

Venom immunotherapy: adverse reactions and treatment failure

Franziska Ruëff and Bernhard Przybilla

Purpose of review

Side effects of venom immunotherapy and lack of efficacy represent significant problems in the treatment of patients allergic to Hymenoptera venom. Among these side effects systemic anaphylactic reactions and large local reactions are the most important. This review aims to discuss new insights in frequency, pathogenesis and handling of these common side effects and of treatment failure during venom immunotherapy.

Recent findings

Several studies showed that severe side effects due to venom immunotherapy are rare. Recently published studies focus on ultrarush protocols and report good tolerance of an ultrarush venom immunotherapy in which the maintenance dose was reached within several hours or 2 days, respectively. Compared to the use of aqueous extracts (administered according to a rush protocol), frequency of local and also systemic side effects was lower when depot extracts and schedules with a slow conventional dose increase were applied. Concomitant treatment with H₁-antihistamines was found to reduce local and mild systemic adverse reactions during venom immunotherapy. Up to 25% of patients are not protected when re-stung while on venom immunotherapy with the usual maintenance dose of 100 µg of venom every 4–8 weeks. These patients can achieve full protection by increasing the maintenance dose.

Summary

Conventional dose increase using depot extracts is better tolerated than if aqueous extracts are being administered. Concomitant treatment with H₁-antihistamines may be helpful. Increasing the venom dose to 200 µg or even more may be therapeutically effective in patients not protected by a lower maintenance dose. To compare tolerance of different treatment protocols prospective comparative studies are required.

Keywords

ACE inhibitor, beta-blocker, dose increase, efficacy, serum tryptase, side effects, sting challenge, venom immunotherapy

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Department of Dermatology and Allergy, Campus Innenstadt, Ludwig-Maximilian University, Munich, Germany

Correspondence to Dr Franziska Ruëff, Klinik und Poliklinik für Dermatologie und Allergologie, Ludwig-Maximilians-Universität, Frauenlobstraße 9–11, 80337 München, Germany
Tel: +49 89 5160 6170; fax: +49 89 5160 6162
e-mail: Franziska.Rueff@lrz.uni-muenchen.de

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Abbreviations

ACE angiotensin-converting enzyme
LLR large local reaction
SAR systemic anaphylactic reaction

Introduction

Systemic anaphylactic reactions (SARs) to Hymenoptera stings are potentially life-threatening. Venom immunotherapy was established as the causal treatment for Hymenoptera-venom-allergic patients more than two decades ago [1,2]. Side effects of this treatment are not rare. Local reactions to varying extents occur in nearly all patients at the site of the injection. In contrast to local reactions, SARs to venom immunotherapy are significantly more relevant for the outcome of the patient. Venom immunotherapy performed with standard venom doses protects most, but not all, patients. Side effects and insufficient efficacy of venom immunotherapy are important aspects in the treatment of allergic patients. In this review we would like to address recent related findings that are relevant for patient management.

Side effects of venom immunotherapy

Venom immunotherapy aims to induce tolerance to re-stings in subjects with a previous SAR to a Hymenoptera sting. However, the treatment itself can be complicated by the SARs that one actually wants to prevent. Other frequent side effects are large local reactions (LLRs) at the site of the injection, commonly defined as swelling and erythema with a diameter of more than 10 cm and usually lasting for more than 24 h. Nonspecific subjective symptoms, such as headache or fatigue, also occur frequently. Analysis of published studies shows that many trials often do not differentiate between SARs and such nonspecific symptoms. Other adverse effects of venom immunotherapy, e.g. serum sickness, are extremely rare, and are not discussed here.

In a recent multicentre study evaluating data from 840 patients, side effects to venom immunotherapy occurred in a total of 20% of the patients [3]. The majority of these reactions was mild, and only one-third required medical treatment. A similar frequency of systemic side effects was seen in a recently published study analysing data of 178 patients [4].

In retrospective studies the frequency of systemic side effects to venom immunotherapy was compared with that to aeroallergens [5,6]. One study reported data of 657 patients on immunotherapy [5]. Of a group of 117 patients on venom immunotherapy, 28% had side effects of some kind. When compared to other allergens, respective frequencies were 53% in 272 patients treated with grass pollen, 59% in 32 patients treated with cat extracts and 57% in 54 patients treated with mite extracts ($P < 0.01$). If nonspecific side effects were not

considered, patients on venom immunotherapy had SARs significantly ($P < 0.01$) less often (9%) than subjects treated with cat (41%), mite (35%) or grass-pollen (29%) preparations [5]. Similar findings were reported in a retrospective study in 1212 subjects on immunotherapy of whom 192 were treated with Hymenoptera venoms [6]. SARs were less frequent in patients treated with venom extracts than in patients treated with pollen extracts, and 96% of SARs occurring in patients on venom immunotherapy were mild.

Thus, the severity of side effects due to specific immunotherapy does not necessarily correlate with the severity of symptoms of the treated allergic disease. Only a few SARs induced by venom immunotherapy are severe, and the large majority of patients tolerate venom immunotherapy without relevant side effects.

Risk factors of side effects

The incremental phase of venom immunotherapy is more often affected by side effects than the maintenance phase [3,7]. In a large prospective study evaluating the tolerance of 26 601 injections in 840 patients, SARs were observed in 1.9% of the injections during the dose-increase phase and only in 0.5% during the maintenance phase ($P < 0.05$) [3].

Several studies confirmed previously published data and showed that treatment with honey bee venom induces SARs more frequently than treatment with vespid venoms [3,8–10,11•].

There are no data indicating that beta-blockers increase the frequency of SARs during venom immunotherapy. However, if a SAR occurs in a patient on beta-blocker treatment, symptoms may be more severe and harder to treat. Therefore, it has been recommended to withdraw beta-blockers before venom immunotherapy is started [12,13]. Recently, a case report described a fatality occurring during the dose-increase phase of venom immunotherapy [14]. This event was not attributable to a venom-immunotherapy-induced SAR but was probably due to the withdrawal of a beta-blocker in a patient who had been treated for ventricular arrhythmia. Thus the recommendation to withdraw beta-blockers before starting venom immunotherapy has to be weighed against individual risk factors of the patient. Life-sustaining drugs, which cannot be substituted by other compounds, will have to be continued. If and how venom immunotherapy is performed in these rare patients has to be decided on an individual basis.

In German-speaking countries a warning against angiotensin-converting enzyme (ACE) inhibitors has been included in the product information of immunotherapy preparations for several years. This recommendation was

based on a case report of two patients who had SARs during venom immunotherapy while being treated with an ACE inhibitor and who tolerated treatment after withdrawal of the drug [15]. Recently, a similar case report from the USA [16] attracted new attention to the possible role of ACE inhibitors as a risk factor for SARs in patients on venom immunotherapy. This patient developed anaphylactic shock during the incremental phase and tolerated treatment well after the drug was discontinued. However, such reactions may also occur in patients not receiving drugs during venom immunotherapy. Thus far, clinical evidence which would convincingly prove ACE inhibitors to significantly aggravate anaphylaxis is not available and further data are required in this respect.

In recent years the role of mast cell disease in anaphylaxis, evident from an elevated baseline serum tryptase concentration and/or mastocytosis, has been assessed in patients with Hymenoptera venom allergy. Elevated baseline serum tryptase levels with or without proven mastocytosis were found to be significantly associated with particularly severe anaphylactic sting reactions [11•,17]. However, there is no indication that patients with mast cell disease would be at risk of a higher frequency of SARs due to venom immunotherapy. Thus frequency of SARs was not higher in patients with mast cell disease than in those without it [11•,18,19]. However, a few patients with mastocytosis repeatedly had severe anaphylactic reactions to venom immunotherapy which resulted in premature stoppage of treatment [20,21].

Ultrarush venom immunotherapy

A plethora of treatment protocols for the incremental phase of venom immunotherapy have been published and are in use. The common aim is to reach a maintenance dose of 100 µg of venom. Treatment protocols vary with respect to number of injections, venom doses and time needed to reach the final dose.

Recently ultrarush venom immunotherapy – dating back to reports published more than two decades ago [22] – has gained new interest. Several retrospective studies compared various rush and ultrarush protocols [8,23]. An ultrarush venom immunotherapy protocol in which the maintenance dose was reached within 3.5 h provoked SARs in 7% of 217 patients, whereas patients in whom the dose increase was performed within 6 h ($n = 21$) or 4 days ($n = 46$) exhibited SARs in 28% [23]. Birnbaum *et al.* [10] reported the use of the ultrarush protocol dose with a dose-increase schedule within 3.5 h in a larger number of patients. In this uncontrolled retrospective study 13% of 258 patients developed SARs when treated with honey bee or vespid venom.

However, Reimers *et al.* [24] reported that 26% of patients had SARs during a 3.5-h ultrarush protocol, although half of them were pretreated with antihistamines. Possibly variations in patient selection may explain the large difference between these results. Thus Reimers *et al.* [24] treated only patients allergic to honey bee venom whereas Birnbaum *et al.* [10] had a mixed group of patients with honey bee or vespid venom allergy.

Another group compared in a retrospective way various rush protocols in which the dose increase was performed within a few days [8]. Some 1055 patients were included in the evaluation. Patients with vespid venom allergy ($n=933$) – but not those with honey bee venom allergy ($n=122$) – had significantly fewer SARs when the dose increase was done within 2 days (SARs in 15%) than within 4 (20%) or 7 (30%) days ($P<0.001$). When the 2-day rush protocol of this study was used to treat 15 honey-bee-venom-allergic patients, there were LLRs in all and SARs in 40% of patients [25]. Thus, the incidence of SARs was surprisingly high in comparison to the rate of adverse reactions (18%) observed with a rush protocol in which maintenance doses were reached within several days [25].

At present, ultrarush protocols should be used only with utmost caution, preferably under emergency conditions. Possibly, they are not appropriate for the routine treatment of patients allergic to honey bee venom. It should be emphasized that studies which found treatment with faster protocols to be tolerated at least as well or even better than treatment according to 'slower' rush protocols were only retrospective in nature, and controlled prospective studies will be indispensable to appreciate the true value of this modified approach.

Depot extracts

Depot extracts for the treatment of venom allergy have been available for two decades [26,27]. These studies revealed good tolerance of depot extracts with regard to the occurrence of LLRs and SARs. Recent prospective or retrospective studies compared different treatment protocols and extracts (aeroallergens, venoms). In general, the frequency of side effects during a conventional dose increase was less in protocols which were done with depot extracts than in those which used aqueous extracts [3,4,28,29,30•].

A recent prospective study analysed the dose-increase phase in 55 patients allergic to honey bee venom receiving either aqueous or depot extracts [28]. It was found that the depot preparation used in 15 patients caused no SARs whereas 20% of the 40 patients treated with the aqueous preparation developed SARs ($P<0.009$). Also LLRs were less frequent in patients

treated with depot extract than in those treated with aqueous extracts (7% versus 20%).

A similar study examined prospectively 65 patients allergic to honey bee venom [30•]. SARs during the dose-increase phase tended to be more frequent in 42 patients on rush venom immunotherapy with an aqueous preparation than in 23 patients who were initially treated according to a conventional schedule with depot preparation (31% versus 13%; $P=0.11$). Use of the depot preparation provoked LLRs less frequently than the aqueous preparation in the incremental phase (4% versus 8%; $P=0.059$) and also during maintenance therapy (12% versus 49%; $P<0.001$).

Compared to therapy with an aqueous preparation, venom immunotherapy with a depot preparation is superior with respect to the occurrence of LLRs and SARs. However, if protection by venom immunotherapy is to be achieved rapidly, initial use of aqueous preparations for rush treatment will be preferred. For maintenance treatment use of the depot preparation is advisable.

Reduction of side effects by pharmacologic treatment

Concomitant treatment with H_1 -antihistamines has been found to reduce side effects (LLRs and SARs) of venom immunotherapy in a placebo-controlled study [31]. A recent study was performed in 57 patients allergic to bee venom [24]. In comparison to the placebo, pretreatment with 180 mg of fexofenadine also reduced the frequency of LLRs (64% versus 89%; $P<0.05$) and of mild objective SARs (affecting only the skin) significantly (4% versus 23%; $P<0.05$). However, the frequency of severe SARs was not reduced by this treatment with antihistamines.

Goldberg and Confino-Cohen. [32] reported a series of nine venom-allergic patients who did not tolerate a slow conventional dose increase as they had repeated SARs. After switching to a rush protocol and simultaneously using antihistamines in part, eight patients subsequently tolerated the maintenance dose.

Thus combining venom immunotherapy with H_1 -antihistamine therapy may reduce the incidence of LLRs and mild SARs and may therefore be helpful. However, there seems to be no protective effect against more severe SARs.

Treatment failure

Besides assessment of the reaction to a re-sting (sting challenge test or, less reliably, 'field' sting) there is no method available to reliably identify patients not responding to venom immunotherapy [33]. When sting

challenges were performed in larger series of patients on maintenance venom immunotherapy, about 75–85% [11•,30•,34,35] or even more than 95% [36,37] were found to be protected. Nevertheless, treatment failure is not so rare.

Attempts to establish laboratory parameters for assessing the efficacy of venom immunotherapy have been unsuccessful. Recently, venom-induced leukotriene release from peripheral blood leukocytes was investigated. In two [38] or 14 [39] subjects on venom immunotherapy who tolerated field stings without SARs, no reduction was found compared with pretreatment values. Also, in comparison to pretreatment values no relevant change of CD63 expression on basophils was found in 20 vespidae-venom-allergic patients who had venom immunotherapy and who had already tolerated a sting challenge [40]. A preliminary study evaluated 48 patients on venom immunotherapy, of whom six turned out not to be protected at a diagnostic sting challenge [41]. The authors reported a strong correlation between treatment failure and a lack of venom-immunotherapy-induced venom-specific IgG4 to major Hymenoptera allergens. However, these promising data could not be reproduced in a subsequent study in 362 patients [42]. Thus laboratory techniques do not allow for the prediction of clinical reactivity of the treated patient.

Risk factors for treatment failure

In a previous study it was shown that venom immunotherapy with honey bee venom is less effective than treatment with vespidae venom [35]. In a recent study 87% of patients on vespidae venom immunotherapy had no SARs to a sting challenge, whereas only 67% of patients allergic to honey bee venom were protected [11•].

There is no indication that the type of dose increase – rush or conventional – would influence the efficacy of treatment [26,30•]. The main determinant of successful treatment is the amount of venom given as maintenance dose [21,36]. Thirty-eight of 40 patients on venom immunotherapy who still reacted systemically to a sting challenge were found to be protected at a further challenge after increasing the maintenance dose from 150 up to 250 µg of venom [21].

Efficacy of venom immunotherapy may be reduced in patients with mast cell disease. A retrospective study analysed serum samples which were taken from 32 patients allergic to honey bee or vespidae venom. All patients were on maintenance treatment with 100 µg of venom and had developed a SAR at sting challenge [21]. An elevated baseline serum tryptase level (>13.5 µg/l) was found in nine of 32 patients (28%). Another study found elevated basal serum tryptase concentrations to be relevant for treatment failure only in patients with vespidae

venom allergy, but not in patients with honey-bee-venom allergy [11•].

Honey-bee-venom immunotherapy is less effective than treatment with vespidae venoms. An increase of the maintenance dose provides protection in nearly all patients with initial treatment failure. Thus it seems appropriate to administer an increased maintenance dose of 200 µg from the start – at least in patients allergic to honey bee venom – to patients with particular risks (e.g. beekeepers or those with mast cell disease).

Conclusion

Severe side effects due to venom immunotherapy are rare. Using depot instead of aqueous extracts and switching from rush to 'slow' dose-increase schedules could reduce the frequency of local and also systemic side effects. However, if a fast onset of protection is required, a rush protocol is preferable. With respect to SARs, there are several retrospective studies showing promising results of ultrarush schedules in which the maintenance dose was reached within several hours or 2 days, respectively. However, these ultrarush protocols seem to be less advantageous for the treatment of allergy to honey bee venom. There are no prospective studies yet by which side effects of venom immunotherapy with ultrarush protocols have been studied adequately in comparison to 'slower' regimens. Pretreatment with H₁-antihistamines may reduce the frequency of LLRs and mild SARs during venom immunotherapy, whereas the frequency of severe anaphylactic reactions cannot be reduced.

Some 5–25% of patients are not protected by standard venom immunotherapy and suffer again from SARs when re-stung. Patients with honey-bee-venom allergy are at higher risk for treatment failure. Increase of the maintenance dose may increase the success rate in patients previously not protected by the usual maintenance dose of 100 µg of venom. Therefore, it is important to use sting challenges for identifying unprotected patients. In addition, an increased maintenance dose (200 µg) from the start should be considered in patients with special risks, particularly in allergy to honey bee venom.

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