

Maintenance venom immunotherapy

David F. Graft

Purpose of review

Venom immunotherapy has proven to be a very effective method for the prevention of future re-sting reactions. However, initiation of the venom injection program is just the beginning. This review looks at recent papers which shed light on other issues that arise during maintenance venom immunotherapy.

Recent findings

Prophylactic antihistamines taken before venom injections reduce the frequency of reactions and one report suggests that they may improve efficacy. The schedule of venom injections usually does not have to be adjusted for patients who develop local reactions; a very large reaction may be the exception. Patients who react to stings should have their maintenance doses increased. Most patients are able to extend the interval between injections to 8 weeks in the third year of treatment. Two groups have proposed a maintenance interval of 12 weeks for routine use.

Summary

Our understanding of insect sting sensitivity continues to improve, leading to better outcomes for allergic patients.

Keywords

venom immunotherapy, yellow jacket, honeybee, Hymenoptera

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Asthma and allergic diseases, Park Nicollet Clinic, Minneapolis, USA

Correspondence to David Graft, Asthma and allergic diseases, Park Nicollet Clinic, 3800 Park Nicollet Boulevard, Minneapolis, MN 55416, USA
Tel: +1 952 993 3095; fax: +1 952 993 2874; e-mail: graftd@parknicollet.com

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Abbreviations

ACE angiotensin-converting enzyme
VIT venom immunotherapy

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Introduction

Hymenoptera sting reactions are associated with significant morbidity and mortality. About 50 deaths annually are attributed to insect stings in the United States [1]. The true incidence may be even higher because sudden deaths on the golf course or at the poolside may be mistakenly ascribed to heart attacks or strokes. One study [2] found a high frequency of venom-specific immunoglobulin E in the post-mortem serum of individuals who had died suddenly of unknown cause. There are many more near-fatal episodes. In the initial controlled trial of venom immunotherapy (VIT) conducted at Johns Hopkins, three of the 14 patients in the placebo and whole body extract treated groups, who sustained challenge sting-induced systemic reactions, had significant hypotension; in two of these patients, the hypotension persisted despite multiple doses of epinephrine; one patient required intubation [3,4]. Adults tend to have more severe systemic reactions; 90% have reactions involving the respiratory or cardiovascular system, whereas this is true for only 30% of reactions in children [5]. VIT is a safe and highly effective therapy for the prevention of recurrent insect sting-induced systemic reactions [6].

Once the decision has been made to initiate VIT and the venoms to be used have been selected, there are many questions which need to be considered over the course of therapy. These include the following: What is the rate of systemic reactions to venom injections? Should prophylactic antihistamines be administered before venom injections? What is the likelihood of protection from future stings? Is this different with different venoms? How should therapy be monitored? Is it still necessary to carry epinephrine? What adjustments should be made if the patient becomes pregnant? What if the patient is started on a beta-blocker or angiotensin-converting enzyme (ACE) inhibitor? How should therapy be monitored? Should venom-specific immunoglobulin G levels be measured? To what extent can the interval between injections of the maintenance dose be lengthened? Should patients receive intentional challenge stings? For how long should they be treated?

Prophylaxis for allergen injections

Systemic reactions from venom immunotherapy are no more frequent than those occurring from inhalant allergen immunotherapy. The Hymenoptera Venom Study III [7] reported a 12% rate of systemic reactions. Tankersley *et al.* [8] reported on their experience with

fire ant whole body extract immunotherapy. In 58 patients, they utilized a 2-day rush immunotherapy protocol followed by maintenance doses for two weeks. Efficacy of the protocol was determined on day 22 by evaluating the patient's response to a pair of fire ant stings delivered two hours apart. Furthermore, they studied the effectiveness of prophylactic treatment (twice daily terfenadine 60 mg, ranitidine 150 mg and prednisone 30 mg for two days before the start of rush immunotherapy) versus placebo on prevention of systemic reactions. Only three patients (5.2%) had mild systemic reactions to rush immunotherapy, with no statistical difference between the two premedication groups (3.6% active and 6.7% placebo; $P=0.87$). Sting challenges in 56 patients resulted in only one systemic reaction.

These findings can be compared with those published recently by Müller *et al.* [9] on the subject of honeybee rush VIT. Patients were randomized to receive terfenadine 120 mg BID on each of the four days of rush immunotherapy and on the first two days of weekly maintenance injections. No further prophylaxis was received throughout the rest of the course of VIT. During rush VIT, 10 of 26 patients in the placebo prophylaxis group had injection-induced systemic reactions compared with four of 26 patients in the terfenadine pretreatment group; this difference was statistically significant ($P=0.0485$). Moreover, in subsequent years they found that six of 21 patients in the placebo group, but none of 21 patients in the terfenadine prophylactic group had mild-to-moderate systemic allergic reactions to insect stings ($P=0.012$). The authors postulated that antihistamine premedication during the initial dose-increase phase may have enhanced the long-term efficacy of bee-venom immunotherapy, perhaps by restoring the downregulating role of the T helper 1 cytokines on the T helper 2 response.

Dose adjustment of immunotherapy following large local reactions

During the course of treatment, large local reactions to venom injections occur in about 25% of patients. Nelson *et al.* [10] reported in 1986 that local reactions after pollen immunotherapy are not predictive of subsequent systemic reactions. Tankersley *et al.* [11•] recently compared the rate of systemic reactions to, presumably, mostly inhalant allergen injections in an allergy clinic in Texas before and after changing their policy regarding dose adjustments for large local reactions. Whereas a 15–19 mm swelling and a 20–25 mm swelling would have previously prompted repeating the dose or reducing to the previous dose respectively, they now advanced the dose per schedule. Also, a 25 mm swelling or greater previously led to a 50% dose reduction of the next

injection. The policy change allowed for dose adjustment if the large local reaction was larger than the palm of the patient's hand (8–10 cm). They reported that the rates of injection-induced systemic reactions were similar, 0.8% and 1.01% ($P=0.24$), before and after the change in policy. Also, the rate of local reactions immediately preceding a systemic reaction did not increase (18.8% and 10.5%, respectively; $P=0.37$). They concluded that dose adjustment for most local reactions is unnecessary and may delay therapy, increase costs, and put the patient at increased risk of administrative errors.

Honeybee versus vespid

Honeybee venom sensitivity is more problematic than vespid venom sensitivity. Patients with a history of honeybee sting reactions are more likely to react to challenge stings (52% versus 25%) [12]. Honeybee-sensitive patients have more reactions to VIT (41% versus 25%) [13]. Honeybee VIT is less effective in preventing future sting-induced systemic reactions (77% versus 91%) [13]. After VIT is stopped, patients who received honeybee VIT are more likely to react to challenge stings (17% versus 4–8%) [14].

Monitoring venom immunotherapy

Graft *et al.* [15] stated that monitoring patients receiving VIT means you are interacting with them. One should reassure them that the protection rate is high. One should ask the following questions: Was there any problem in achieving the maintenance dose? Are the injections given on schedule? Have they had any stings since starting VIT? If a reaction occurred, consider raising the maintenance dose. If no reaction, did the patient self-administer epinephrine prophylactically or was there no reaction to the sting without epinephrine being administered?

Measuring the venom-specific immunoglobulin G level while on maintenance VIT is controversial. Golden *et al.* [16] reported that patients with a venom-specific immunoglobulin G level of less than 3 $\mu\text{g/ml}$ had a higher chance of reacting to stings. However, most (five of every six) patients with levels under 3 $\mu\text{g/ml}$ tolerated stings; therefore, some experts have recommended against routine measurements.

Some patients wonder if they need to continue to carry self-injectable epinephrine. My advice is that they do, although it is unlikely that it will be required even if they are stung. Venom treatment is usually not initiated during pregnancy. Schwartz *et al.* [17] found no significantly increased risk to the mother or fetus during 43 pregnancies among 26 women on VIT. In one closely studied case, VIT during pregnancy did not result in allergic sensitization to venom in the child [18].

Venom immunotherapy in patients on beta blockers and angiotensin-converting enzyme inhibitors

Patients taking beta-receptor blocking drugs are at risk for severe anaphylaxis and may not respond as well to treatment of anaphylaxis with epinephrine [19,20]. When larger than normal doses of epinephrine are utilized, these patients may paradoxically develop dangerous hypertension. Therefore, other drugs should be substituted for the beta-blocker, especially if VIT is recommended. Tunon-de-Lara *et al.* [21] reported two patients who had venom injection-induced systemic reactions on more than one occasion while taking an ACE inhibitor that did not occur when the ACE inhibitor was not used [21].

Maintenance dose for venom immunotherapy

There has been some debate about what the maintenance venom dose should be. The Hopkins group (Hunt *et al.*) [3] used 100 μg in their first controlled trial in the late 1970s. This is also the dose recommended in the package insert. Reisman and Livingston [22] have advocated a 50- μg dose and in 1992 published their experience. Conversely, some have called for a higher venom dose. Müller [23] advises a 200- μg dose of honeybee venom for sensitized beekeepers. Recently, Rüeff *et al.* [24**] reported 40 patients who had systemic reactions to honeybee ($n=18$) or yellow jacket ($n=22$) stings while treated with VIT with a maintenance dose of 100 μg . After an increase of the maintenance dose to 150 μg in some patients, two of four patients allergic to honeybee and six of six patients allergic to yellow jacket no longer reacted systemically to the sting challenge. The reactors had their dose further increased. Most patients' doses were increased from 100 μg to 200 μg before a repeat challenge sting. This maintenance dose protected 13 of 14 and 15 of 16 honeybee and yellow jacket-sensitive patients respectively. They concluded that the majority of patients allergic to Hymenoptera venom, who still reacted systemically to a sting challenge despite VIT with a dose of 100 μg every 4 weeks, could be fully protected by an increased maintenance dose.

Lengthened interval between maintenance dose venom injections

After reaching the maintenance dose, the interval between injections is lengthened each time by 1 week until 4 weeks is reached. The interval is generally lengthened to 6 weeks and then 8 weeks for the second and third years of therapy, respectively [25]. Several investigators have studied the possibility of extending the maintenance injection interval to 12 weeks. Kochuyt and Stevens [26] reported their experience with 178 patients who underwent rush VIT, then had their maintenance interval lengthened by 1 week at each visit to a maximum of 12 weeks. This was achieved in

117 of 128 (91%) of yellow jacket venom- and 35 of 50 (70%) of honeybee venom-allergic patients. While on maintenance VIT, the 152 patients were stung 290 times; only one mild systemic reaction occurred.

Goldberg *et al.* [27] initially reported on 28 patients who were able to extend their maintenance venom interval to 3 months after being at 1-month intervals for a mean of 16 months. The investigators challenge-stung 19 patients with honeybee; one patient had mild urticaria. Recently, Goldberg and Confino-Cohen [28**] extended their findings. In 160 patients, mostly allergic to honeybee venom, the 3-month interval was reached in 96% of patients after 16 months of VIT. Systemic reactions to venom injections administered at 3-month intervals were observed in 2.6% of patients. Mild systemic reactions occurred after 2.8% and 4.5% of field and challenge stings respectively. After discontinuation of VIT after 5 years of treatment, two of 24 patients (8.3%) who experienced a field sting had a systemic reaction. Twenty-two patients allergic to honeybee venom were sting challenged after honeybee VIT was discontinued. Only one patient (4.5%) had a mild objective systemic reaction.

The duration of VIT is a subject unto itself. A position paper from the American Academy of Allergy Asthma and Immunology summarized the state of the art in 1998 [29].

Conclusion

Over the past 25 years, major advances have been made in the diagnosis and treatment of insect sting allergy. For most patients, diagnosis is straightforward and treatment with venom injections is very effective. This review of recent literature on the subject of maintenance venom immunotherapy notes the progress investigators are making toward even better outcomes.

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- of special interest
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