

Editorial

Hymenoptera immunotherapy

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Allergic reaction to stinging insects is one of the more dramatic allergic diseases. The combination of sudden pain, acute onset of reactions, and knowledge of sting-induced fatalities will often make the victim seek medical advice. Judged from the rather low mortality rate reported, emergency treatment is often sufficient to manage such cases. Therefore, many physicians do not refer patients with insect-sting reactions for further investigations. A lack of knowledge of immunotherapy or limited access to an allergy service might be additional factors. However, even if nonfatal, a systemic reaction to an insect sting is extremely unpleasant, and most patients would prefer to have preventive treatment rather than carry emergency medication and seek medical treatment when stung. The preventive treatment presently available is immunotherapy. In 1978, the pioneer work by Hunt et al. (1) demonstrated the almost complete protection obtained by treatment with insect venom. In contrast, the whole-body extracts used previously turned out to have an effect equivalent to placebo. Subsequently, venom immunotherapy has been investigated in a large number of studies. The effect has uniformly been confirmed, and during the period when the need for immunotherapy in general was debated and safety regulations in some countries led to a reduction in the use of this kind of treatment, the need for venom immunotherapy was not questioned among specialists.

Economy - resources

The basic concept of administering increasing amounts of the relevant allergen is the same as in all other kinds of allergen-specific immunotherapy. A large variety of dose regimens have been studied, but no alternatives to the subcutaneous injection have been tried, as in inhalant allergy. As in all kinds of medical treatment, the efficacy has to balance the costs. Immunotherapy is highly effective, but the costs are not negligible either. Apart from money costs, there are side-effects and the time required for a complete treatment sequence. Since the collection of pure venom from small insects is a laborious task, the venom extracts are fairly expensive. However, of equal importance is the time consumption in connection with the injections. With many injections, much time would have to be spent in the doctor's office during and especially after the injections, and many visits would increase the time taken for transportation. Subsequently, efforts have been made to develop treatment regimens with a reduced number of injections and a reduced number of visits. The efficacy and side-effects of several such studies have been reported. The paper by Laurent et al. in this issue (2) presents data from a rush protocol and confirms the finding that rapid treatment regimens are fairly safe.

In general, the dose-increase phase of the treatment is the most costly. The traditional dose

regimen with weekly injection would imply 8–16 visits before the maintenance dose is reached (3). By clustered treatment, a few injections are given at each visit, usually with intervals of 1 week or less. The most rapid form, the rush regimen, can reduce the up-dosing to a few day or even a few hours and has gained increasing popularity. If the rush regimen can be performed on an outpatient basis, the reduction in resources is evident. In-hospital treatment over a few days would probably reduce the inconvenience for the patient, but the expenses for the health system might increase.

The most rapid up-dosing would lead to an accumulated dose of 100 µg in only 3½ h (4), but treatment periods of 1–5 days have been reported (3–5). In the protocols, the number of injections has been reduced by skipping the very low initial doses and by increasing the interval mainly between the lowest doses.

Other attempts to reduce the costs of the treatment have been tried such as lowering the intended top dose from the usual 100 to 50 µg (6), increasing the treatment interval from 1 to 3 months for aqueous extracts (7), and reducing the treatment period to 2–3 years in mild cases (8).

Efficacy

The prognosis after a systemic reaction is highly dependent on the severity of the initial reaction and on the offending insect, the risk of another reaction ranging from less than 25% after mild systemic reactions and in wasp-allergic patients (9), to more than 70% in patients highly sensitized to honeybee sting (10). In parallel to these findings, bee-venom immunotherapy, as judged from frequency of systemic reaction to re-sting, is slightly less efficacious than wasp-venom treatment (11). When the efficacy of different dose regimens reported by different centres is to be compared, it must be ensured that the offending insects, as well as the severity of the clinical reactions, are similar. Finally, although sting challenge is the best way to confirm a successful treatment, repeated challenge in the same patient does not give identical reactions (12), and differences in the way sting challenges are performed in various centres might influence their results (13).

The venom content in the maintenance dose of 100 µg is equivalent to two or more stings, depending on the insect species (14). "Challenge" with injection of venom extract cannot replace the sting challenge, but it is reasonable to expect the efficacy of the immunotherapy to depend on the top dose of venom extract administered and tolerated. As a consequence, a rapid dose increase would give rapid protection, a fact that might be important

during the insect season and especially in bee-keepers. Patients could be protected so rapidly that adrenaline for self-administration and other emergency medication would be unnecessary. In addition to the maintenance dose, this efficacy is determined by the dose interval and the duration of this phase. Apart from the initial benefit, the way the dose increase is performed probably does not affect the efficacy in the long run.

Side-effects

If side-effects occur during immunotherapy with extracts from pollen or other inhalant allergens, they often appear as acute worsening of the allergic disease; i.e., rhinoconjunctivitis or asthma. A similar recurrence of the sting-induced systemic reactions after Hymenoptera immunotherapy would be highly unpleasant, and although more and more studies have proven the frequency of side-effects to be very low, a fear of severe symptoms is probably why the treatment has been confined to allergy centres to a much higher degree than with immunotherapy with pollen extracts. Side-effect data are highly dependent on the way collection has been performed, and this process is difficult to standardize from one centre to another. When comparing side-effect data, the selection of patients must be taken into account as well. Preliminary data from a large European multicentre study revealed systemic side-effects during various kinds of up-dosing only after 2% of injections (15). In general, the rush regimens in most comparative studies have a slightly higher frequency of patients with reactions than in conventional regimens. The 3½-h ultrarush is an exception, with only 7% of reactors compared to 28% in the 6-h and the 4-day rush therapy (4). As for efficacy, a striking difference is seen between insect species, with systemic side-effects in 13% of bee-allergic patients but in only 2% of patients with wasp reactions (5).

Open questions

Although the efficacy and side-effects of Hymenoptera venom immunotherapy have been investigated in a large number of studies, several questions remain to be answered. The selection of patients for the treatment is presently made from the severity of the sting reaction, skin test result, and level of venom-specific IgE. Of patients offered immunotherapy based on these parameters, only about half would have reacted systemically when re-stung without this treatment. For the other half, the treatment is superfluous. The big problem is that, at present, we cannot identify the risk group more precisely. It has been proposed

to include sting challenge in the diagnostic work-up (9, 17). This approach reduces the number of patients to be treated, but, on the other hand, up to about 20% of patients with an initially negative sting challenge would react systemically to a subsequent sting (12, 17).

During and after immunotherapy, there is a similar need for easy methods to assess the degree of protection. Such methods could identify patients needing high-dose treatment, could help in determining when to stop therapy, and could be used to monitor the duration of the protection after having stopped the treatment.

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