

Safety and efficacy of a 12-week maintenance interval in patients treated with Hymenoptera venom immunotherapy

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Summary

It is currently recommended to administer a maintenance dose of 100 μ g of venom at 4–6 week intervals for Hymenoptera venom immunotherapy (VIT). Because the optimal duration of therapy is not known, we decided to progressively prolong the interval between maintenance injections instead of accepting the risk of anaphylactic reactions when VIT is discontinued after a predetermined period. We report here on the results of a first phase of this interval extension programme, covering the gradual increase of the interval from 1–12 weeks over 19 months in 178 patients. A 12-week interval maintenance VIT could be achieved in 117/128 (91%) of yellow jacket venom (YJV) and in 35/50 (70%) of honeybee venom (HBV) allergic patients. At the time of the interview these 152 patients had been treated with 12-weekly 100 μ g venom injections for an average period of 2 years without any untoward reaction to VIT. During this period 48 YJV allergy sufferers experienced 77 field re-stings without systemic reaction (SR), and 17 HBV allergic subjects were restung at least 213 times in total, with one patient developing a very large local reaction and one a mild systemic reaction. In 26 of the 178 patients the interval of 12 weeks was not reached for various reasons, with a higher failure rate among the HBV allergic patients. Most Hymenoptera venom allergic patients can thus be safely and effectively treated with 12-weekly injections of 100 μ g venom.

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Introduction

The generally recommended interval for venom immunotherapy (VIT) with 100 μ g of Hymenoptera venom is 4 weeks. This period has been established on an empirical basis. According to the literature the interval may be lengthened up to 6 weeks after the second year [1], and gradually even to 8 weeks [2,3].

The optimal duration of VIT is, however, not known and varies from 3 to 5 years according to different authors [4–6], although initially life-long treatment was regarded as the safest option. The length of VIT should be determined in view of its long-lasting protective effect. At present, the duration of therapy is in the process of being

established by trial and error, comparing the frequency of re-sting anaphylaxis in patients who have been desensitized for varying lengths of time. Such a procedure implies, however, that anaphylactic reactions are expected and accepted as proof of therapeutic inefficiency. As an alternative to that procedure, we developed a treatment regime based on a progressive extension of the interval between two injections. Theoretically, such a regime will protect the patient from any recurrence of serious systemic reactions (SR), because on lengthening the interval, the appearance of large local reactions (LR) will alert the clinician that tolerance may be subsiding. Furthermore, if any SR would occur, it is likely to happen in a hospital environment where all available emergency treatments are on hand.

In a first phase, we progressively extended the injection interval to 3 months, which was then continued for

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various lengths of time. In this paper we report on the results of this first phase of the progressive interval extension programme.

Materials and methods

Venom immunotherapy regime

Between January 1982 and December 1990 we have treated 217 subjects with VIT with yellow jacket venom (YJV) ($n=151$) or honeybee venom (HBV) ($n=66$). Of the HBV allergic population 73% were either beekeepers ($n=17$) or relatives ($n=31$). All 217 patients had suffered at least one SR after a Hymenoptera sting. The severity of the reactions was expressed in grades I–IV according to the method of Mueller [7]. All patients were proven to be sensitized to either YJV or HBV by a positive skin test and/or RAST before the start of VIT. Intradermal skin tests were performed with 0.05 ml of 10^{-6} – 10^{-1} $\mu\text{g/ml}$ solutions of a commercial YJV or HBV extract (Pharmalgen®, Pharmacia, Sweden). After 15 min, the weal-and-flare diameters were recorded and graded according to Voorhorst *et al.* [8]; a 3+ reaction was considered positive. Specific serum IgE antibodies to HBV and YJV were measured with the commercially available Phadebas RAST system (Pharmacia, Sweden). Results were expressed in five classes according to the producer's scoring system.

Single venom VIT was initiated in our in-patients department at the University Hospital. Aqueous YJV and HBV (Pharmalgen®, Pharmacia, Sweden) were injected according to the rush protocol presented in Fig 1. One week after the end of the rush VIT a 100 μg dose maintenance VIT was started in our hospital or that of the referring physician, on an out-patient basis. The interval between the injections was lengthened by 1 week at each visit to a maximum of 12 weeks (Fig. 2). This frequency

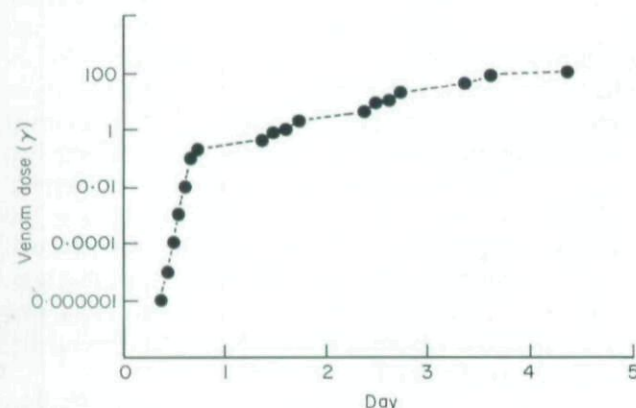


Fig. 1. Rush venom immunotherapy regimen.

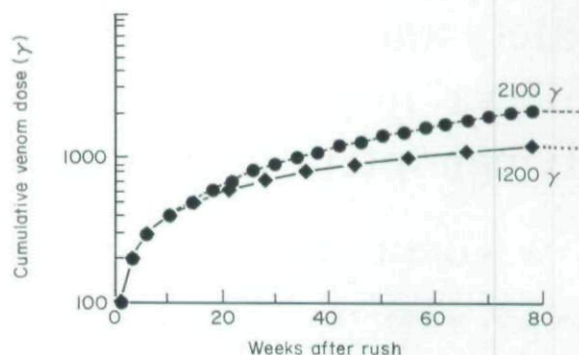


Fig. 2. Cumulative dose during maintenance VIT with 100 μg venom injections. A regime with maximal intervals of 4 weeks and a regime with intervals increasing to 12 weeks are compared. —▲—. Low injection frequency. -●- . High injection frequency.

was reached 19 months after the initiation of the maintenance VIT and then continued indefinitely. Protective medication which could have prevented either SR or LR was never used. In all patients the standard schedule was applied irrespective of the positivity of skin tests and/or RAST to YJV and HBV and of the severity of the SR to preceding stings. Exceptions to the standard regime, however, were made when very large LR (>15 cm) or SR to the 100 μg injections occurred, and the interval was then either not increased or, in the event of a SR, shortened.

Efficacy of immunotherapy

At the end of 1992 all 217 patients who, according to our standard schedule, should have been on a 12-week maintenance VIT either in our hospital ($n=58$) or elsewhere ($n=159$), were interviewed by one of our collaborators, using a standardized questionnaire.

If patients were still on treatment, the present interval between the 100 μg venom injections, the total number of field re-stings since the start of VIT, the date of these re-stings and the identity of the insect were noted. For patients who were resting after having reached the 12-week injection interval, the length of this 12-week interval treatment until the moment of the re-sting was calculated. The estimated size of the local swelling and the occurrence of SR after injections and insect field re-stings were recorded.

For patients who had stopped VIT deliberately, the duration of treatment was noted. If they were resting after discontinuation of VIT, the time from the end of VIT to the field re-stings was calculated and the symptoms caused by the re-sting were registered.

Results

We interviewed 217 patients of whom 178 were still being treated with either YJV ($n=128$) or HBV ($n=50$). At the time of the interview 152/178 patients were on a 12-week interval maintenance VIT, while 26/178 patients had not reached this prolonged interval for several reasons. Of these 26 patients, 11 and 15 were treated with YJV and HBV respectively, which means that 91.5% of all YJV allergic patients but only 70% of HBV allergic patients had reached the 12-week interval. Of the 15 HBV allergic patients who still received injections every 3–8 weeks, 10 (66%) experienced SR when the interval was increased, while this occurred in only one YJV allergic subject. All the patients with SR during maintenance VIT had also manifested one or more SR during the initial rush VIT phase. Of the 217 subjects who have been interviewed, 39 patients had deliberately interrupted the maintenance VIT with YJV ($n=23$) and HBV ($n=16$).

Patients who were treated with a 12-week interval regime ($n=152$)

This group of 152 patients was composed of 117 YJV and 35 HBV allergics, who at the time of the interview had completed their first 12-week interval for 26 (range 2–96) and 25 (range 5–76) months respectively (Fig. 3). Forty-one per cent of the subjects (63/152) were on this regime for more than 2 years. Only 17/152 patients had a LR > 10 cm, which persisted for > 24 h in half of them. No SR occurred.

Re-stings during the incremental phase. Twenty-five of the 152 patients were restung while the interval between two consecutive injections was 8–11 weeks. Thirteen YJV and 12 HBV allergic patients had 19 yellow jacket (YJ) and 75 honeybee (HB) field re-stings during this incremental phase without any untoward reaction.

Re-stings during the 12-week interval maintenance therapy. Forty-eight YJV and 17 HBV allergic patients were

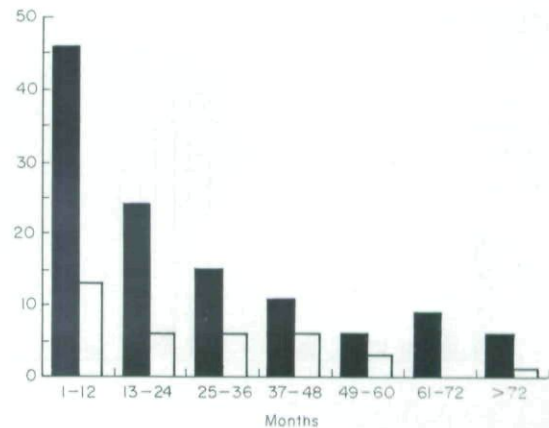


Fig. 3. Distribution of the length of maintenance therapy with 12-weekly injections in 152 patients.

restung 77 and 213 times in total, while on the 12-week interval steady state (Table 1). The 77 YJ field re-stings did not cause a single SR. Of the 213 HB re-stings one supra-orbital sting resulted in a very large facial oedema, and one sting in the hand caused an angioedema at previous sting sites on the upper arm and the eyelids. There were no untoward side-effects to re-stings in the other patients.

The 65 restung patients were then further analysed. Eight-five per cent of the 48 YJV allergics and 69% of the 17 HBV allergics had experienced a grade III or IV reaction prior to VIT. The RAST results at the start of VIT were significantly ($\chi^2: 8.01, P < 0.01$) higher for HBV than for YJV. The mean duration of the 12-week interval maintenance regimen at the time of the field re-stings was 31.5 months for the YJV and 25 months for the HBV allergic patients. Figure 4 shows the number of restung YJV and HBV allergic patients and the number of stings during the 12-week interval treatment. Generally, there was no doubt about the identity of the insect. The

Table 1. Patients on a 12-week interval maintenance venom immunotherapy: systemic side reactions to field re-stings

Stings of	Patients (n)	Re-stings (n)	First 12-week interval completed for	With side reactions (n)
Yellow jacket	48	77	31.5 months (3–96)	0
Honeybee	17	213	25 months (5–76)	2*
Total	65	290		2

* One patient with very large local reaction and one patient with reactivation of previous local sting reactions. These patients had their first 12-week interval completed for 5 and 14 months respectively.

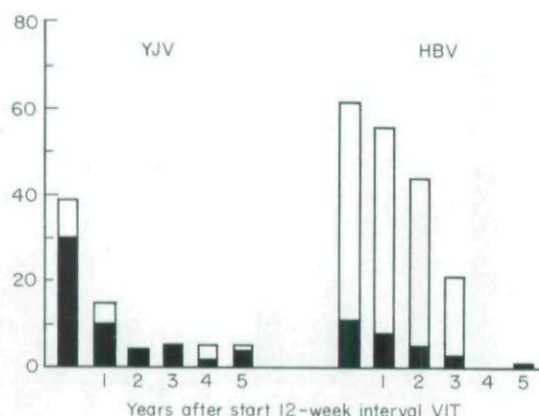


Fig. 4. Number of re-stings and restung patients in 48 YJV and 17 HBV allergic patients, restung while on a 12-week interval maintenance VIT for 1–5 years. (Ten subjects were restung on 2, and 7 on 3 different occasions.) □, Re-stings (n). ■, Restung patients (n).

majority (82%) of these HBV allergic patients were either beekeepers or members of their family. They were all restung at home by an insect they positively identified as a HB. Eight-three per cent of the YJV allergic patients had seen the offending insect and were convinced it was a YJ. The remaining patients thought a YJ was most likely because of environmental factors and the absence of a sting at the sting site.

We compared the size of the LR to the 12-week interval maintenance VIT injections with the estimated LR to the field re-stings. In the majority (82%) of the subjects the local swellings after the re-stings were comparable to or smaller than the LR to injections.

Patients who were not treated with a 12-week interval regime (n = 26)

Twenty-six of the 178 patients who were still being treated at the time of the interview, had not reached the 12-week interval for various reasons. This was the case in 9% (11/128) of the YJV and in 30% (15/50) of the HBV allergic patients. Of these 26 subjects, one YJV and 10 HBV allergic patients still received the 100 µg dose every 3–8 weeks because of SR when the interval was increased. In the remaining 15/26 patients the interval was not increased because of large LR of > 15 cm or because the treating physician had decided to not extend the interval, for various reasons which were difficult to evaluate. These patients were at intervals ranging from 6 to 10 weeks.

Re-stings. Of the 26 patients who had not reached the 12-week interval, 10 had been restung. Six of them (one YJ and five HBV allergics) had experienced 15 stings (one YJ and 14 HB) while on an injection interval of at least

8 weeks. In one of them, a HB sting was followed by a generalized pruritus without eruption. At that time she had received VIT injections for 16 months and was still on an 8-week interval maintenance treatment. A beekeeper who was treated for almost 5 years, occasionally developed urticaria and rhinitis when stung by a HB when he was on an 8-week injection interval. This patient had suffered repeated SR during the initial rush VIT.

Patients who deliberately discontinued VIT (n = 39)

Of the 39 patients who deliberately stopped VIT, seven YJV and four HBV allergic subjects were restung seven (range 1–2) and 109 (range 1–100) times in total, 28.5 (range 10–56) and 12.5 (range 3–30) months after discontinuing the 12-week interval regime. No SR to field re-stings occurred. These patients had been on VIT for an average of 43 months (range 24–84) in the seven YJV and 25 months (range 24–28) in the four HBV allergic subjects.

Discussion

The optimal duration of treatment has been estimated from trial and error experiences since the early days of allergen immunotherapy: if the frequency of relapses after a preset treatment period exceeds what is considered acceptable, the period is considered too short. Such an approach takes many years before any conclusions can be reached, and even then, the durations that are proposed vary from approximately 3 to 5 years [9]. As this is still the case for inhalant allergens which have been used for injection treatment for 80 years [10], we should not be surprised that the matter is not settled for VIT that has only recently been introduced [11]. For inhalant allergy, the trial and error approach may be justifiable because relapses are announced by a reappearance of symptoms that, in the beginning, are not life threatening. However, the matter is different for venoms. To sit and wait for anaphylactic reactions as evidence for an inappropriate treatment period is much less appealing than to wait for an itchy nose during the pollen season. Furthermore, it might be that a standard duration for therapy cannot be defined, because an optimal treatment period might be determined by individual patient characteristics.

When we were confronted with this problem 11 years ago, we intended to solve it more safely by a different approach. In order to avoid the wait and see situation after the end of a treatment, we decided to continue treatment indefinitely after rush immunotherapy, but to increase the intervals between the 100 µg maintenance injections progressively. We speculated that a breakdown of clinical tolerance would be announced by an increase in

the LR. If, unfortunately, this were not the case, untoward SR would occur in a treatment setting, which allows for optimal medical intervention, compared with field conditions. A less important, but not negligible advantage, would be economical; the progressive increase in injection interval would reduce the treatment cost considerably, compared with the classical 4–6 week schedule and therefore improve patients' compliance.

A lengthening of the injection interval beyond 6 weeks, has been incidentally reported. In 1981, Golden *et al.* demonstrated that after 2 years of monthly maintenance injections of 100 µg, the interval between the injections could be increased from 4 to 6 weeks, without any change in clinical and immunological efficacy [1]. Extending the interval to 8 weeks, however, resulted in SR in 23% of the 22 patients who were restung during the second year on this regime [3]. Unfortunately, this author did not mention the number of patients treated with HBV and with YJV and how many subjects experienced SR during the initial VIT. In 1988, Goldberg & Reisman reported on an extension of the interval between 50 µg venom doses to 8 weeks [2]. However, only patients who had been on a 4 and then on a 6 week interval maintenance VIT for 2 consecutive years were treated at longer intervals. Three out of his series of 10 patients have been restung without SR. He then extended the interval between the injections to 12 weeks in three patients. Re-stings during this treatment regime were not mentioned.

To our knowledge there are no longitudinal studies on a more than 6 week interval maintenance VIT with 100 µg venom doses in large patient groups. Hence, literature data were of no help in designing a programme to evaluate the potentialities of longer injection intervals. Therefore, we projected a first phase that would end with a period of 3-monthly injections. We felt that a further increase beyond 3 months, without a pause to evaluate whether this already unusual interval would give rise to a breakdown of tolerance, was unacceptable. Consequently, an interim analysis was carried out on 152 patients who were started on VIT before 1991 and had reached a 12-week interval steady state regime before December 1992. None of these patients had ever experienced a SR to the 100 µg injections but in 17 the LR was > 10 cm. There are no reports in the literature on the size of LR during classical maintenance VIT, nor has the appearance of SR to injections or field re-stings been correlated with the size of LR to previous injections. In his article on treatment failures in HBV allergic patients, Bousquet *et al.* [12] state that a large LR may predict a subsequent SR. Unfortunately, they did not mention what they consider to be large. In any case we did not register a progressive enlargement of LR to injections which might have been predictive of forthcoming SR, nor

did we notice such SR. Because 41% of our 152 patients were on the 12-week interval maintenance VIT for more than 2 years, we concluded that the treatment is safe. Moreover, seven out of the 17 patients with LR > 10 cm to the injections have been restung with comparable or even smaller LR and without signs of a SR.

Tolerance for 100 µg venom injections during treatment suggest protection for field re-stings. However, because several 'patient related' and 'venom related' factors may determine a different outcome for field stings and for venom injections, the protective effect of therapy had to be documented separately for both circumstances.

Forty-eight YJV allergic patients have been restung 77 times without any untoward reaction since they were on a 12-week interval VIT (Table 1). The number of HB field re-stings per patient was much higher because the eight beekeeping patients continued their activities after the start of treatment. The 17 restung HBV allergics had received at least 213 HB field re-stings. A HB re-sting resulted in a very large LR in one patient and in a re-activation of previous local sting reactions in a second patient. Thus none of these 65 Hymenoptera allergic patients experienced a severe reaction to field re-stings during their 12-week interval maintenance VIT, although 80% had experienced a SR of grade III and IV, to stings prior to VIT. For patients with such severe sting reactions, the risk for anaphylaxis at re-exposure may be as high as 50% for HBV and 25% for YJV allergics [13,14]. Thus, if our treatment regime had been ineffective we would have expected at least 16 patients to experience the same type of SR. However, all but two field re-stings, which caused very mild reactions, have been well tolerated. This adequate protection could be achieved by a lower cumulative dose than is used for standard treatment. In our schedule, patients receive a cumulative dose of 1200 µg venom during the 19 months that follow the initial rush VIT phase. Afterwards, while on a 12-week interval treatment, the annual cumulative dose is 400 µg. At the time of the interviews, 63 patients had received this annual dose for more than 2 years (Fig. 3). This dose is much lower than the currently recommended doses of 900–1200 µg, and only a small portion of the 2400 µg used by Bousquet *et al.* [15]. On the other hand, some authors advocate a maximum dose of 50 µg per injection [16]. During a 6 week interval maintenance VIT this would result in an annual cumulative dose of 400 µg as in our regime. Reisman *et al.* report an excellent tolerance of field re-stings in patients treated with a 50 µg maintenance dose [16], but he does not mention the interval between injections. In our study most field re-stings ($n=172$) occurred at a time the patients had received 12-weekly injections for a period of 6–24 months (Fig. 4). Yet 17 patients have been restung without reaction while being

treated for 2–4 years, and seven for more than 4 years, with a 400 µg annual dose.

Protection for field stings during the period of treatment does not warrant a long-lasting protective effect after discontinuation of treatment. Therefore, we investigated whether patients who had deliberately interrupted VIT, continued to tolerate Hymenoptera stings. The fact that there was not a single severe reaction can hardly be explained by a spontaneous loss of sensitivity in these patients. The four HBV and seven YJV allergic patients who had been treated for 2–3.5 years respectively, and have been restung 28.5 months and 12.5 months on average after discontinuation of the 12-week maintenance VIT, did not react. This indicates that our unusual treatment regime induces a protection that persists 2 years after cessation of VIT, at least in this small group of patients.

At this point, we have to realize that the discussion of our results is still restricted to patients during and after a 12-week interval VIT period. This period, however, is preceded by a rush therapy and a long phase of 19 months during which the interval is gradually lengthened to 12 weeks. In principle, this might give rise to difficulties that are not or less frequently associated with the standard treatment that prolongs intervals to only 6 weeks. In fact a number of patients, especially HBV allergics, did not tolerate our progressive increase in injection interval, and therefore had to remain at a higher injection rate. This did happen, however, before as well as after the classic 6 week interval and it is therefore not typical for the regimen we used. It is not known why HBV allergic people are more prone to develop SR to VIT than YJV allergics. We find the mean levels of specific IgE to be much higher in a HBV allergic population than in YJV allergics. Even in patients successfully desensitized with HBV, the pretreatment RAST scored significantly higher than in the YJV allergic people. A comparable observation has been described recently by Mueller *et al.*, who also found stronger positive skin tests in HBV allergic patients [17]. The high degree of sensitization to HBV might contribute to the adverse reactions during VIT in HBV allergics. Several authors have observed this difference in efficacy and safety for VIT with YJV and with HBV [17,18]. Moreover, Mueller *et al.* have demonstrated that the risk of SR on subsequent field re-stings remains considerable in HBV patients who develop SR during the initial VIT [17]. Whatever the reason for this difference between YJV and HBV allergics may be, our observations merely suggest that the length of the tolerated injection interval is inversely related to the sensitivity of the patient at any moment in the course of VIT. This relationship is known for inhalant immunotherapy as well. We speculated that a careful observation of the LR to injections would enable

us to decide which patients belong to this very sensitive minority and to establish adequate injection intervals for such cases which may be shorter or longer than 6 weeks depending on the patients' sensitivity. This approach was successful.

The protection to field re-stings was investigated separately for patients during the increasing interval period of VIT. Indeed, it could not be ruled out that an aberrant regime might induce a temporary decrease in tolerance after rush VIT, which might be due, e.g. to a lower increase of the cumulative dose. Twenty-five of our patients have suffered 94 re-stings in the period when the interval was 8–11 weeks without untoward reactions. This suggests that, in the initial stage of maintenance VIT, the continuous prolongation of the interval to 8 weeks after the rush induction is as effective as a regular 4–6 week interval VIT.

In conclusion, we have demonstrated that it is safe to progressively extend the injection interval up to 3 months during maintenance VIT, provided that LR are carefully observed and the regime is adapted when such reactions tend to increase. The efficacy of the treatment is comparable to that of classical VIT. Consequently, we are now starting the second part of our programme which will analyse the effect of a further increase of the injection intervals. In this way we hope to design a VIT procedure that is based on individual patient characteristics. We hope that this method will help prevent relapses due to the application of general rules on treatment duration, which may not be appropriate for every subject.

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