Clinical Commentary Review

When Can Immunotherapy for Insect Sting Allergy Be Stopped?

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Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Ulrich R. Müller, MD, and Johannes Ring, MD, PhD

Activity Objectives

1. To understand the risk factors associated with systemic allergic reactions (SAR) to Hymenoptera stings after stopping efficient venom immunotherapy (VIT).

2. To understand the recommended duration of VIT.

3. To understand the measures that are helpful to know when stopping VIT in the presence of risk factors for SAR.

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BACKGROUND: Stings by Hymenoptera (honey bees, vespids, ants) can cause systemic allergic reactions (SARs). Venom immunotherapy (VIT) is highly effective and reduces an allergic patient's risk of a recurrent SAR to less than 5-20%. The risk of a recurrent SAR to a re-sting decreases the longer VIT is continued. The recommended duration of VIT is at least 3 to 5 years.

RISK FACTORS: Risk factors for recurrent SARs to a sting after stopping VIT have been identified and discussed:

- **older age**
- **concomitant cardiac and pulmonary disease**
- **mast cell disorders, elevated baseline serum tryptase**
- **severe reactions before VIT**
- **SARs during VIT to treatment injections or stings**
- **repeated stings after VIT.**

Recommendations concerning stopping VIT: For patients without any of the identified risk factors, VIT should be continued for 5 rather than 3 years. In patients with definite risk factors, a longer duration of VIT has to be discussed before stopping it. In mast cell disorders, VIT for life is recommended. Because of the residual risk of SARs after VIT, all patients are advised to carry an epinephrine autoinjector indefinitely and to continue to take measures to avoid Hymenoptera stings. © **2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:324-8)**

Key words: *Hymenoptera venom allergy; Honey bees; Vespids; Venom immunotherapy; Efficacy of VIT; Duration of VIT; Risk factors for recurrence after VIT*

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Stings by insects of the order Hymenoptera, especially from vespids and honey bees, sometimes also from ants (*Myrmecia pilosula, Solenopsis invicta*), can cause systemic allergic reactions (SARs) due to specific IgE antibodies to the venom injected by these insects. Some of these reactions can be very severe and sometimes even fatal.[1] Venom immunotherapy (VIT) is highly effective for the treatment of patients with SARs to Hymenoptera stings. According to controlled studies, more than 95% of patients allergic to the vespid venom of yellow jacket (*Vespula spp.*), and 80% to 90% of those allergic to honey bee venom (*Apis mellifera*), will not develop systemic allergic symptoms if re-stung during VIT with monthly subcutaneous injections of 100 μg of the responsible venom.[2-10]

After the introduction of VIT in the late 1970s, it was initially believed that this therapy had to be continued for life. However, later reports were published that described protection from re-stings in patients who had stopped VIT for various reasons. Moreover, sensitivity to the venom according to skin tests and specific serum IgE to venoms decrease during VIT, and some patients even lose venom sensitivity according to these tests. Since the 1980s a number of studies have been initiated to determine whether and when VIT could be safely stopped.

We will discuss these studies and analyze the risk factors for a recurrent SAR to Hymenoptera stings after the discontinuation of VIT.

DURATION OF VIT

Today it is suggested that VIT should be given for a minimum of 3 to 5 years.[7-11] This recommendation is based on the following studies:

- One year of treatment: An early retrospective study evaluated a recurrent SAR to stings in 82 patients who chose to stop VIT after varying amounts of time, with a mean duration of treatment of 14 months.[12] Over the ensuing 3 to 4 years, 22% of those who were re-stung had SARs compared with 1% to 3% of patients who remained on VIT. Thus, 1 year of VIT did not provide sufficient protection for nearly one-quarter of patients.
- At least 3 years of treatment: Several prospective studies evaluated the protection afforded by VIT if it was given for at least 3 years and then stopped.[12-19] Most of the patients in these early studies were selected because they showed evidence of a reduction in sensitivity to venom in response to VIT, either through skin tests or serum tests. After 3 years of VIT, 83% to 100% of patients remained protected against recurrent SARs in the first 1 to 3 years after stopping. Most or all of the patients who did develop SARs with stings after stopping VIT had only mild symptoms (Table I).
- At least 5 years of treatment: Studies of ≥5 years of treatment show slightly higher rates of protection, even in unselected groups of patients. In one study of Lerch,[13] the percentage of patients who developed SARs after stopping VIT was significantly lower (5%) among patients who had received VIT for ≥50 months compared with 18% among those who received treatment for 33 to 49 months ($P < .01$). In a study of Golden of 29 adults with vespid venom allergy, there were no recurrent SARs on challenge 1 year after stopping treatment.[20] A later study of Golden[21] evaluated 74 patients treated with VIT for at least 5 years, who volunteered to stop treatment and undergo periodic testing and sting challenges every 1 to 2 years. Over the ensuing 2 to 5 years, systemic symptoms occurred in 7/74 patients (9.5%), or in 8/270 challenges (3%), and just 2 reactions required epinephrine injection (Table I).

RISK FACTORS FOR RECURRENT SARS AFTER VIT

A number of patient-specific risk factors for the recurrence of an SAR to Hymenoptera stings after VIT were identified by analyzing the studies reviewed above. Other characteristics, such as sex or the presence of atopic disorders, do not influence the risk of a relapse.[14,16]

Older age

Children have a lower risk for recurrent SARs than adults after discontinuing VIT.[14-16] In a representative study, SARs were reported in 8.3% of children compared with 13.1% of adults who were stung within 7 years after stopping VIT.[13] Other studies reported that only 5% of treated children experienced recurrent SARs when evaluated more than 10 years after VIT compared with a rate of 16% in treated adults.[22,23]

Severe pretreatment reaction

Patients with severe initial sting reactions are at a higher risk for a recurrent SAR both during and after completion of VIT.[24] Combining the data from 4 prospective studies that involved 386 patients[13,21,25,26] severe relapses were observed in 4/124 (4%) of those with mild initial reactions compared with 38/263 (14.5%) of those with severe pretreatment reactions ($P < .001$).

Bee venom allergy

Patients with bee venom allergy are at a higher risk for recurrent SARs than those allergic to vespid venoms, before, during, and after VIT. Before treatment, 51% of bee-allergic patients develop recurrent SARs on sting challenge compared with 25% of those allergic to vespid venoms.[27,28] During and after VIT, patients allergic to bee venom remain at higher risk.[13,14] In one study on VIT of 3-year duration, the relapse rate in patients allergic to bee venom was 16% compared with 8% of patients allergic to vespid venoms.[13] The reasons for this difference are not entirely clear.[5,6] The venom content of a honey bee sting (approximately 50 μg) is much higher than that of a vespid sting (3-5 μg). It is also possible that vespid stings are more variable in venom content than bee stings, because vespids retain their stingers after stinging, and thus insects can sting more than once, whereas honey bees lose their stinging apparatus. The higher recurrence of an SAR and side effects during bee VIT may also be explained by the fact that the percentage of venom during a bee sting as compared with the usual maintenance dose of 100 μg is approximately 50%, and for a vespid sting only approximately 5%.[5]

Systemic reactions to injections or stings during VIT

Patients who develop general allergic reactions to VIT injections or to repeat stings during VIT are at higher risk for reactions after VIT.[16,20] In one study, those who had systemic reactions to injections during VIT had a 38% chance of relapse compared with a 7% chance among those who tolerated injections.[16] Patients who have recurrent SARs during maintenance VIT should be evaluated for mast cell disorders with a baseline serum tryptase level. In addition, a higher maintenance dose of venom is recommended to achieve protection in such individuals.[29,30] These issues are discussed separately.