

Discontinuing venom immunotherapy

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The decision to discontinue venom immunotherapy requires a great deal of clinical judgement because of the potential for a life-threatening reaction to a sting. The risk of recurrence is a combination of the frequency of reaction and the severity of reaction. Early studies reported a relapse rate of 8–14% in radioallergosorbent test-negative patients when therapy was stopped after 3 years. Unfortunately, the venom skin test or radioallergosorbent test becomes negative in only 25% of patients after 5 years of treatment. An alternative criterion for stopping treatment after 5 years regardless of the skin test has been equally successful, with most post-treatment reactions being much milder than pre-treatment reactions. There was no evidence of a rebound of venom sensitivity when therapy was stopped, even when patients were stung. The level of venom-specific IgE antibodies is better suppressed by 5 than by 3 years of treatment. The risk of relapse is higher in honeybee-allergic patients and in patients who had a systemic reaction (to a sting or an injection) during therapy. The frequency of reaction may be low, but patients who had very severe pre-treatment reactions have a greater chance of the reaction being severe again, and should remain on therapy for life. Long-term observations show that the incidence of systemic reaction to a sting remains 10% for each sting that occurs, even 10–15 years after stopping treatment. Because patients may not react to one sting and then subsequently react to another sting, the cumulative frequency of sting reactions is approximately 17% after 10 years off treatment. Moreover, negative venom skin tests are not a guarantee of safety because there is almost the same 10% frequency of reaction in patients who appear to lose sensitivity. It is not yet clear whether some low-risk patients (children, mild reactors) could discontinue treatment after just 3 years. *Curr Opin Allergy Clin Immunol* 1:353–356. © 2001 Lippincott Williams & Wilkins.

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Abbreviation

RAST radioallergosorbent test

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Introduction

Venom immunotherapy has been a model for the efficacy and reliability of allergen immunotherapy using standardized extracts and treatment regimens. Venom immunotherapy was the first such model and remains one of the best models of immunotherapy, as investigators have explored the long-term outcome of treatment and the immunological changes that occur during treatment [1–3]. Venom immunotherapy has become a routine clinical practice, and there are established guidelines for treatment [4–6]. During maintenance venom immunotherapy, the efficacy is well maintained with treatment every 4–8 weeks, with 98% protection from systemic reactions to stings as long as maintenance therapy is continued. Monitoring of long-term venom immunotherapy should include a periodic measurement of venom skin test sensitivity (or radioallergosorbent test; RAST), a review of any local or systemic reactions that occur from injections or intervening field stings, and an updating of the medical profile of the patient for medical conditions or medications that could affect the treatment or outcome of the insect allergy condition or venom immunotherapy.

The most difficult decision in most cases is whether and when to stop treatment [7]. In the case of inhalant allergen immunotherapy, the decision is often based on the observed efficacy as well as the duration of treatment (usually 3–5 years), although relapses certainly occur and may require changes in medication or the resumption of immunotherapy. Venom immunotherapy has been held to a different standard, presumably because of the potentially life-threatening nature of the disease, which makes physicians and patients unwilling to accept a risk of recurrence, which they would probably accept with ragweed immunotherapy, but which is considered ‘high risk’ for insect sting allergy. Also, there has been no clear agreement on how much risk is ‘too high’ in the case of sting anaphylaxis. The 30–70% risk of a systemic reaction to a subsequent sting in untreated adult patients with sting anaphylaxis is clearly too high, and the 5–10% risk of subsequent systemic reactions in large local reactors is considered acceptable, but there is a grey zone in between in which physician and patient judgement must play an important role in decision-making. Of course, even a 10% risk might be unacceptable if the reaction was likely to be life-threatening. These considerations apply equally to the initiation and the discontinuation of venom immunotherapy. Much research has focused on the ability to predict both the frequency and severity of subsequent reactions to stings,

with limited success. For example, although there is a statistical correlation between the strength of venom skin tests and the chance of systemic reaction, there are many individual exceptions such that the skin test is not a reliable indicator of the frequency or severity of subsequent sting reactions. Many factors have been investigated but none have had a better predictive value.

Loss of sensitivity

The venom product package insert in the USA states that 'at the present time it appears necessary to continue maintenance injections indefinitely', and does not even specify whether therapy could be stopped if the skin test becomes negative (at which time there would, theoretically, no longer be an indication for treatment). The prospect of treatment forever leads many patients to refuse therapy or discontinue treatment early on. Studies of patients who 'dropped out' of treatment after 1–3 years of venom immunotherapy [8,9] reported a 20–30% risk of reaction to subsequent stings. Because one would expect reasonable safety if the sensitivity disappears, early studies of discontinuing venom immunotherapy focused on patients who had lost venom sensitivity. Reports of stopping venom immunotherapy in patients who had a negative RAST [10,11] described systemic reactions to subsequent stings in 5–14% of cases (despite the apparent absence of specific IgE antibodies). Unfortunately, most patients do not lose sensitivity during 5 years or more of treatment. For example, venom skin tests become negative (at 1.0 µg/ml) in only 25% of cases after 5–6 years' treatment [12,13]. This approach to the problem would thus only allow for discontinuation in a minority of patients after 5 years of therapy, and would require 7–10 years of treatment in most patients.

Duration of therapy

An alternative approach is to define a specific length of time such as 3 or 5 years, after which stopping treatment would not lead to an unacceptable frequency of significant systemic reactions to subsequent stings. Some investigators reported success in stopping treatment after 3 years, but they generally also included other criteria such as a negative RAST and negative sting challenge during therapy [14–16]. Once again, the potential for stopping treatment after 3 years would only apply to a small portion of patients and might not be feasible in practice when sting challenge during therapy could not be performed. Immunological observations of maintenance venom immunotherapy showed that the venom-specific IgE levels, which rise during the initial months of therapy, decline gradually during years of treatment, generally falling to low levels by the fourth or fifth year on treatment. The venom-specific IgG antibody levels are maintained at therapeutic levels during this treatment. The relationship of the venom-IgG level to clinical protection is significant in the first 3 years of treatment

but not after 4 years [17]. It was these early observations that led to the hypothesis that after 4 years of therapy there was a suppressive mechanism of protection that might persist even if treatment was discontinued.

Our studies at Johns Hopkins therefore selected patients who had at least 5 years of maintenance treatment, regardless of any other factors. We found after a mean of 6 years of treatment that skin test sensitivity, although still present in most patients, had diminished by a factor of 10 in 95% of the patients. In the years after stopping treatment, venom sensitivity continued to decline without being affected by the challenge stings we performed every 1–2 years in the 74 patients studied [13]. Immunologically, we were able to show that the venom-specific IgE level declines in parallel with the venom skin test sensitivity during 5–8 years' venom immunotherapy, and both continue to decline in a linear fashion during the 5 years after stopping venom immunotherapy. Of special interest is the fact that the risk of systemic sting reaction did not increase either spontaneously after discontinuing venom immunotherapy (de-suppression), or as a result of stings (re-sensitization). These results implied that the risk of a systemic reaction to a sting would ultimately diminish to zero. Sting challenges revealed that the reaction rate was less than 3% in skin test-negative patients and only 8% in patients who remained skin test positive at the time of sting. Similar studies in children who stopped therapy after 5 years also showed a very low risk of reaction to subsequent stings [18].

Initially, several investigators observed that the risk of reaction actually seemed to decrease with time after stopping treatment. In the early studies at Johns Hopkins, there were mild-to-moderate systemic reactions in the first 2 years after stopping treatment, but only a few mild reactions after 4–5 years. The Mayo Clinic studies of Keating *et al.* [19] reported similar results, showing that sting reactions occur more commonly in the first year or two after stopping prolonged venom immunotherapy. However, in patients who had received only 1–3 years of therapy, systemic sting reactions tended to occur even up to 10 years after discontinuing treatment, again distinguishing the immunological effects of prolonged immunotherapy. Keating *et al.* [19] also showed that venom-specific IgE antibody levels are suppressed only after 4–5 years of venom immunotherapy, which correlated with the safety of discontinuing venom immunotherapy after 5 years. Our data suggest that the suppression of venom-specific IgE antibodies may also be isotype specific, because the venom-specific IgG antibody response to challenge stings was significantly greater than the IgE response. One notable exception was the patients who relapsed and had a systemic reaction to challenge sting, in whom

the IgE response to the sting was significantly greater than in non-reactors.

Severity of history

Another important criterion has emerged as a predictor of the risk of relapse. The severity of the sting reaction before venom immunotherapy has been reported as perhaps the most important determinant of the risk of reaction after stopping therapy [16,19]. The studies at Johns Hopkins showed the same rate of reaction in subjects with a previous history of mild cutaneous reactions (2/20) as in the total group (7/74), and Muller *et al.* [15] found 'no difference between reactors and non-reactors regarding severity of the systemic reaction before treatment'. However, all these investigators agree that even if the chance of reaction is the same for all patients, patients with a history of extreme (near-fatal) anaphylaxis have a higher chance of the reaction being dangerous once again. This leads to the conclusion that patients who had life-threatening reactions should continue venom immunotherapy indefinitely.

Some experts suggest that therapy be discontinued after just 3 years in patients who are at 'low risk' because of either a very mild history or younger age. There is limited evidence in this regard. In most of the studies suggesting discontinuation after 3 years, the patients studied had a range of 3–7 years of venom immunotherapy (with a mean duration of 4–5 years), but relatively few had only 3 years' treatment, so firm conclusions are not easily drawn. Most of the children studied had mild anaphylaxis, which is in itself a predictor of lower risk. Very few adults with mild reactions have been studied, so the safety of stopping after 3 years in such patients is uncertain. The Mayo Clinic studies found a lower risk of systemic reaction after 5 years than after 3 years' treatment. Lerch and Muller [20] initially suggested that 3 years was sufficient, but extended studies have led them to conclude that 5 years' therapy is associated with a lower chance of relapse.

One additional concern has been the difference between honeybee and vespid-sensitive patients. Honeybee venom immunotherapy is associated with a higher frequency of systemic reactions to the venom injections and a higher incidence of treatment failures [21]. It should therefore not surprise us that honeybee-sensitive patients also have a greater chance of relapse when therapy is discontinued, regardless of the historical severity, the skin test or RAST results, or the duration of therapy [5].

Long-term outcome

The long-term outcome of discontinuing venom immunotherapy seemed certain to be benign on the basis of the results of early studies showing the progressive

disappearance of the venom IgE (by skin test or RAST) and the lack of re-sensitization by intervening stings. Those studies also reported that the risk of reaction seemed to decline with time after discontinuation. However, subsequent reports have revealed some unexpected problems, and suggest that the risk does not disappear. During our prospective observation of patients at Johns Hopkins who discontinued venom immunotherapy, we observed that some patients did have systemic reactions to stings more than 10 years after stopping treatment. An analysis of the data on 113 patients [22] showed that the frequency of systemic reaction to a sting was 10% for stings occurring in the first 4 years off therapy, and was also 10% for stings occurring 5–13 years after treatment. The early reports of a declining risk of reaction with time may thus not be correct. Reisman [16] also found that the time elapsed since stopping venom immunotherapy did not seem to affect the incidence of sting reactions, with approximately a 10% reaction rate even after 5 years or more off therapy (although the published report does not indicate the full range of years off treatment). However, it is interesting that Lerch and Muller [20] noted a higher reaction rate in years 3–5 after stopping treatment (14%) than in years 1–2 (5.5%) or in years 6–7 (7.5%). Their data would still hold out the hope that the risk would become very small after more than 10 years, but there are not enough reports of such long-term observations, especially beyond 7 years.

In the Johns Hopkins population, we also found that the reaction rate was the same (10%) in patients who developed negative skin test responses to venoms. We described a total of eight patients with negative venom skin tests who subsequently had systemic reactions to stings [22,23]. Although most of those reactions were relatively mild, a few were severe and one was nearly fatal. All the skin test-negative patients had detectable venom-IgE in our laboratory assay. We also observed that there were patients who had no reaction to one sting and then had a reaction to a subsequent sting. Conversely, there were some patients who had a reaction to a sting, refused to resume venom immunotherapy and had a subsequent sting that did not cause any reaction. This is no different from the observation that untreated patients can react to some stings and not react to others [24] (see Table 1).

Conclusion

The decision to discontinue venom immunotherapy must take into account the available published observations, the individual's pattern of reaction and the judgement of both the allergist and the patient. Several specific factors are associated with a greater risk of relapse, but all patients must be aware that they will continue to have a 10% chance of having a reaction to a

Table 1. Discontinuing venom immunotherapy: reported studies and criteria

Author (ref.)	Patients	Criteria studied	Criteria recommended
Graft <i>et al.</i> [18]	Children	5–7 years ^a	5 years
Urbanek <i>et al.</i> [10]	Children	RAST neg	RAST neg
Randolph and Reisman [11]	Adults and children	RAST neg	RAST neg
Keating <i>et al.</i> [19]	Adults, some children	2–10 years ^a	5 years
Haugaard <i>et al.</i> [14]	Adults	3–7 years ^a	3 years
Muller <i>et al.</i> [15]	Adults; some children	3–10 years ^a	3 years ^a
Reisman [16]	Adults and children	1–6 years	3+ years
Golden <i>et al.</i> [13]	Adults	5–7 years	5 years
Lerch and Muller [20]	Adults, some children	3–10 years ^a	5 years
Golden <i>et al.</i> [22]	Adults	5–7 years	5 years ^b

RAST, Radioallergosorbent test.

^aNegative sting challenge included as criterion for discontinuation.

^bExcluding patients with life-threatening reaction history, honeybee allergy or systemic reaction during venom immunotherapy.

future sting, even if venom skin tests become negative, and even if there is no reaction to a sting after stopping treatment. The only way to keep the risk down to 2% is to remain on maintenance venom immunotherapy.

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References

- Lichtenstein LM. Insect allergy: The state of the art. *J Allergy Clin Immunol* 1979; 64:5–12.
- Valentine MD. Insect sting anaphylaxis. *Ann Intern Med* 1993; 118:225–226.
- Reisman RE. Venom hypersensitivity. *J Allergy Clin Immunol* 1994; 94:651–658.
- Golden DBK, Schwartz HJ. Guidelines for venom immunotherapy. *J Allergy Clin Immunol* 1986; 77:727–728.
- Muller U, Mosbech H. Position paper: immunotherapy with *Hymenoptera* venoms. *Allergy* 1993; 48 (Suppl. 14):37–46.
- Portnoy JM, Moffitt JE, Golden DBK, *et al.* Stinging insect hypersensitivity: a practice parameter. *J Allergy Clin Immunol* 1999; 103:963–980.
- Graft DF, Golden DBK, Reisman RE, *et al.* The discontinuation of Hymenoptera venom immunotherapy. Report from the Committee on Insects of the American Academy of Allergy Asthma and Immunology. *J Allergy Clin Immunol* 1998; 101:573–575.
- Golden DBK, Johnson K, Addison BI, *et al.* Clinical and immunologic observations in patients who stop venom immunotherapy. *J Allergy Clin Immunol* 1986; 77:435–442.
- Reisman RE, Dvorin DD, Randolph CC, Georgitis JW. Stinging insect allergy: natural history and modification with venom immunotherapy. *J Allergy Clin Immunol* 1985; 75:735–740.
- Urbanek R, Forster J, Kuhn W. Discontinuation of bee venom immunotherapy in children and adolescents. *J Pediatr* 1985; 107:367–371.
- Randolph CC, Reisman RE. Evaluation of decline in serum venom-specific IgE as a criterion for stopping venom immunotherapy. *J Allergy Clin Immunol* 1986; 77:823–827.
- Golden DBK, Addison BI, Gadde J, *et al.* Prospective observations on patients who discontinue venom immunotherapy. *J Allergy Clin Immunol* 1989; 84:162–167.
- Golden DBK, Kwiterovich KA, Kagey-Sobotka A, *et al.* Discontinuing venom immunotherapy: outcome after five years. *J Allergy Clin Immunol* 1996; 97:579–587.
- Haugaard L, Norregaard OFH, Dahl R. In-hospital sting challenge in insect venom-allergic patients after stopping venom immunotherapy. *J Allergy Clin Immunol* 1991; 87:699–702.
- Muller U, Berchtold E, Helbling A. Honeybee venom allergy: results of a sting challenge 1 year after stopping venom immunotherapy in 86 patients. *J Allergy Clin Immunol* 1991; 87:702–709.
- Reisman RE. Duration of venom immunotherapy: relationship to the severity of symptoms of initial insect sting anaphylaxis. *J Allergy Clin Immunol* 1993; 92:831–836.
- Golden DBK, Lawrence ID, Kagey-Sobotka A, *et al.* Clinical correlation of the venom-specific IgG antibody level during maintenance venom immunotherapy. *J Allergy Clin Immunol* 1992; 90:386–393.
- Graft DF, Schuberth KC, Kagey-Sobotka A, *et al.* The development of negative skin tests in children treated with venom immunotherapy. *J Allergy Clin Immunol* 1984; 73:61–68.
- Keating MU, Kagey-Sobotka A, Hamilton RG, Yunginger JW. Clinical and immunologic follow-up of patients who stop venom immunotherapy. *J Allergy Clin Immunol* 1991; 88:339–348.
- Lerch E, Muller U. Long-term protection after stopping venom immunotherapy. *J Allergy Clin Immunol* 1998; 101:606–612.
- Muller U, Helbling A, Berchtold E. Immunotherapy with honeybee venom and yellow jacket venom is different regarding efficacy and safety. *J Allergy Clin Immunol* 1992; 89:529–535.
- Golden DBK, Kwiterovich KA, Addison BA, *et al.* Discontinuing venom immunotherapy: extended observations. *J Allergy Clin Immunol* 1998; 101:298–305.
- Golden DBK, Kagey-Sobotka A, Lichtenstein LM. Survey of patients after discontinuing venom immunotherapy. *J Allergy Clin Immunol* 2000; 105:385–390.
- Franken HH, Dubois AEJ, Minkema HJ, *et al.* Lack of reproducibility of a single negative sting challenge response in the assessment of anaphylactic risk in patients with suspected yellow jacket hypersensitivity. *J Allergy Clin Immunol* 1994; 93:431–436.