIT with continuous maintenance therapy provides long-term protection. This study has provided an useful alternative schedule which is economical in time for both doctor and patient. In addition, the patients benefit from continuous monitoring and hence a superior life quality due to the resulting long-time protection.

Efficacy of long term treatment is finally illustrated by a case of wasp venom allergy. The patient who initially showed a wasp sting reaction of grade II had two re-stings during a treatment period of four years without anaphylactic symptoms. Six years after unilateral cessation of treatment another re-sting provoked a *de-novo* grade II reaction and hence therapy was re-started.

Finally, additional aspects and data have to be mentioned. During the last 25 years more than 1000 patients received the build-up phase of VIT in our clinic. Maintenance therapy according to our protocol was given by their family doctors and no serious or severe side effects were reported. In some patients therapy was interrupted for various reasons, e.g. for pregnancy, but could be resumed using our protocol without dose reduction. The findings indicate that our long-term 6-month protocol provides sufficient security, even for prolongation of the maintenance interval. As to our experience the maintenance protocol can be subsequently added to any previous protocol bringing up the dose to 100 μg. Of particular interest is the finding in our study that also older patients tolerated this modification of VIT and benefited by it.

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