

Position Paper: Immunotherapy with Hymenoptera venoms

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1. Introduction

In 1987 the EAACI working group on immunotherapy published a first position paper on immunotherapy with Hymenoptera venoms (15). Since then a considerable number of important publications on this topic have appeared, and new insights have been gained which necessitate a thorough revision.

In Europe, Hymenoptera venom allergy is most often caused by stings of the honeybee (*Apis mellifera*) and the wasp (*Vespula germanica*, *V. vulgaris*)* – in Mediterranean countries, also by the genus *Polistes* (*P. gallicus*, *P. dominulus*)* – and occasionally by other vespids (*Vespa crabro*, *Dolichovespula* spp.)*, bumblebees (*Bombus* spp.), and carpenter bees (*Xylocopus*) (14, 80). The most frequent clinical patterns are large local reactions exceeding 10 cm in diameter and 24 h in duration, and generalized, immediate-type allergic reactions such as urticaria, angioedema, asthma, and anaphylactic shock. Between 2 and 19% of an adult population in Europe and the USA have a history of large local reactions, and between 0.8 and 5% a history of a generalized allergic reaction, to Hymenoptera stings (18, 31, 80). These reactions may rarely be fatal (3, 70, 80) or be followed by long-lasting morbidity caused, for instance, by myocardial or cerebral infarction (80).

The first attempts at specific immunotherapy involved extracts of venom sacs (4), but then only whole-body extracts were used for almost 50 years. In the late 1970s, two controlled prospective studies (52, 74) showed clearly that venom preparations are largely superior to whole-body extracts for immunotherapy and that whole-body extracts give patients no better protection than placebo. In the following years numerous publications on venom immunotherapy (VIT) appeared, and it became obvious that on a maintenance dose of 100 µg of venom protein, more than 80% of patients are completely protected (14, 80). Most of the remaining patients develop only

minor systemic allergic symptoms when reexposed to the respective insect.

Issues still controversial include the appropriate selection of patients for VIT in order to avoid unnecessary treatment or to exclude patients at risk from treatment; the optimal treatment protocol and maintenance dose with regard to protection and safety; measures to avoid side-effects; and the duration of VIT.

2. Selection of patients requiring venom immunotherapy

The *diagnosis* of Hymenoptera venom allergy is based on a history suggesting an allergic sting reaction and the demonstration of IgE-mediated allergy by positive skin tests and the presence of venom-specific IgE serum antibodies to the respective venom. Prospective studies have, however, shown that only some of these patients will react again when restung. This risk seems to be largely dependent on the severity of the preceding reaction (Table 1). After a large local reaction, less than 5% of subjects will develop a systemic reaction, and after a mild systemic reaction, only 15–30%, while after a severe systemic reaction, probably more than 50% will present with a systemic reaction again. It appears that spontaneous loss of sensitivity is not only more frequent in mild than in severe anamnestic reactions, but also in children than in adults (102, 115), and in vespid-sting than in honeybee-sting allergy (8, 117).

Skin tests with Hymenoptera venoms and *estimation of venom-specific serum IgE antibodies* are the most common diagnostic tests. The threshold concentration (the lowest concentration resulting in a wheal of at least 5 mm in diameter with erythema) distinguishing best between persons with and without an anamnestic allergic sting reaction in intracutaneous endpoint titration is given as 10^{-3} g/l (= 1 µg/ml) by some authors (51, 120), and as 10^{-4} g/l (= 0.1 µg/ml) by others (20, 26, 88); in prick tests, it ranges from 10^{-1} g/l (100 µg/ml) (7, 41, 43) to 1 g/l (72). For estimation of venom-specific IgE, the commercial RAST is somewhat less sensitive than the skin test, especially when performed more than a year after the last reaction (80) and in patients with previous allergic reactions to vespids (83, 92, 120). The specificity of the two tests is comparable.

* Considerable confusion is caused by the fact that common names for vespids are different in Europe and the USA, as shown below:

Genus	Common name in	
	Europe	USA
<i>Vespula</i>	wasp	yellow jacket
<i>Dolichovespula</i>	wasp	hornet
<i>Vespa</i>	hornet	European hornet
<i>Polistes</i>	wasp	wasp

Some of the newly developed, commercially available methods seem to be more sensitive and as specific as RAST for the detection of specific serum-IgE antibodies (42, 57). Both skin test (7, 26, 51, 88, 120) and serum specific IgE (47, 69, 73, 105, 109) distinguish well between persons with and without a history of allergic reactions to Hymenoptera stings: within a year from the last allergic reaction, more than 90% of history-positive persons are skin-test positive, and 70–90% are RAST positive, while only 10–20% of history-negative persons are test positive. However, the predictive value of diagnostic tests with regard to the outcome of a later sting, although significant, is less impressive: in both tests, most test-positive persons (skin test 44–84%; RAST 55–76%) do not react to a later sting, while some test-negative persons do (skin test 0–31%; RAST 0–28%) (8, 20, 33, 72, 80, 87). Prospective studies on test-positive control subjects have shown that they are at a higher risk of reacting to a later sting than are test-negative controls – 19–39% and 2–7%, respectively (20, 33, 124) – but at a lower risk than are history- and test-positive patients (Table 1).

More sophisticated and expensive diagnostic tests, such as the *histamine-release assay* (85, 108) and the *basophil degranulation test* (121), are not superior to the skin test in sensitivity and specificity; therefore, they are not recommended for routine clinical use.

High levels of *venom-specific IgG* and *IgG-subclass antibodies* are sometimes found in untreated patients with Hymenoptera allergy. They do not predict protection from further stings (8, 58, 80) and are therefore irrelevant to the selection of patients for VIT. These antibodies are related to allergen exposure and are often high in beekeepers irrespective of their allergic state.

Two groups (8, 58) have proposed submitting every patient with a history of Hymenoptera sting

allergy to a *provocation test* with the sting of a living insect in the intensive care unit before VIT, treating only those who do react to this provocation test again. However, for ethical reasons, most European allergists refuse to do provocation tests in untreated patients with a potentially fatal allergy. Observations from a placebo-controlled study (52, 107) support this view. Other allergists (24) recommend performing diagnostic provocation testing only in patients with a history of non-life-threatening sting reactions.

Apart from ethical problems, it must be stressed that the provocation test, though the most reliable diagnostic procedure, has its limitations, too. The amount of venom injected during a sting depends not only on the duration of the sting, but also on the age of the insect (86) and the amount of venom contained in the venom sac at the time of the sting (48). This quantity can be very much reduced if the insect has given several previous stings without losing its stinger. When threatened, vespids can squirt their venom without actually stinging, as when seized for a provocation test (48). This may explain why provocation tests with vespids are less frequently positive than those with honeybees (8, 83). Finally, a well-tolerated provocation test in an untreated patient may boost the IgE response in such a way that a systemic reaction will occur again following the next sting. A recent report (25) supports this view by showing that 6 of 26 (23%) untreated vespid allergic patients who tolerated a first sting challenge reacted to a second within 2 years. For all these reasons, provocation tests in untreated patients are not recommended.

The *degree of exposure* of patients can be estimated from the number of times they have already been stung, from the regions in which they live, and from their lifestyles. The degree of exposure, together with the severity of reaction to previous stings, determines the risk of future, life-threatening reactions and thus the indication for VIT.

Finally, VIT demands good *compliance* from the patient. Therefore, before starting VIT, it should be established that the patient is able and willing to cooperate in a treatment that will continue for years.

The *indications for VIT* are summarized in Table 2. An absolute indication is given by a history of severe systemic reactions with respiratory or cardiovascular symptoms and positive diagnostic tests, either skin test or serum specific IgE. In a patient with such a history, both negative skin tests and the absence of serum specific IgE are only rarely observed. In these exceptional cases, close documentation of the reaction should be obtained, and further diagnostic tests such as the histamine-release assay (85, 108) may be performed. It is not advisable to start VIT

Table 1. Prospective studies on the natural history of Hymenoptera sting allergy

Authors	Previous reaction	Reexposure		
		No pts	by	% with systemic reactions
Graft et al. (37)	Large local	64	FS	4
Mauriello et al. (68)	Large local	28	FS	4
Schuberth et al. (102)	Mild systemic, children	85	FS	16
Blaauw et al. (8)	Mild systemic, adults	30	PT	20
Van der Zwan & van der Linden (117)	Mild systemic, bee	17	PT	24
	Mild systemic, wasp	120	PT	14
Blaauw et al. (8)	Severe systemic	58	PT	34
Van der Zwan & van der Linden (117)	Severe systemic, bee	37	PT	51
	Severe systemic, wasp	134	PT	41

FS=field sting; PT=provocation test with living insect.

Table 2. Indications for venom immunotherapy

Type of reaction	Diagnostic tests ST and sIgE	Decision regarding venom immunotherapy
<i>Severe systemic</i>		
Respiratory and cardiovascular symptoms	Positive	Yes
	Negative	No
<i>Mild to moderate</i>		
Urticaria, angioedema, etc.	Positive	Usually not; only in heavily exposed parts with repeated reactions
	Negative	No
Large local	Positive	No
	Negative	No
Unusual	Positive	No
	Negative	No

ST=skin test; sIgE=venom-specific serum IgE.

without documented IgE-mediated allergy. Mild systemic reactions, such as urticaria and angioedema without respiratory or cardiovascular involvement, have a favorable prognosis, especially in children (24, 102, 115), but also in adults, as shown in Table 1. Therefore most European allergists recommend VIT only for highly exposed patients in whom such reactions recur, or for those whose quality of life has been greatly impaired by fear of flying insects. Other allergists treat all adult patients with generalized sting reactions, including those with only cutaneous symptoms, when their diagnostic tests are positive. Large local (37, 68) and unusual reactions, such as vasculitis, nephrosis, fever, thrombocytopenia, etc. (14, 80) are not indications for VIT.

2.1. VIT in special situations

Beekeepers are at high risk of bee-venom allergy. In several studies the prevalence has been estimated to range from 15 to 43% in this group (11, 13, 73), as compared with 0.8 to 5% in the general population (18, 31, 80). Within the beekeeper population, the degree of sensitization is inversely related to the number of stings per year (11, 13). Most persons who are stung by fewer than 50 honeybees a year have both a positive skin test and venom-specific serum IgE antibodies, although only a minority of them experience anaphylaxis (13). VIT should be offered to all beekeepers with recent anaphylaxis who wish to continue beekeeping and to those with severe anaphylaxis, even when they stop working with bees. A maintenance dose of 200 µg per month is advised because beekeepers are often stung by more than one bee at a time (80), and protection should be documented with a sting challenge in the intensive care unit before these patients return to work with bees. Once the sting challenge has been tolerated,

protection may be maintained in active beekeepers during the summer months by having them exposed to a bee sting at their own hives every 1–2 weeks. Safety precautions such as wearing protective clothes and the immediate availability of an emergency kit are essential (82). During the winter months, treatment injections should be restarted.

Pregnancy is usually not considered to be a contraindication for continuation of an established and well-tolerated VIT, but this treatment should not be started during pregnancy (104).

During *infancy* and early childhood, severe allergic reactions are extremely rare (102, 103), and fatalities are almost unknown (3, 80). Only in heavily exposed cases with severe reactions, as in the children of beekeepers, should VIT be started before the age of 5. Such therapy should be given by a pediatric allergist, who is well trained in establishing a venous access in small children. In *elderly patients*, allergic reactions to Hymenoptera stings may be more severe (80), and the fatality rate is higher (3), than in children and in young adults, probably because of the more frequent association with preexisting cardiovascular and respiratory disease. On the other hand, the risk of reexposure is usually lower. Therefore, in contrast to inhalation allergies, immunotherapy for Hymenoptera venom allergy may be indicated in heavily exposed elderly patients with a history of severe systemic reactions and positive diagnostic tests.

Several patients with urticaria pigmentosa and systemic reactions following Hymenoptera stings have been described (76). In some, no specific serum IgE could be detected, suggesting direct mediator release by mast-cell degranulating venom components. Nevertheless, a few of these patients were successfully treated by VIT. Contraindications for VIT are similar to those for immunotherapy with other allergens, as discussed in the EAACI position paper on immunotherapy (67).

3. Selection of venom

Except for beekeepers and their families, patients are often unable to identify the offending insect. It may be helpful to know that after a bee sting, the stinger usually remains in the skin, but it does not do so after most vespid stings. Therefore, identification of the offending insect must often rely on diagnostic tests, which are frequently positive with more than one venom. Cross-reactivity between the venoms of *Vespula*, *Dolichovespula*, and *Vespa* is strong (49, 61, 62, 75, 95, 119), but that between these three genera and *Polistes* is weaker (10, 40, 96). Vespid venoms available in Europe are from *Vespula* spp. (European mix) and *Vespa crabro*, the European hornet. The commercial *Dolichovespula* and *Polistes* venoms are

obtained from North American species, which – although strongly cross-reactive – are not identical to those of the respective European species.

In central and northern Europe, the aggressive representatives of the genus *Vespula* are certainly responsible for most allergic reactions. However, in the Mediterranean region, *Polistes* may be equally or even more important (9). Theoretically, the difficulty in distinguishing among *Vespula*, *Dolichovespula*, and *Polistes* means that treating with a mixture of all these venoms would be quite proper. In view of the extensive cross-reactivity between *Vespula* and *Dolichovespula* and the relatively limited clinical importance of *Polistes* in temperate European climates, treatment with *Vespula* venom alone is usually sufficient in these areas. In the Mediterranean area, venom of both *Vespula* and *Polistes* should be considered for treatment, when tests are positive to both. *Vespa crabro*, the European hornet, is easily identified by most patients because of its fearsome size. Since *Vespula* stings are much more common than hornet stings in most areas, it can be assumed that most patients with allergic reactions to hornet stings were primarily sensitized by *Vespula* stings. Therefore, these patients will probably be well protected by *Vespula* venom immunotherapy. Where *Vespa crabro* is locally important and in the rare case of monovalent sensitivity to *V. crabro*, its venom should be used for immunotherapy.

The cross-reactivity between honeybee and vespid venoms is much more limited (50, 97). In the presence of positive diagnostic tests to both honeybee and vespid venoms and when the culprit insect cannot be identified from history, further diagnostic tests may be helpful: specific IgG is often elevated after a recent sting (80). The RAST inhibition (97) and the histamine-release assay (45) may also give a clue to the responsible insect. If not, both venoms should be used for VIT.

Bumblebee venom for VIT is not available commercially. It cross-reacts with honeybee venom (14, 80). In the rare case of systemic allergic reactions to bumblebee stings, honeybee venom may be used for treatment.

4. Treatment protocols

The generally recommended maintenance dose is 100 µg of venom protein, corresponding to about two bee stings and probably many more *Vespula* stings (48). Golden (29) found that 100 µg of venom protected significantly more patients than 50 µg. Maintenance doses up to 200 µg are indicated in beekeepers, who are often stung by several insects at the same time, and in treatment failures (16). A recent study (17) suggests that skin-test sensitivity and RAST decrease more rapidly under a maintenance

dose of 200 µg, and VIT may therefore be shortened. This observation needs confirmation.

For the dosing intervals, many schedules have been devised, all attempting to obtain satisfactory protection, minimal side-effects, and optimal convenience for patients. Rush protocols (12, 17, 74, 112) provide more rapid protection than slow schedules, with sessions every 1–2 weeks and a dose increase to maintenance over several months. However, slow protocols are usually better tolerated (93, 98). Birnbaum (6) and van der Zwan (116) have described ultrarush protocols over 3.5 and 6 h, respectively. These seem to be very well tolerated in *Vespula*-venom-allergic patients. Results in bee-venom-allergic patients, however, are controversial (6, 12, 123). Cluster protocols (28, 66) are another convenient alternative. Some examples of treatment protocols are given in Table 3.

Table 3. Treatment protocols for venom immunotherapy

Protocol		Dose in µg venom				
Day	Hour	Ultrarush (6)	Rush (80)	Cluster (28)	Conventional (80)	Al-hydroxide ads. (71)
1	0	0.1	0.01	0.001	0.01	0.02
	0.5	1	0.1	0.01	0.1	
	1	10	1	0.1		
	1.5	20				
	2.5	30	2			
	3.5	40				
2	0		4			
	1		8			
	2		10			
	3		20			
3	0		40			
	1		60			
	2		80			
4	0		100			
8	0		100	1	1	0.04
	1			5	2	
	2			10		
15	0	50	100	20	4	0.08
	1	50		30	8	
22	0			50	10	0.2
	1			50	20	
29			100	100	40	0.4
36				100	60	0.8
43		100	100		80	2
50					100	4
57					100	6
64				100		8
71		100	100		100	10
78						20
85					100	40
92				100		60
99		100	100			80
106					100	100

Further injections of the maintenance dose of 100 µg every 4 weeks during the first year, every 6 weeks during further years, of venom immunotherapy.

Aluminum hydroxide adsorbed venoms are now widely used in conventional schedules or after reaching maintenance in rush protocols (70, 122). They may induce fewer side-effects than aqueous extracts, although the only controlled study comparing aqueous and aluminum hydroxide adsorbed *Vespula* venoms did not establish this (71). In a double-blind study, honeybee venom coupled to methoxypolyethyleneglycol (mPEG-BV) was extremely well tolerated, inducing an IgG response similar to that of native bee venom. However, after a sting challenge, patients on immunotherapy with mPEG-BV developed more frequent and more severe systemic reactions than those treated with native bee venom (78). Other chemical modifications of Hymenoptera venoms (89) have not been analyzed in clinical trials so far.

5. Follow-up

5.1. Efficacy monitoring

The accepted standard for effective VIT is a well-tolerated reexposure, by either a *field sting* or a hospital provocation test (sting challenge). The *provocation test* is more reliable, because the possibility of misidentification of the insect is excluded and abortive stings can be avoided by leaving the stinger in the skin for a fixed time, e.g. 1 min, or by fixing the insect to the skin for an equal time in the case of vespids (83). However, the provocation test also has its flaws, as mentioned above.

Table 4 shows a number of studies in which patients on maintenance VIT were exposed to a provocation test. More than 90% of vespid-allergic patients were fully protected, as compared with only 75–80% of bee-venom-allergic subjects. The remaining patients mostly developed only minor systemic symptoms, indicating at least partial protection, but occasional severe reactions have been reported (16, 80, 101), again more often in bee-venom- than in vespid-venom-sensitive subjects. The reason for the discrepancy between VIT with bee and vespid venom is still not clear. The topic is discussed extensively

in a recent paper (83). While the provocation test is the most reliable test for judging the efficacy of VIT, it is expensive and inconvenient for the patient. Other *in vivo* and *in vitro* diagnostic tests are discussed below with reference to their value in monitoring efficacy of VIT.

After an initial rise, both *skin-test* sensitivity and *specific serum IgE antibodies* decrease steadily during VIT and are usually below initial values after 1 year of treatment (110). During prolonged VIT over several years, these tests may actually become negative. Specific IgE usually disappears more rapidly than skin-test sensitivity (38). Tests to *Vespula* venom decline faster than those to honeybee venom (83, 92), and both tests may become negative more rapidly under a maintenance dose of 200 µg (17). It is obvious that both tests are of no predictive value in the early phase of VIT: by sting challenge, protection can be demonstrated already a few weeks after starting VIT (52, 112), at a time when skin sensitivity and serum specific IgE are usually higher than before treatment. However, if, during prolonged VIT, the skin test turns negative (intracutaneous end-point concentration greater than or equal to 10^{-3} g/l) and venom-specific serum IgE disappears, this indicates clinical protection (81, 100). On the other hand, disappearance of specific IgE alone is not a reliable indicator in this regard (81).

Venom-specific IgG increases rapidly during the initial phase of VIT and remains elevated throughout the treatment (110). A strong IgG1 response is observed in the initial phase, while the IgG4 response predominates more and more during prolonged VIT (22, 54, 114, 118). Together with the observation of high specific IgG (especially IgG4) in long-term, highly exposed beekeepers (1, 13, 77, 90, 118), who tolerate bee stings often without even a local reaction, this suggests a protective role for venom-specific IgG in Hymenoptera allergy. This concept is further supported by publications on successful passive immunization of bee-allergic patients by beekeeper gamma globulin (12, 55, 64, 77, 90). On the basis of all these observations, some authors have postulated "protective levels" of venom-specific IgG (30, 35). From prospective studies, where serum was taken immediately before a sting challenge, it is quite evident that specific IgG or IgG4 is of no predictive value in untreated patients (8, 58), in patients on long-term VIT of more than 3 years' duration, and in patients in whom VIT was stopped (30, 63, 79, 81). During the first 1–2 years of VIT, the predictive value of serum specific IgG is controversial: while Lawrence et al. (63) found a significant association with protection, others (14, 79, 110) could not confirm this. Even in the study of Lawrence, however, some of the patients with a "protective" IgG level reacted to the challenge, while most of those with

Table 4. Efficacy of venom immunotherapy according to a sting challenge during treatment

Authors	Insect	Sting challenge	
		No. patients	No. with systemic reaction (%)
Gillman et al. (27)	Honeybee	18	4 (22)
Müller et al. (83)	Honeybee	148	34 (23)
Przybilla et al. (91)	Honeybee and wasp	157	33 (20)
Golden et al. (29)	Wasp	147	4 (3)
Mosbech et al. (71)	Wasp	19	0
Müller et al. (83)	Wasp	57	5 (9)

specific IgG below this level did not. The research of some authors suggests that a heterogeneity of the IgG and IgE responses to single bee-venom allergens may explain the lack of association of total venom-specific IgG with treatment success (24, 60, 84). Others could not confirm this (77). Differences in affinity of specific IgG against the relevant venom allergens between beekeepers and protected patients, on one hand, and treatment failures, on the other hand, are an alternative explanation (21). Sensitivity in basophil histamine release (85, 108) decreases during VIT. However, a low sensitivity in basophil histamine release does not predict protection reliably, according to one study (45).

5.2. Safety monitoring

The most frequent side-effects of VIT are immediate-type allergic reactions. They occur mainly during the initial phase of dose increase, most often between 10 and 50 µg and only rarely at doses below 1 µg. Large local reactions are observed incidentally in almost all patients; systemic allergic side-effects in 5–40% of patients (6, 28, 80, 93, 98, 110, 112). Honeybee venom induces more side-effects than *Vespula* venom (2, 65, 83, 101) for unknown reasons. Side-effects are also more frequent, as a rule, during rush protocols (12, 80, 123) than during slower regimens (93, 98). A reduced incidence of systemic side-effects has, however, been described in ultrarush protocols with *Vespula* venom (6, 116), as compared with rush protocols over 3–5 d.

Occasionally, patients complain of unusual side-effects such as abnormal fatigue, headache, or arthralgia for several days after the injection, usually without showing any objective symptoms. In some of these cases, an immune complex disease was excluded (19).

With VIT the normal precautions for any allergen immunotherapy must be observed, as described in the EAACI immunotherapy position paper (67). Treatment with beta blockers can enhance allergic type I reactions, since the body's own defense mechanisms, as well as the effect of therapeutically administered sympathomimetic drugs, are partially blocked (53, 111). Although a case control study has not shown an increased incidence of side-effects of immunotherapy in patients on beta blockade, these may be more severe (46). Beta blockers should therefore be avoided, especially during the initial phase of VIT. Care should also be taken with the use of angiotensin-converting-enzyme inhibitors during VIT, since these drugs are known to induce angioedema by interfering with the metabolism of bradykinin and neuropeptides (106). Despite all safety precautions, systemic allergic side-effects may occur; they are to be treated exactly like immediate allergic

reactions after Hymenoptera stings (82). For continuing VIT after allergic side-effects, the following procedures are recommended:

- 1) Large local reactions do not necessitate a dose reduction. They may be treated with topical anti-inflammatory measures such as cold packs or corticosteroid creams. If such reactions recur, prophylactic oral antihistamines may be given (5).
- 2) After subjective systemic symptoms such as paraesthesias, itching, dizziness, or headache, the previous dose is repeated at the next injection. If symptoms recur, prophylactic antihistamines are prescribed.
- 3) After objective systemic symptoms the dose is reduced by one or two steps and the further dose increase performed under antihistamine pretreatment 12 and 2 h before each injection. Prophylactic antihistamines have been recommended for general use during immunotherapy (56). In a controlled study comparing terfenadine with placebo during rush immunotherapy with bee venom (5), a significant reduction was observed for local and generalized cutaneous symptoms but not for respiratory or cardiovascular symptoms.

The combination of active immunotherapy with bee venom and passive immunotherapy with beekeeper gamma globulin was studied by three groups (12, 77, 90); it resulted in a significant reduction of side-effects. However, beekeeper gamma globulin is not commercially available, mostly for economic reasons.

The use of aluminum hydroxide adsorbed Hymenoptera venoms is another possible way to reduce side-effects (71). Despite all these measures, a protective maintenance dose of at least 50 µg may not be reached in a small number, probably less than 3%, of mostly bee-venom-sensitive patients (16, 80, 101).

5.3. Duration of venom immunotherapy

The question of whether VIT can be discontinued after a certain time has been considered in a number of studies (32, 36, 44, 59, 81, 94, 113) in which patients were observed for their reaction to a field sting or a sting challenge at various times after stopping VIT (Table 5). Previous publications have shown (34, 94) that patients who stopped VIT after only 1–2 years' duration, of their own accord, are at a relatively high risk of reacting again to stings. Therefore a minimum VIT duration of 3–5 years is usually recommended (39, 100).

Some authors (94, 113) used a strong decrease or even a disappearance of venom-specific serum IgE as a reason to stop VIT. They could show that only very few of their patients developed systemic reactions to later stings. Others have stopped VIT irre-

Table 5. Duration of venom immunotherapy

Authors	Criteria for stopping	Reexposure after stopping		
		After years	No. patients	No. with reaction
<i>First exposure after stopping</i>				
Urbanek et al. (113)	Strong decrease of venom-specific IgE	1	29	1 (3)
Randolph & Reisman (94)	Negative RAST	2-5	24	2 (8)
Golden et al. (36)	> 5 years of VIT	1	29	0
Müller et al. (81)	> 3 years of VIT	1	86	15 (17)
Haugaard et al. (44)	> 3 years of VIT	2	25	0
<i>Repeated exposure after stopping</i>				
Urbanek et al. (113)	Strong decrease of venom-specific IgE	2	14	2 (14)
Golden et al. (36)	> 5 years of VIT	2-5	87	10 (11)

spective of the result of diagnostic tests after at least 3-5 years (32, 36, 44, 81). In studies dealing mainly with vespid-allergic patients, no relapses were observed after the first sting challenge 1 (32) or 2 years (43) after VIT cessation. On the other hand, Müller et al. (81) found 17% relapses in 86 bee-venom-allergic patients after a sting challenge 1 year after stopping successful VIT.

In two trials (36, 112), patients have been challenged several times after cessation of VIT. Both studies showed that the risk of relapse increases with repeated reexposures. The rate of relapse is independent of age, sex, and coexisting atopic disease, but it is significantly increased in patients with systemic allergic side-effects from VIT injections (81). In this group, 38% relapsed, as opposed to only 7% in the group with no systemic allergic side-effects from VIT injections. In all studies the sting reactions during the first reexposure after VIT cessation were mild. More severe reactions have, however, been observed after repeated testing. For this reason, repeated sting challenges *after* stopping VIT are not recommended.

Because of the – albeit small – risk of relapse, some authors recommend (81) that all patients continue taking emergency medications (82) after stopping VIT. Others confine this recommendation to those who reacted again to a field sting. Of the diagnostic tests, only the combination of a negative skin test and the disappearance of venom-specific serum IgE reliably predicts long-lasting protection (81). However, some of the patients with no serum specific IgE but positive skin tests, and vice versa, relapsed. Specific serum IgG usually decreases rapidly after cessation of VIT (36, 44, 81). It does not predict lasting protection.

On the basis of all these observations, the following recommendations regarding treatment duration

are made: VIT may be stopped provided that 1) it has lasted for at least 3-5 years; 2) it has not induced systemic allergic side-effects. It is further desirable that the efficacy of VIT be demonstrated by a well-tolerated field sting or a sting challenge with the responsible insect during VIT. However, we are aware that in many places facilities to perform sting challenges are limited and that this procedure is even prohibited by law in some countries.

For all other patients, skin sensitivity and serum specific IgE may be used as guidelines, although more clinical data are still needed (81, 94, 113). If both skin sensitivity and serum specific IgE disappear, treatment may be discontinued.

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