

Venom immunotherapy: When is it reasonable to stop

Properly administered venom immunotherapy is extremely effective, providing almost 100% protection to patients at potential risk for insect-sting anaphylaxis.¹ As this treatment for venom-allergic patients has evolved during the past 10 years, unsettled issues remain. One of the major unresolved problems is the duration of immunotherapy, when to stop injections, and assure continued lack of allergic reactions to subsequent stings.

To establish criteria for adequate length of venom immunotherapy, it is necessary to understand the natural history of the disease process. Historically, this begins with the 40-year experience of presumed effectiveness of insect whole body extracts as appropriate therapy for insect-allergic individuals. We now recognize that these whole body extracts are impotent, lacking venom content, ineffective for skin test diagnosis, and comparable to placebo therapy.² The only explanation for this erroneous confidence in whole body extracts is that insect-sting allergy is a self-limiting process for most patients. This point has important ramifications when the effectiveness of venom immunotherapy or criteria for starting or stopping venom immunotherapy are considered.

The appropriate allergens became available for the diagnosis and treatment of insect-allergic patients with the commercial distribution of purified venoms. It became possible to follow the course of individuals presumed to be allergic to insect stings because of a past history of a sting reaction and the presence of venom-specific IgE (positive skin tests or RAST) without intervening immunotherapy. The initial study at The Johns Hopkins Hospital that documented the therapeutic efficacy of venom also demonstrated that 40% of patients suspected to be allergic did not react to intentional stings after placebo or whole body-extract therapy.³ The excellent studies by Schuberth et al.⁴ then demonstrated that the children who have had dermal reactions as the only clinical manifestation of sting anaphylaxis have a remarkably benign course. Re-stings were generally tolerated with no reaction,

and when the reaction did occur, it was similar to the initial set of symptoms. Our own studies have demonstrated that the likelihood of a re-sting allergic reaction is influenced by the time between the re-sting exposure and initial allergic reaction and, most importantly, the severity of the symptoms that occurred with the initial insect-sting reaction.⁵ The longer the interval between the sting exposures, the less likely a re-sting reaction. The milder the initial allergic symptoms, in both adults and children, the less likely a re-sting reaction will occur. Adults with dermal reactions only are unlikely to have subsequent sting reactions. In this regard, these data are not yet sufficient to make the same recommendations as made for children, that these adults do not require venom immunotherapy. In contrast, those individuals, both children and adults, who have had more severe symptoms of anaphylaxis, such as throat edema, hypotension, and loss of consciousness, have a much higher risk of subsequent re-sting anaphylaxis.⁶ Unfortunately, there are no immunologic parameters that can predict the likelihood of a re-sting reaction. The degree of skin test reactivity or titers of serum venom-specific IgE do not predict the occurrence or severity of a re-sting reaction. These clinical and immunologic observations must be taken into account when criteria are developed to define adequate duration of venom immunotherapy.

In recent years, three criteria have been suggested as possible guidelines for stopping venom immunotherapy. Two of these criteria are based on immunologic parameters, the development of negative venom skin tests, and the fall in serum venom-specific IgE to insignificant or undetectable levels. The third criterion is specific duration of therapy generally ranging from 3 to 5 years, independent of the persistence of positive skin tests or serum IgE antibodies.

Conversion to negative skin tests would certainly suggest that sensitivity is no longer present and that therapy can be stopped. In most studies, after 5 years of treatment, only a minority of patients have negative venom skin tests.⁷⁻⁹ In my opinion, the occurrence of negative skin tests would be a definite indication for stopping therapy. It might be reasonable to retest insect-allergic patients who are receiving treatment about every 2 years.

In our own studies, we have used the fall in serum

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venom-specific IgE to insignificant levels as a criterion for stopping therapy.¹⁰ This parameter was chosen because of the concern that the skin test may be too sensitive a test, analogous to those patients with so-called "burned out" ragweed hay fever, who retain positive skin tests for many years. The results of studies applying this criterion did suggest that it is a reliable indicator. The re-sting reaction rate after cessation of therapy in these patients was extremely low. The average duration of therapy was approximately 2 years. Perhaps more importantly, and certainly most impressively, were the results of field re-stings in a control group of patients who stopped therapy by self-choice. The characteristics of this group of patients were almost the same as those in whom treatment was stopped because of a fall in antibody titer. The re-sting reaction rate in patients who stopped therapy by self-choice after an average duration of 2 years was approximately 10%.

The suggestion that a finite period of treatment is sufficient regardless of the persistence of immunologic reactivity was made by The Johns Hopkins Group. Studies in children by Schuberth et al.¹¹ and in adults by Golden et al.⁹ have demonstrated persistent lack of reactions after intentional re-stings for several years after stopping therapy.

In this issue of the JOURNAL, there are two articles^{12, 13} addressing the issue of stopping venom therapy and applying the criterion of a specific duration of therapy, 3 years. There are similarities and differences in the two studies. Müller et al.¹² selected only honeybee venom-allergic patients who had had severe anaphylactic symptoms. Most patients treated by Haugaard and Nørregaard¹³ also had severe symptoms (17 of 25) and were allergic to yellow jacket and honeybee venoms. The average duration of venom therapy was slightly more than 3 years in both studies. All patients of Müller et al.¹² tolerated a sting (field sting or intentional challenge) while they were receiving venom immunotherapy. In the series by Haugaard and Nørregaard, only six of the 25 patients had field re-stings. All stings were tolerated with no difficulty. Intentional re-sting challenges after venom immunotherapy was stopped were done after 1 year by Müller et al.¹² and after 2 years by Haugaard and Nørregaard.¹³ In the patients of Müller et al. there were 15 reactions after 86 re-stings, an incidence of 17%. However, none of these challenge re-sting reactions were severe, and approximately half the patients reported entirely subjective symptoms. Patients with these re-sting reactions had more problems with reactions during immunotherapy, leading the authors to suggest that there might be greater risks stopping therapy in more highly sensitive individuals. The difference in the results be-

tween those patients tolerating field re-stings and those patients tolerating intentional challenges while they were receiving therapy led to their recommendation that therapy could be stopped after 3 years, provided that there is documentation of efficacy by a sting challenge. Obviously, wide spread application of this requirement would be most difficult and impractical. In contrast, in the series by Haugaard and Nørregaard, there were no reactions after 28 sting challenges in 25 patients. Both studies concluded that there are no immunologic parameters that can be applied to document the loss of clinical sensitivity, such as titers of serum venom-specific IgE or venom-specific IgG. The association of minimal skin test reactivity and undetectable serum IgE antibodies, found in only a few patients in the series by Müller et al.¹² did suggest loss of allergy. Taken together, the results of these studies indicate that 3 years of venom immunotherapy is sufficient treatment for insect-sting allergy in high-risk patients, those patients with severe anaphylaxis. Differences in the results of the two studies that are not substantive may be a reflection of the patient's sensitivity or the inclusion of honeybee-sensitive patients only in the series by Müller et al.¹² The authors should be commended for these time-consuming, difficult studies that mark a major contribution to the treatment of venom-allergic individuals.

How then can the allergist practically apply the results of these studies? The major concern is that those patients who have had severe symptoms of insect-sting anaphylaxis have lasting protection. As previously mentioned, if skin tests become negative, therapy can be safely stopped. The issue is management of those patients who have had severe sting anaphylaxis and retain positive skin tests. In these patients, if they are left untreated, the re-sting reaction rates are 50% to 60%. After 2 years of treatment, this risk probably falls to 10% or less. It would appear that further treatment diminishes the likelihood of having a reaction. The additional criterion suggested by Müller et al. that patients tolerate an insect sting, particularly an intentional sting, while they are receiving treatment, is impractical and appears unnecessary in view of the marked effectiveness of venom immunotherapy. At this point, 3 years of treatment appears to be a satisfactory criterion for stopping therapy and should be adopted as a standard of therapy. The current alternatives are additional therapy for a finite period, such as 2 years, making a total of 5 years and indefinite therapy. The results of treatment administered for 3 or 5 years are essentially the same. Indefinite therapy may be advisable only on rare occasions and is unnecessary for most insect-allergic patients.

This final decision requires careful discussion with the patient. If therapy is stopped, it is prudent to continue to recommend the availability of emergency medication. It is hoped that in the future, a specific parameter, perhaps immunologic, can be applied to this clinical decision-making process.

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