

Rapid venom immunotherapy update

Troy A. Scribner^a and David I. Bernstein^b

Purpose of review

This paper will review new indications for the administration of rapid or ultrarush venom immunotherapy and the advantages of pretreatment with antihistamines.

Recent findings

Rapid and ultrarush venom immunotherapy protocols have been successfully employed to achieve protective maintenance venom doses rapidly. These have been associated with systemic reactor rates as low as 5–7%. Recently, rapid venom immunotherapy protocols have been successfully employed to reach ultra-high maintenance doses for patients not previously protected with standard maintenance doses (i.e. 100 µg). There is also evidence that pretreatment with antihistamines before venom injections during rapid venom immunotherapy may reduce the numbers and severity of injection-related systemic reactions, as well as improve long-term outcomes in preventing subsequent resting systemic reactions in the field.

Summary

Pretreatment with antihistamines should be considered in patients receiving rapid or ultrarush venom injections. Ultrarush or rapid immunotherapy regimens compare favorably with conventional modified rush protocols in terms of side-effects, and may be considered in order to achieve higher but effective maintenance venom doses in those rare patients who are treatment failures.

Introduction

The indications for the administration of venom immunotherapy (VIT) are well-established [1,2]. The modified rush protocol is the protocol that is predominantly used in North America for the initiation of VIT [3]. However, alternative protocols have been advocated for the rapid initiation of VIT over intervals ranging from 1.5 h to 7 days in order to achieve maintenance doses quickly [4,5]. These methods are quite variable, and despite established practice guidelines for VIT no standard rapid venom immunotherapy (RVIT) protocols have been widely adopted. In this article, data will be discussed that begin to address optimal dosing regimens and the role of premedication for RVIT. A new application of RVIT will also be discussed, which is the use of this approach to achieve ultra-high maintenance venom doses in rare *Hymenoptera*-allergic patients who experience systemic reactions on standard maintenance venom doses.

Optimal induction protocols for rapid venom immunotherapy

An ideal alternative VIT protocol should present no greater risk than modified rush, the current standard of treatment. Various RVIT protocols have been reported with time-to-target maintenance doses ranging from 2 days to 7 weeks. These generally employ a more rapid induction phase, and are often conducted in the hospital. With the introduction of VIT, investigators studied a variety of protocols for the rapid delivery of venom. In 1979, Yunginger *et al.* [6] reported a study of RVIT in which he delivered a maximal single dose of 200 µg of honey bee venom over 2–3 days, which was planned to be repeated monthly. As a result of an unacceptably high rate of treatment-related anaphylaxis and high frequencies of treatment failure (i.e. inability to tolerate a live sting challenge), this approach was abandoned [6]. In 1983, Van der Zwan *et al.* [7] proposed a novel protocol in treating wasp allergic patients by giving incremental doses every 30 min (5, 20, 30, 60 and 100 µg) on a single day. This was consolidated by 100 µg booster injections given at 7, 14 and 28 days. No systemic reactions occurred during the build-up phase or with the booster injections, nor did any of the 11 patients experience reactions to live wasp stings [7].

There have been few attempts to compare directly the safety profiles of different RVIT protocols. In a study by Birnbaum *et al.* [5], three separate protocols for rapidly increasing venom doses were used with induction phases of 3 h, 6 h and 4 days. The cumulative doses delivered

Curr Opin Allergy Clin Immunol 3:295–298. © 2003 Lippincott Williams & Wilkins.

^aCincinnati Children's Hospital, Division of Allergy and Medical Center, Cincinnati, Ohio, USA; and ^bUniversity of Cincinnati College of Medicine, Department of Internal Medicine, Division of Immunology/Allergy, Cincinnati, Ohio, USA

Correspondence to David I. Bernstein, MD, University of Cincinnati College of Medicine, 231 Albert Sabin Way, M.L. #563, Cincinnati, OH 45267, USA
Fax: +1 513 558 3799; e-mail: bernstd@email.uc.edu

Current Opinion in Allergy and Clinical Immunology 2003, 3:295–298

Abbreviations

VIT venom immunotherapy
RVIT rapid venom immunotherapy

© 2003 Lippincott Williams & Wilkins
1528-4050

were 101.1, 226.6 and 527.6 μg , respectively. The authors found lower percentages of systemic reactors in the group with the shortest induction time and lowest cumulative total dose; i.e. 7% reacted during the 3 h protocol versus 29 and 28% during the 6 h and 4 day protocols, respectively. They concluded that a high cumulative dose was associated with an increased risk of systemic reactions. That experience was supported by studies reported by Bernstein *et al.* [8] in which a cumulative dose of 58.55 μg per treatment venom was given over 90 min on day 1 of treatment. In the 77 patients treated by this protocol, only four patients (5.2%) experienced mild systemic reactions.

A recent report by Brehler *et al.* [9] described a comparison of three RVIT protocols. These investigators compared three induction schedules whose aim was to achieve a 100 μg maintenance dose over 2 days (nine injections), 3–6 days (10–14 injections) or 7–9 days (20 injections). The investigators found that the group receiving nine injections over 2 days had a lower percentage of systemic reactors. For those receiving yellow jacket RVIT, the percentages of patients experiencing systemic reactions were 11.0, 13.9 and 22.9 for 2 days, 3–4 days and 5–7 days, respectively. A similar trend was seen in those patients receiving honey bee RVIT; however, differences between reactor rates were not significant. The authors concluded that the number of injections is directly proportional to the incidence of systemic reactions. However, unlike other studies, there was no correlation between the cumulative dose and systemic reactor rates. Studies using modified rush protocols have reported systemic reactor rates of between 12 and 18% [3,10]. It thus appears that systemic reactor rates with RVIT are either equivalent or in some cases lower than those reported in clinical trials for modified rush VIT.

Whereas the group of Brehler *et al.* [9] concluded that there was no direct correlation between the cumulative dose and the rate of systemic reactors, their data deserve further examination. The two longer protocols had low cumulative doses on day 1, never exceeding 30 μg . The latter protocols may thus not be comparable with the 2-day protocol and those proposed by Bernstein *et al.* [4] and Birnbaum *et al.* [5]. The increased systemic reactor rates of the 5–7 day and 3–4 day protocols may be related to inadequate build-up doses on day 1 and ineffective desensitization. In the 2-day protocol reported by Brehler *et al.* [9], the majority of the systemic reactions occurred at the last dose on day 1; i.e. at a cumulative dose of 151 μg and after an 80 μg dose. Although the data were not provided by the authors, it is likely that the systemic reactor rate may have been considerably reduced had dosing on day 1 been stopped after a 71 μg cumulative dose had been achieved. Current data thus

suggest that the best therapeutic index can be achieved with RVIT by the administration of cumulative doses of 50–100 μg per venom on day 1 [4,5]. In view of the difficulty in comparing different studies by different authors or conducted at different timepoints, these results need to be confirmed in a prospective randomized controlled trial.

A novel application for rapid venom immunotherapy

Most patients receive excellent protection from VIT at the standard maintenance doses. Golden *et al.* [3] initially evaluated the efficacy of different maintenance doses. They demonstrated nearly 100% efficacy with a 100 μg dose, but the maintenance dose of 50 μg resulted in only 79% protection from re-sting challenges. A recent paper examined the efficacy of ultra-high venom maintenance doses in patients who failed conventional maintenance doses (i.e. 100 μg). A retrospective analysis was conducted on 40 patients who had positive sting challenges while receiving 100 μg every 4 weeks, and were subsequently administered higher doses followed by a repeat sting challenge [11]. These investigators employed a 3-day protocol that increased the maintenance dose from 100 to 200 μg . After achieving dose increases to either 150 or 200 μg , 15 out of 18 patients receiving honey bee venom and 21 out of 22 patients receiving yellow jacket venom had no reactions to live sting challenge. The dose increases were well tolerated, although systemic reaction rates were not well defined. Bousquet *et al.* [12] reported five patients who were treatment failures and experienced systemic reactions while on conventional doses of maintenance immunotherapy. Maintenance doses were increased by a rush protocol until monthly doses of 200–400 mg of honey bee venom were achieved, which were protective. RVIT is thus a viable modality for achieving higher maintenance doses in patients who are not protected by VIT at conventional maintenance doses.

Premedication with antihistamines

Randomized, placebo-controlled studies [13–15] have evaluated the effects of pretreatment with antihistamines before VIT. The frequency and severity of local reactions are reduced with pretreatment. However, these benefits have been reported exclusively during the early stages of VIT. While the benefit of H₁-antagonists is well documented in VIT, the value of H₂-antagonists administered in combination with H₁-blockers or alone has not been substantiated [15].

The influence of antihistamine pretreatment on systemic reactions associated with RVIT is controversial. Most studies have not shown reductions in the incidence of systemic reactions. However, Brockow *et al.* [15] reported that antihistamine pretreatment was associated

with a much lower rate of discontinuation of VIT as a result of systemic reactions. Sturm *et al.* [16••] recently reported their experience in 101 *Hymenoptera*-allergic patients over 8 years who were administered a rapid immunotherapy protocol. The dose schedule employed cumulative doses of 0.7, 13.8, 138, and 180 μ g venom on days 1, 2, 3 and 4, respectively. Of the patients treated, 51% were sensitized to honey bee venom. Patients were pretreated with intravenous dimetidine maleate, a first-generation H_1 -antagonist, 60 min before venom dosing. After completion of the RVIT regimen, patients were treated monthly with 100 μ g of alum-adsorbed venom. The rate of systemic reactions per number of injections administered was 0.79% for bee venom and 0.12% for yellow jacket venom, confirming previous studies showing a higher number of reactions associated with honey bee venom [16••]. Seven per cent of treated patients experienced systemic reactions, including 12% of honey bee venom-treated and 2% of yellow jacket venom-treated patients. However, none of the systemic reactions were considered severe; epinephrine was not required to treat one of the eight systemic reactions. This outcome was impressive compared with 14 previous investigations of rush or cluster regimens associated with a mean 11.3% systemic rate [16••]. A similar benefit was observed with a protocol that employed antihistamine pretreatment with birch or grass-pollen immunotherapy [17]. A common concern focuses on the potential for H_1 -blockers to mask the early signs of potentially serious systemic reactions. Four placebo-controlled studies employing antihistamine pretreatment showed no greater number of severe systemic reactions or late-onset systemic reactions in pretreatment versus placebo groups [13–15].

It has recently been suggested that pretreatment with antihistamines can also increase the efficacy of immunotherapy. Muller *et al.* [18] reported the results of a long-term follow-up of 47 patients enrolled previously in a placebo-controlled trial of antihistamine pretreatment for VIT. Forty-one of the patients had been stung while receiving maintenance immunotherapy, either by field sting or in-hospital challenge. Six of the 21 patients from the placebo-treated group had systemic reactions after sting challenge, whereas none of the terfenadine pretreated patients reacted. Although the reactions were primarily mild (urticaria and angioedema), 29% of patients in the placebo group were incompletely protected. The inhibition of T helper type 2 cytokine production by antihistamines has been hypothesized to explain the latter observation [19].

Conclusion

RVIT can be accomplished with either an equivalent or lesser risk of systemic reactions than conventional modified rush protocols. Generally shorter RVIT proto-

cols (<24 h) are better tolerated than those that span several days. Optimal first-day induction schedules appear to employ cumulative doses of between 50 and 100 μ g. The utilization of RVIT can reduce the cost and time commitment for clinics as well as patients. Pretreatment with antihistamines during RVIT lowers the frequency and severity of local cutaneous reactions, and may reduce the number of treatment failures caused by injection-related systemic allergic reactions. Pretreatment with H_1 -blockers provides improved patient comfort during the procedure without interfering with the physician's recognition of systemic reactions to venom. There is minimal evidence to suggest that pretreatment with antihistamines prevents systemic reactions. The observation that pretreatment with antihistamines improves the long-term efficacy of VIT is interesting but must be confirmed in future clinical trials.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
 - of outstanding interest
- 1 Hunt KJ, Valentine MD, Sobotka AK, *et al.* A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 1978; 299:157–161.
 - 2 Barsky HE. Stinging insect allergy. Avoidance, identification, and treatment. *Postgrad Med* 1987; 82:157–158; 161–162.
 - 3 Golden DB, Valentine MD, Sobotka AK, Lichtenstein LM. Regimens of *Hymenoptera* venom immunotherapy. *Ann Intern Med* 1980; 92:620–624.
 - 4 Bernstein DI, Mittman RJ, Kagen SL, *et al.* Clinical and immunologic studies of rapid venom immunotherapy in *Hymenoptera*-sensitive patients. *J Allergy Clin Immunol* 1989; 84:951–959.
 - 5 Birnbaum J, Charpin D, Vervloet D. Rapid *Hymenoptera* venom immunotherapy: comparative safety of three protocols. *Clin Exp Allergy* 1993; 23:226–230.
 - 6 Yunginger JW, Paull BR, Jones RT, Santrach PJ. Rush venom immunotherapy program for honeybee sting sensitivity. *J Allergy Clin Immunol* 1979; 63:340–347.
 - 7 van der Zwan JC, Flinterman J, Jankowski IG, Kerckhaert JA. Hyposensitisation to wasp venom in six hours. *BMJ (Clin Res Ed)* 1983; 287:1329–1331.
 - 8 Bernstein JA, Kagen SL, Bernstein DI, Bernstein IL. Rapid venom immunotherapy is safe for routine use in the treatment of patients with *Hymenoptera* anaphylaxis. *Ann Allergy* 1994; 73:423–428.
 - 9 Brehler R, Wolf H, Kutting B, *et al.* Safety of a two-day ultrarush insect venom immunotherapy protocol in comparison with protocols of longer duration and involving a larger number of injections. *J Allergy Clin Immunol* 2000; 105:1231–1235.
 - 10 Lockett RF, Turkeltaub PC, Olive CA, *et al.* The *Hymenoptera* venom study. II: Skin test results and safety of venom skin testing. *J Allergy Clin Immunol* 1989; 84:967–974.
 - 11 Rueff F, Wenderoth A, Przybilla B. Patients still reacting to a sting challenge while receiving conventional *Hymenoptera* venom immunotherapy are protected by increased venom doses. *J Allergy Clin Immunol* 2001; 108:1027–1032.
 - 12 Bousquet J, Menardo JL, Velasquez G, Michel FB. Systemic reactions during maintenance immunotherapy with honey bee venom. *Ann Allergy* 1988; 61:63–68.
 - 13 Reimers A, Hari Y, Muller U. Reduction of side-effects from ultrarush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial. *Allergy* 2000; 55:484–488.
 - 14 Berchtold E, Maibach R, Muller U. Reduction of side effects from rush-immunotherapy with honey bee venom by pretreatment with terfenadine. *Clin Exp Allergy* 1992; 22:59–65.

- 15 Brockow K, Kiehn M, Riethmuller C, *et al.* Efficacy of antihistamine pretreatment in the prevention of adverse reactions to *Hymenoptera* immunotherapy: a prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 1997; 100:458–463.
 - 16 Sturm G, Kranke B, Rudolph C, Aberer W. Rush *Hymenoptera* venom •• immunotherapy: a safe and practical protocol for high-risk patients. *J Allergy Clin Immunol* 2002; 110:928–933.
- A 4-day regimen of rapid venom immunotherapy combined with a novel pre-treatment regimen of an intravenous H1 blocker was successfully used to treat 101 patients with *Hymenoptera* anaphylaxis
- 17 Nielsen L, Johnsen CR, Mosbech H, *et al.* Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 1996; 97:1207–1213.
 - 18 Muller U, Hari Y, Berchtold E. Premedication with antihistamines may enhance efficacy of specific-allergen immunotherapy. *J Allergy Clin Immunol* 2001; 107:81–86.
 - 19 Munakata Y, Umezawa Y, Iwata S, *et al.* Specific inhibition of TH2-type cytokine production from human peripheral T cells by terfenadine *in vitro*. *Clin Exp Allergy* 1999; 29:1281–1286.