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Short Communication Open Access

Investigating the Changes in Venom-Specific IgE Induced by Wasp Venom Immunotherapy

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Abstract

Patients with systemic reactions (SR) to Hymenoptera stings are successfully treated by venom immunotherapy (VIT), but there is not yet a general agreement on the criteria for stopping VIT. We discuss the importance of the venom-specific IgE levels among these criteria. In particular, the results from a recent study evaluating the IgE changes during a 5-year VIT, in patients stung and protected within the first 3 years (SP 0-3) or in the last 2 years (SP 3-5), and in patients not stung (NS) are considered. A total of 232 yellow jacket venom (YJV) allergic patients were included and divided into the following groups: 84 NS, 72 SP 0-3 and 76 SP 3-5. IgE levels decreased during VIT compared to baseline values (χ^2=346.029, p<0.001). Recent vespid stings accounted for significantly higher IgE levels despite clinical protection. IgE levels after 5 years of VIT correlated significantly with Mueller grade (F=2.778, p=0.012) and age (F=6.672, p=0.002). More than one third of the contacted patients had at least one tolerated sting during a prolonged follow-up (up to 10 years) after stopping VIT. The stopping criterion of a duration of 5 years resulted in a decrease of IgE levels ranging from 58% to 70%, but no negative level was detected. This confirms the adequacy of the temporal criterion compared to the immunological criterion of developing negative IgE tests to decide for stopping VIT for vespid venom.

Keywords: Hymenoptera venom allergy; Hymenoptera venom immunotherapy; Specific IgE levels; VIT long-lasting protection; VIT discontinuation

Short Communication

Among the different hypersensitivity diseases, hymenoptera venom allergy (HVA) is the most strictly related to the IgE-mediated mechanism, as reactions to stings caused by other mechanisms are very rare [1]. Patients with systemic reactions (SR) to Hymenoptera stings are successfully treated by venom immunotherapy (VIT) with the causative venom according to the results of diagnostic tests [2]. A number of studies investigated the optimal duration of VIT necessary to achieve long-term protection after discontinuation of treatment. Due to their pivotal role in eliciting SRs, the development of negative skin tests and/or serum specific IgE (sIgE) tests was the first criterion to be proposed [3,4]. However, in the ensuing years it was apparent that such outcome was obtained quite rarely and that most patients maintaining a positive response to sIgE tests were clinically protected from stings [5-8]. Thus, the temporal criterion, based on duration of VIT of 5 years, especially when associated to a reduction of skin tests and venom-specific IgE levels, was generally accepted [9-11].

Indeed, the mechanisms of action of VIT, similarly to immunotherapy with inhalant allergens, include a shift from the Th2 to a Th1 cytokine pattern [12] and the generation of IL-10 producing T-regulatory cells [13]. These modifications of the immunologic response are mirrored by a decline in production in sIgE and an increase in sIgG, as already noted in early studies [14]. Though the decision to stop VIT must consider some risk factors for a future relapse, such as patient's age, type of venom, severity of pre-VIT reaction, and occurrence of SRs during VIT [15,16], the changes in sIgE remain an essential factor.

A recent study evaluated the changes in venom-specific IgE during the recommended duration of 5 years in 3 groups of patients treated with Vespula species (yellow jacket venom, YJV). All patients were treated in the Clinical Allergy and Immunology Unit of Policlinico Hospital in Milan, Italy. The first group included patients stung with clinical protection within the first 3 years of treatment; the second group included patients stung with clinical protection in the last 2 years of treatment; the third group included patients never stung during the treatment. A follow-up after VIT stopping assessed the outcome of further stings to study the persistence of protection in patients stung during VIT and the protection in patients who were not stung during the treatment [17]. The Mueller grades were used to classify the severity of SRs [18]. The recommended maintenance dose of 100 mcg of YJV every 5 weeks for the entire course of VIT was used. The mean decrease of YJV-specific IgE, the comparison of the sIgE decline in patients stung within the first 3 years or in the last 2 years of treatment, and the comparison of the mean decrease of YJV-specific IgE in patients protected from stings and in patients not stung during the treatment were analyzed. Also, the possible correlations between decrease in sIgE and patients' risk factors (age, reaction severity and number of stings), and the long-lasting protection in all patients were assessed. The measurement of YJV-specific IgE was performed by the ImmunoCAP System (Phadia, Uppsala, Sweden) using the kU/L as measure units, with 0.35-kU/L as positive cutoff level. An overall number of 232 YJV-allergic patients (144 males, 88 females; mean age 45.05 ± 15.48 years) who completed 5 years of VIT were included in

the study. No patient experienced SR during VIT as a result of field stings or as an adverse reaction to immunotherapy itself. Among them, 84 patients were never stung during VIT (group NS), 72 patients were stung without SR by vespids within the first 3 years of VIT (group SP 0-3) and 76 patients were stung during the last 2 years of VIT (group SP 3-5). In the whole cohort YJV-sIgE levels significantly decreased during VIT compared to baseline levels (χ^2=346.029, p<0.001). The mean CAP values at the first (3rd year) and last (5th year) control were decreased by 44.2% and 34 %, respectively; the mean CAP percentage decrease between the baseline and the 5th year control reached 65.6 %. No significant difference was found between NS and SP 3-5 patients and between SP 0-3 and SP 3-5. The patients who were not stung during the first 3 years of VIT (NS and SP 3-5) showed a similar mean percentage reductions in CAP values, 48.2 and 53.7 %, respectively, while the reduction of the SP 0-3 patients was only 30.7 %. At the final VIT control, the patients who were recently stung (SP 3-5) had significantly higher CAP values than those who were not stung or were stung during the first 3 years of VIT. The sIgE final percentage reduction in the SP 3-5 group was less than 60 % when compared to baseline, while NS and SP 0-3 patients presented a reduction of approximately 70%. IgE levels after 5 years of VIT correlated significantly with Mueller grade (p=0.012) and age (p=0.002). Concerning the follow-up after VIT cessation, 13 of NS patients, 21 of the SP 0-3 patients and 22 of the SP 3-5 patients had been stung, with no systemic reaction, from 1 to 10 years after VIT cessation. In the patients who underwent sIgE measurement, after the field sting IgE levels increased, independently from the period of field sting during VIT and from the time between VIT stopping and field sting. These finding offer confirmation to the significant decrease of venom-specific IgE over time during VIT [9,14,19]. Differently from previous reports, in this recent study at VIT cessation no patient developed a completely negative YJV-sIgE test, even though most of them (63.8 %) had at least one well tolerated vespid field sting. Hence, a correlation between clinical protection and negativity of sIgE may not exist and should not be considered a reliable indicator of successful VIT. As far as risk factors for relapse after VIT are concerned, in elderly patients and in patients with higher Mueller grade reactions, a smaller decrease in sIgE during the VIT course is observed. Of interest, a significant difference in CAP values at the 3rd year control between NS and SP 0-3 patients was found, because of the sIgE increase associated to the recent vespid sting in the latter group. Considering the mean percentage reduction between CAP3 and CAP5, SP 3-5 patients achieved only a 17 % reduction, while NS and SP 0-3 patients had reductions of 37% and 50 %, respectively. In the few patients available for further evaluation after stopping VIT (13, of whom 7 from the SP 0-3 group and 6 from the SP 3-5 group) the venom-specific IgE raised after the field sting to levels comparable to the 3rd year of VIT. However, a clinical protection from stings was generally reported until 3 years after VIT cessation, and some patients were protected up to 10 years after VIT.

In conclusion, when the temporal criterion of at least 5 years is fulfilled a mean IgE decrease ranging from 58% to 70 % compared to baseline is likely to be expected, but the decrease may be less striking in elderly patients or in subjects with a higher pre-treatment Mueller grade SR. This confirms the adequacy of the temporal criterion compared to the immunological criterion of developing negative IgE tests.

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Competing Interests

The Authors declare that no competing interests exist.

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