Ann Allergy Asthma Immunol 110 (2013) 51–54

Contents lists available at SciVerse ScienceDirect

Efficacy of venom immunotherapy given every 3 or 4 months: a prospective comparison with the conventional regimen

Livio Simioni, MD [*]; Alberto Vianello, MD [*]; Patrizia Bonadonna, MD [†]; Guido Marcer, MD [‡]; Maurizio Severino, MD [§]; Mauro Pagani, MD [¶]; Luca Morlin, MD [‡]; Mariangiola Crivellaro, MD [‡]; and Giovanni Passalacqua, MD [||]

[*] Allergy and Clin. Immunology, Internal Medicine Department, "S. Maria del Prato" Feltre Hospital, Italy
[†] Allergy Unit, Verona General Hospital, Verona, Italy
[‡] Occupational and Environmental Medicine, University of Padua, Padua, Italy
[§] Allergy Clinic, Nuovo Ospedale San Giovanni di Dio, Florence, Italy
[¶] Allergy and Oncology Unit, Asola Hospital, Asola, Italy
[||] Allergy and Respiratory Diseases, DIMI, University of Genoa, Genoa, Italy

ARTICLE INFO

Article history:
Received for publication April 12, 2012.
Received in revised form September 2, 2012.
Accepted for publication September 18, 2012.

ABSTRACT

Background: Standard venom immunotherapy involves the administration of the maintenance dose every 4 to 6 weeks. This regimen may have adherence problems, especially in the long term; thus, extended intervals have been proposed.
Objective: We prospectively compared the efficacy of 3- or 4-month extended maintenance dose vs the conventional regimen.
Methods: Patients receiving immunotherapy with a single venom were offered the extended maintenance dose (EMD) and were then followed up for field re-stings. Only the re-stings by the insect for which the patients received immunotherapy were considered. A comparable group of patients receiving the conventional maintenance dose (CMD) was used for comparison by logistic regression analysis.
Results: Seventy-six patients (60 male; mean age, 48 years) receiving the EMD were re-stung on 247 occasions by the insect for which they were receiving immunotherapy. The group receiving CMD included 110 patients (82 male; mean age, 44 years) certainly re-stung on 167 occasions by the specific insect. The percentage of re-sting without reaction was 93.5% in the EMD group and 81.5% in the CMD group, with a significant difference in favor of the former (P=.001). At logistic regression analysis, only age, but not maintenance dose protocol, was predictive of subsequent systemic reactions.
Conclusion: The EMD is as effective and safe as the CMD. An increased maintenance seems to be the best option in term of convenience and economic savings.

Introduction

Hymenoptera venom allergy has a prevalence ranging from 0.5% to 7.5% in the general population[1–5] and represents a major risk factor for severe systemic reactions, including anaphylaxis. The diagnostic procedures and the treatment of the disease have been uniformly approved in official documents, where venom immunotherapy (VIT) is recommended as the mainstay of the management[6–8] because it confers an efficient protection against reactions induced by new stings in more than 90% of patients. VIT with purified extracts is indicated in most patients with systemic reactions, and the maintenance dose of 100 μg of venom is indicated as the optimal choice in most patients.[7,8] Although the vaccination for Hymenoptera allergy is acceptably standardized, some gray areas still remain in this field.[9] For instance, the opportunity of discontinuing the treatment after some years,[10] the use of premedication,[11] and the use of vaccination in patients at higher risk, such as those with mastocytosis.[12]

Another discussed aspect is the most appropriate timing of the maintenance dose, although there is an almost general consensus that a 4- to 6-week interval is adequate. In our experience, however, the monthly regimen is not well accepted by many patients and induces a relevant work charge for the allergy clinic, with subsequent problems of organization and resource allocation. In addition, longer intervals between maintenance doses would be convenient, especially if VIT is prosecuted indefinitely.

On the basis of those considerations and previous observations,[13–17] we attempted to assess whether an extended maintenance dose, with the VIT given every 3 or 4 months, retains

Reprints: Giovanni Passalacqua, MD, Allergy & Respiratory Diseases, Department of Internal Medicine, Padiglione Maragliano, L.go R. Benzi 10, 16132 Genoa, Italy; E-mail: passalacqua@unige.it.
Disclosures: Authors have nothing to disclose.

1081-1206/12/$36.00 - see front matter
http://dx.doi.org/10.1016/j.anai.2012.09.014

a protective efficacy comparable to the conventional regimen. The evaluation of the clinical efficacy was based on the outcome of field stings, namely, the severity of reaction. To avoid the possible confounding factors, only patients receiving one single venom and at least one re-sting by the insect for which they were vaccinated were considered.

Methods

This is a prospective, observational study involving patients with ascertained Hymenoptera allergy and vaccinated with a single venom. The interval between the first sting and the prescription of VIT never exceeded 1 year. The number and severity of reactions at re-stings during an extended maintenance dose (EMD) regimen were evaluated and compared with those of patients receiving a conventional maintenance dose (CMD). After the maintenance dose was reached, patients were offered the EMD. The patients were trained to recognize stinging Hymenoptera and followed up for field re-stings by assessing their reactions during the maintenance period. The severity of reactions was graded as follows: no reaction and local reactions, large local reaction (LLR), and systemic reaction (Grade I to IV) according to Mueller.[18] The enrollment of patients receiving a CMD that served for comparison was started later. Subanalyses according to the protocol of vaccination and to the venom used were also performed. The primary objective was to assess the protective efficacy of the maintenance given at an extended interval vs the conventional regimen. The study was observational, and all the procedures are part of the standard clinical practice in Hymenoptera allergy. Thus, Italian law only requires notification to the ethical committees. All patients (or parents in the case of minors) signed a written informed consent for the treatment of their personal data, for the diagnostic procedure, and for the vaccination, according to our routine practice.

Patients and Diagnosis

Only adult and adolescent patients receiving at least one re-sting by the insect for which they had been vaccinated were evaluated. The diagnosis of venom allergy involved, as per guidelines,[6] clinical history, identification of the stinging insect (whenever possible), skin prick tests, intradermal test, and CAP radioallergosorbent assay. The diagnostic extracts, provided by Stallergenes, Anallergo, and Alk-Abellò, were *Apis mellifera* (honeybee) and *Vespula* species (yellow jacket). VIT was subsequently prescribed according to guidelines.[8] All the patients were warned against the risk of potential re-stings, whenever possible. This was obviously useless in beekeepers.

Immunotherapy maintenance regimens

The build-up phase had a duration of 3 weeks in all patients. In the first day 0.01, 0.1, 1, and 2 μg at 30-minute intervals were given. In the subsequent week, the dose was escalated in the same day to 4, 8, 12, and 20 μg, and in the third week 20, 30, and 50 μg were given. The maintenance dose was always set at 100 μg. In patients who had reactions during the build-up, a slower escalation (weekly increases of 0.01, 0.1, 1, 3, 5, 10, 20, 30, 40, 60, 80, and 100 μg) was applied. In the EMD regimen the maintenance, achieved in 3 weeks, was progressively delayed at 6 weeks, 2 months, and 3 months. The 3-month interval was reached in approximately 4.5 months.[16] Starting from the beginning of the fifth year, the maintenance was extended to 4 months. In the CMD regimen the maintenance dose was given every 4 to 6 weeks for the whole duration of the VIT course. In the case of severe field reactions during the EMD, the interval between doses was shortened to 1 month according to the traditional protocols.

Statistical Analysis

Means were compared using the *t* test for independent samples and frequencies using the χ^2 test with Yates correction for continuity. Rank correlation with the Spearman coefficient of rank correlation (ρ) was used to correlate months of VIT with severity of reactions in VIT. A 2-tailed $P<.05$ was considered significant. A logistic regression analysis (backward, forward, and stepwise methods) was also used. The *P* value for entering variables was $<.05$, and the *P* value for removing variables was $>.10$. Systemic reactions in VIT (regardless of severity) were the dependent variable: LLRs were considered as no reaction. Predictive factors were the protocol regimen (CMD and EMD), age, sex, number of field stings or episode, venom used for immunotherapy, regimen, months of VIT, and months of maintenance at the time of field sting or episode.

Results

Seventy-six patients receiving an EMD and 110 patients receiving a CMD (only 10 of 186 were adolescents), receiving a single VIT, and field-stung by the same insect were analyzed. The groups were well matched for demographic characteristics and sensitizations. Of the 76 patients receiving an EMD (60 male; mean age, 48 years), 39 received honeybee VIT and 37 yellow jacket VIT. They were re-stung on 247 occasions by the insect that they were receiving immunotherapy for (148 honeybee and 99 yellow jacket stings). The mean duration of VIT in those patients was 73 months. In the group receiving a CMD (82 male; mean age, 42 years), 54 patients received honeybee VIT and 56 yellow jacket VIT. They had a total of 167 re-stings (89 by honeybees and 78 by yellow jackets). In this group, the mean duration of VIT was 22 months. Before VIT, grade III reactions were 25 in the EMD group (in addition to urticaria and malaise, 15 had dyspnea and 10 had dyspnea and stridor) and 35 in the CMD group (in addition to urticaria and malaise, 19 had dyspnea and 16 had dyspnea and stridor). For those patients the mean (SD) time elapsed from the reaction and the VIT was 3.1 (1.8) months. Grade IV reactions occurred in 37 EMD patients (in addition to urticaria and malaise, 12 had dyspnea and hypotension; 10 had dyspnea, stridor, and hypotension; and 15 had loss of consciousness, without prodromes) and in 40 CMD patients (12 had dyspnea and abdominal pain; 8 had dyspnea, stridor, and hypotension; and 20 had loss of consciousness). In those patients the mean (SD) time elapsed from the reaction and the VIT was 3.6 (1.1) months. The characteristics of the two populations are summarized in Table 1, and the characteristics of the sting reactions before VIT are summarized in Table 2. Of note, a relevant proportion (approximately 60%) of patients were beekeepers, and this

Table 1
Characteristics of the patient population

Characteristic	EMD patients (n=76)	CMD patients (n=110)
Male/female, No.	60/16	82/28
Age, mean (range), y	48 (44-51)	42 (39-45)
VIT, No.		
Honeybee	39	54
Yellow jacket	37	56
Specific IgE to honeybee, mean (SD), kU/L	8.4 (11.4)	7.9 (15.3)
Specific IgE to yellow jacket, mean (SD), kU/L	9.1 (17.1)	11.6 (12.2)
Re-stings, No.		
Total	247	167
Honeybee	148	89
Yellow jacket	99	78
Mean VIT duration, mean (range), mo[a]	73 (68-78)	22 (20-24)

Abbreviations: CMD, conventional maintenance dose; EMD, extended maintenance dose.
[a] *t* test $P<.001$.

Table 2
Grade of reactions before VIT and during VIT in the EMD and CMD patients

Reaction grade	CMD patients, No.				EMD patients, No.			
	Honeybee		Yellow jacket		Honeybee		Yellow jacket	
	Before VIT	During VIT	Before VIT	During VIT	Before VIT	During VIT	Before VIT	During VIT
None	0	70	0	66	0	140	0	91
I	6	4	3	4	4	5	1	0
II	13	2	13	1	4	1	5	0
III	17	0	18	0	15	2	10	0
IV	18	0	22	0	16	0	21	0
LLR	0	13	0	7	0	0	0	8
Total	**54**	**89**	**56**	**78**	**39**	**148**	**37**	**99**

Abbreviations: CMD, conventional maintenance dose; EMD, extended maintenance dose; LLR, large local reaction; VIT, venom immunotherapy.

certainly accounts for the high number of re-stings.[19] No relationship was found between the baseline specific IgE concentration and the severity of reaction at the first sting.

None of the patients was stung during the build-up phase. The severity of reactions at re-sting in the CMD group was as follows: grade I, 8; grade II, 3; and LLR, 20. In the remaining 136 of the 167 re-stings (81.5%), no reaction occurred at all. In the EMD group the severity of reactions at re-stings was as follows: grade I, 5; grade II, 1; grade III, 2; and LLR, 8. In the remaining 231 of the 247 re-stings (93.5%), no reaction occurred (Table 2). In this group, of the 2 patients who had grade 3 reaction (asthma and generalized urticaria) with VIT, one was treated by reducing the interval between doses at 2 months and the other received a maintenance dose of 200 μg. In both cases, subsequent re-stings produced had only local reactions. The grade II reaction occurred in a patient who, before VIT, had had a grade 4 reaction and monoclonal mast cell activation syndrome. Neither doses nor intervals were modified, and subsequent re-stings were not associated with systemic reactions. No statistical comparison could be performed between adults and adolescents because the latter were too few, and only one of them had a grade III reaction before VIT and no reaction during VIT. The subanalysis of patients with grade III and IV reactions before VIT in the EMD group, who are at higher risk, did not reveal relevant differences, and the number of reactions during VIT was near zero in all categories (Table 3).

The percentage of re-stings without reactions was significantly higher in the EMD group than in the CMD group (93.5% vs 81.5%, χ^2 P=.001), and the frequency of LLR was greater in the CMD group (11.9% vs 3.2%, χ^2 P=.001). In addition, considering only the first re-sting episode, no difference was found between the 2 groups (χ^2=5.84, P=.21, data not shown). No difference in reactions was found between the patients receiving the EMD at 3 and 4 months (Table 4). A significant correlation was found (Spearman ρ=−0.229, P<.0001) between duration of VIT and severity of reactions during VIT (data not shown). According to the logistic regression analysis,[20] none of the considered variables (CMD or EMD, sex, number of field stings, venom, regimen, months of VIT, or months of maintenance at the time of field sting) were predictive for systemic reactions, except age (Table 5). Given the demonstrated dependency of the severity of reactions on the duration of VIT and the significant difference between the 2 groups in term of VIT duration, we considered the frequency of systemic reactions in the 2 groups, limiting the duration of VIT to 48 months for both groups (data not shown). Finally, no significant difference was detected between groups, with systemic reactions occurring in 11 of 163 (6.7%) in the CMD group and 4 of 72 (5.5%) in the EMD group (P=.96).

Concerning the safety, in the CMD group there were in total 4 LLRs and 4 grade I reactions during the induction phase. Three of the grade I reactions occurred with a dose of 8 μg of venom. All those reactions were managed with symptomatic treatment and did not impede achieving the scheduled maintenance dose. Four patients receiving an EMD had systemic mastocytosis. Three patients had only a LLR at re-sting, and 1 (receiving VIT for a yellow jacket sting) had a grade II reaction. Of note, this reaction occurred after a bumblebee sting, for which the diagnostic test results were negative.

Table 3
Characteristics and outcome of the patients with grade III and IV reactions before VIT in the extended maintenance dose group

Characteristic	Grade III		Grade IV	
	Honeybee (n=15)	Yellow jacket (n=10)	Honeybee (n=16)	Yellow jacket (n=210)
Male/female, No.	10/5	7/3	11/5	17/4
Age range, y	44-52	45-54	39-48	40-50
Beekeepers, No.	12	0	14	0
Specific IgE, mean (SD), kU/L	13.5 (13.0)	10.2 (8.2)	18.9 (9.9)	14.5 (8.8)
Skin test positivity, No.				
Prick test (100-μg dose)	8	6	10	13
Intradermal				
0.001-μg dose	3	1	2	4
0.01-μg dose	1	1	1	1
0.1-μg dose	2	1	2	2
1-μg dose	1	1	1	1
Grade of reaction during VIT, No.				
I	3	0	2	0
II	0	0	1	0
III	1	0	1	0
IV	0	0	0	0

Table 4
Total number of re-stings according to maintenance dose interval and protocol

Maintenance dose	Grade of reaction					Total
	None	I	II	III	LLR	
EMD						
3 months	192	4	1	2	6	205
4 months	39	1	0	0	2	42
Total EMD	231	5	1	2	8	247
CMD	136	8	3	0	20	167
Total CMD	136	8	3	0	20	167
TOTAL	367	13	4	2	28	414

Abbreviations: CMD, conventional maintenance dose; EMD, extended maintenance dose; LLR, large local reaction.

Table 5
Best model predicting systemic reactions according to logistic regression analysis (goodness of fit of the logistic regression model according to hosmer and lemeshow test)

Variable	OR (95% CI)	
	No. of stings as continuous variable[a]	No. of stings as categorical variable (1 or >1)[b]
CMD vs EMD protocol	2.22 (0.01-547.11)	2.04 (0.01-494.06)
Age (every 10 years)	1.40 (1.00-1.80)	1.40 (0.99-1.70)
Female vs male sex	1.15 (0.41-3.26)	1.11 (0.34-3.13)
Yellow jacket vs bee venom	0.43 (0.14-1.28)	0.46 (0.15-1.35)
No. of stings[c]	0.71 (0.40-1.27)	0.44 (0.11-1.74)
Maintenance dose interval (1 vs 3 or 4 months)	1.01 (0.05-19.28)	0.96 (0.06-18.21)
Months of maintenance dose	0.97 (0.92-1.02)	0.97 (0.92-1.01)
Months of VIT	0.99 (0.96-1.03)	0.99 (0.96-1.02)

Abbreviations: CMD, conventional maintenance dose; EMD, extended maintenance dose; LLR, large local reaction.
[a] χ^2 = 6.68, P=.60.
[b] χ^2 = 5.01, P=.76.
[c] One re-sting vs more than 1 re-sting.

Discussion

VIT is universally considered the cornerstone of treatment for patients with Hymenoptera venom allergy who experienced systemic reactions. Independently, on the build-up schedule, the maintenance dose should be administered every 4 to 6 weeks to maintain an adequate protection. This interval was identified in accordance with the clinical experience of respiratory allergens and the results of earlier studies. Nevertheless, in principle, there is no fixed rule for the maintenance interval. This aspect is relevant because the timing of maintenance can affect to some extent the adherence to the treatment, especially in the long term. In clinical practice, when at the end of the standard 5 years of VIT patients are advised that protection could be progressively lost, many chose to continue the treatment indefinitely.[10] In this regard, it is true that patients may lose their sensitization over time,[21] which explains the absence of reactions to re-stings, but it is also true that some patients experience severe reactions once the treatment has been stopped,[22] so VIT is sometimes continued for long periods (even for life).

Finally, as a practical consideration, the 4-week schedule may cause problems with resource allocation, when the number of patients is high. For those reasons, extended or delayed maintenance dose schedules have been sporadically proposed. For instance, Gadde et al[14] and Goldberg et al[15] more than 20 years ago proposed a 2-month interval for the maintenance dose, and this interval is also suggested for long-term maintenance in recent guidelines.[23] This approach was reconsidered in more recent trials,[16,17] where a 3-month extended interval was found to be effective in maintaining the protection. It is clear that for VIT to be effective the dose interval cannot be extended indefinitely. In fact, a 6-month interval was found to be inadequate.[24,25] One of the problems in assessing the efficacy and comparing different regimens is that a field re-sting would be necessary to uncontrovertibly demonstrate the protection. Another aspect is that the effective protection should be demonstrated against the insect for which the patient is vaccinated to avoid the possibility of confounding cosensitizations or cross-reactions.[26] Another is that the efficacy of the EMD should be compared with the recommended conventional regimen.

On the basis of those considerations, we undertook this trial to evaluate whether an EMD interval (3 and 4 months) is suitable in terms of efficacy and safety. In our study, we considered only patients receiving VIT for a single venom and who were certainly re-stung by the specific causal insect. Under these conservative conditions, we found that the grade of protection of the EMD is not inferior to that conferred by a conventional schedule. In addition, we found that the outcome of VIT improves in parallel with its duration. Of note, for each immunotherapy access the cost is €35 for VIT plus €25 for medical, nurse, and “structural” costs; thus, the total cost is €60. Therefore, the cost of 1 year of EMD varies from €240 to €180, whereas the yearly cost of CMD varies from €480 to €720, with an economic saving equal or greater than 50%.

In conclusion, the EMD approach is at least as effective and safe as the conventional one and seems to be the best option in term of convenience and economic savings.

Acknowledgment

We thank Carla Zanella and Daniela Ferrazza for their contribution in the follow-up of patients.

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