High adherence to hymenoptera venom subcutaneous immunotherapy over a 5-year follow-up: A real-life experience

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Clinical Implications

- High and sustained adherence to hymenoptera venom immunotherapy (VIT) was observed. Beyond a patient's perception of a life-threatening disease, a thorough counseling, enforced by peer-to-peer confrontation during the VIT build-up phase, guided by an experienced staff could be an efficient strategy to increase adherence.

TO THE EDITOR:

Hymenoptera venom immunotherapy (VIT) is a highly effective treatment that can improve the quality of life of patients with hymenoptera venom allergy (HVA).[1-3] A treatment course of at least 3-5 years of duration is necessary to achieve long-lasting protection against severe allergic reactions on re-sting.[1,2,4] Lack of adherence to therapy is a matter of concern in real-life setting; low rates of adherence to allergen-specific immunotherapy (AIT) with inhalants have been extensively reported in the literature, regardless of the route and location of treatment administration.[5,6]

Aside from 2 studies on few patients with HVA in the USA.[7,8] solid data on VIT adherence are still lacking.

We prospectively collected data on real-life adherence to VIT of every patient referred to our allergy unit, from January 2000 to December 2006, who signed an informed consent for anonymous data gathering for study purposes, including adherence assessment.

Before initiation, we performed as daily practice a thorough per-patient counseling, concerning efficacy, safety, and importance of a full 5-year course to achieve long-lasting protection. The same information was shared during the rush or ultrarush build-up phase while patients were treated in groups of 3-4 in a protected setting, a moment when peer-to-peer confrontation and mutual support were often observed.

No further reminders regarding VIT adherence and its assessment were carried out by our staff, to avoid any methodological bias during the remaining VIT course.

Adherence was defined as the completion of a 5-year cycle of VIT and was assessed as follows.

A database developed for routine VIT monitoring and statistical analysis was used (Microsoft Excel; Microsoft, Redmond, Wash), including demographic data, severity of sting reaction, type of venom, build-up scheme, serum baseline tryptase levels, mastocytosis, date of VIT initiation, dosing interval, side effects, re-sting outcome, payment modality, and reasons for discontinuation.

Clinical monitoring differed according to patients' geographical origin; patients from our region (Marche) were monitored in our clinic during the full VIT course and each injection was recorded. By contrast, patients from border regions performed only the build-up phase in our clinic and were referred to the local allergist or general practitioner for maintenance. Compliance in out-of-region patients was assessed during yearly scheduled follow-up visits. A multiple-choice questionnaire was administered to assess reasons for nonadherence during scheduled appointments or phone interviews.

Any subject who either missed at least 2 consecutive VIT administrations, failed to show up at the yearly follow-up visit, or could not be reached after several phone call attempts for an assessment interview was defined as noncompliant. At the study end, pooled data were analyzed at 3 different time points, namely 1, 3, and 5 years from the start of VIT.

Five-hundred and eight patients (male/female ratio 3:1), mean age 46 years (range 9-86 years), were included in this study. Among these, 61% were residents of Marche region, whereas 39% commuted from border regions. Baseline clinical features are summarized in Table I.

Mean dosing intervals were 4.22 weeks in the first year of maintenance VIT, prolonged to 6.93 and 8.52 weeks by the third and fifth year, respectively.

The cost of VIT was refunded (directly or indirectly) in 83% of subjects by the Italian National Healthcare System.

During each time point, we experienced high compliance rates and eventually 83.7% of patients were adherent to the full course of treatment (Figure 1).

Concerning adherence, no statistical difference between patients from Marche and border regions was seen (84.9% vs 81.6%, P value = .33, χ^2 test).

Major reported reasons for discontinuation were lack of compliance (28.9%), inconvenience (25.3%), and onset of a new disease (16.8%) (Table E1 in this article's Online Repository at www.jaci-inpractice.org).

As for re-sting occurrence, 8.1% of subjects experienced at least one field re-sting during follow-up and only a small fraction (2.03%) of re-stung patients experienced a systemic reaction during VIT maintenance.

This is the first study that assessed the real-life adherence to VIT. The strengths of this study were the number of enrolled subjects, the prospective design, and duration of follow-up. Our VIT dropout rates differed significantly from other studies on AIT adherence, in which treatment discontinuation occurred more frequently and earlier.[5] However, a comparison between AIT and VIT is inappropriate, being specific treatments for different diseases.

Higher adherence rates were seen compared with other studies on VIT. In a retrospective study focusing solely on fire ant VIT,[7] after 1 year of maintenance, 35% of 76 patients were still undergoing VIT, with inconvenience and fear being main reasons for poor adherence. In a cross-sectional study on AIT, including an unstated number of patients on VIT,[8] adherence rate dropped down to 83% after a 3-month follow-up, because of inconvenience, precluding medical conditions and adverse reactions.

TABLE I. Baseline clinical features of the enrolled subjects

Total no. of enrolled patients = 508	
Clinical features	**n (%)**
Sting reaction severity*	
I	31 (6.1)
II	116 (22.8)
III	134 (26.4)
IV	227 (44.7)
Build-up scheme	
Ultrarush	412 (81.1)
Rush	94 (18.5)
Both	2 (0.4)
Tryptase levels (ng/mL)	
<11.5	430 (84.7)
>11.5	36 (7.1)
No data	42 (8.3)
Mastocytosis	
No	476 (93.7)
Yes	8 (1.6)
No data	24 (4.7)
Venom type	
Vespula spp.	231 (45.5)
Polistes spp.	25 (4.9)
Vespula crabro	8 (1.6)
Polistes dominulus	25 (4.9)
Apis mellifera	86 (16.9)
Two venoms	133 (26.2)

*According to Müller classification.

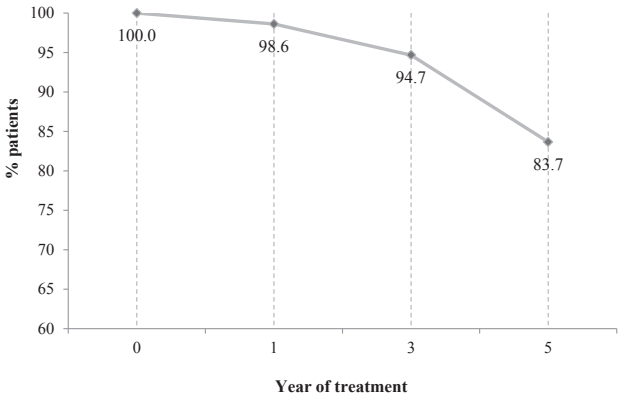

FIGURE 1. Trends of adherence during the 5-year venom immunotherapy course: percentages of compliant patients by the first, third, and fifth year from the start of immunotherapy were shown.

Both studies were performed in military populations with high relocation rates; therefore, a selection bias could have been responsible for the poor adherence observed. In our opinion, our results are faithful to the real-life experience of HVA specialized units, whereas no consistent data on adherence to VIT from nonspecialized settings are available to date.

We observed similar adherence rates between commuting patients, who underwent maintenance VIT in nonspecialized settings, and those monitored by our clinic, thus showing how sustained adherence is possible, regardless of location, as seen in AIT.[6]

Patients' awareness of being monitored was limited, because the adherence study was mentioned only during the informed consent signing and no further reminders were carried out over time. However, we cannot exclude that out-of-region patients could have been influenced by their local physician.

In our study, only few reasons for treatment discontinuation were adduced; lack of compliance (ie, missing >2 consecutive VIT administrations or having spontaneously interrupted treatment without any reason stated, loss to follow-up) was the major reason for treatment discontinuation, although less relevant than other reports.[5-8]

Inconvenience (ie, travel issues, work incompatibilities, change of residence) was the second motive present at each time point. VIT cost was not reported as a reason for quitting, even by nonadherent subjects who did not receive any refund. However, given the presence of conflicting data on this topic in AIT[6,9] and differences in health care policies worldwide, our results are insufficient to rule out these as potential reasons for VIT discontinuation in other countries.

The occurrence of field re-sting and proof of VIT clinical efficacy played a negligible role in early treatment discontinuation. The impact of injection intervals, occasional forgetfulness, or injection delay less than 2 weeks on adherence was evaluated only in patients from Marche region, and no conclusive evidence can be drawn because of the small number of discontinuations seen.

We demonstrated high adherence rates to VIT in a real-life context. We speculate 2 main reasons for these results: (I) an effective pre-VIT counseling, enforced by peer confrontation and administration of the VIT build-up phase inside a hospital facility by an experienced staff; (II) patients' self-motivation driven by the perception of an unpredictable life-threatening risk and the compelling need for VIT's rapid protection; this concepts is, however, hard to prove without any direct confrontation between AIT and VIT in risk and benefit perception. No difference between adherence in patients monitored in HVA-specialized and nonspecialized settings during maintenance therapy was observed. However, further studies are needed to assess VIT adherence in broader realities.

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