



Venom immunotherapy in Europe and the United States

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Abstract

Background Hymenoptera stings are accountable for significant morbidity and deterioration in health-related quality of life due to the allergic reactions they cause, the most severe of which can culminate in fatal anaphylaxis. The availability of high quality venom extracts for use in the diagnosis and treatment of insect venom allergy has improved the prognosis and the health-related quality of life of venom-allergic patients. All over the world subcutaneous venom immunotherapy is currently the most effective form of allergen-based immunotherapy with an early, sustained and long-term efficacy. Even though the type of insect responsible for allergic reactions may be different from Europe and US and therefore also the type of extract, nevertheless indications and contraindications are quite similar, as well as treatment protocols and treatment duration. However, neither the efficacy nor the safety of the treatment are optimal, especially with regard to bee venom immunotherapy, and so there is considerable room for further improvement in these important areas.

Purpose This review presents the current practice of venom immunotherapy in Europe and United States discussed at the EAACI (European Academy of Allergy

and Clinical Immunology) Allergy School on Insect Venom held in Groningen in April 2019.

Keywords Anaphylaxis · Effectiveness · Hymenoptera stings · Subcutaneous immunotherapy · Venom allergy

Abbreviations

EAACI	European Academy of Allergy and Clinical Immunology
FAB	Facilitated antigen binding
HB	Honeybee
HBV	Honeybee venom
HRQL	Health-related quality of life
HVA	Hymenoptera venom allergy
iTreg	Inducible regulatory T cell
LLR	Large local reaction
SLIT	Sublingual immunotherapy
SR	Systemic reaction
TGF- β	Transforming growth factor β
VIT	Venom immunotherapy

Introduction

Hymenoptera stings can induce allergic systemic and occasionally fatal reactions. In Europe the prevalence of systemic reactions (SRs) in the adult general population is 0.3–8.9% and raises to 14–32% among beekeepers [1]. According to data from the European Anaphylaxis Registry, Hymenoptera venom allergy (HVA) is the first cause of severe allergic reactions in the adult population and the second in children [2]. The incidence of insect sting fatalities from anaphylaxis ranges from 0.03 to 0.48 fatalities per one million inhabitants per year. Cases of fatal insect sting anaphylaxis account for around 20% of fatal anaphylaxis from any cause [1].

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Table 1 Indications for venom immunotherapy in HVA patients according to the 2018 EAACI Guidelines [4] and 2016 American Practice Parameter [3]

Type of reaction in <i>adults</i>	Indication EAACI 2018	Indication AAAAI-ACAAI 2016	Type of reaction in <i>children</i>	Indication EAACI 2018	Indication AAAAI-ACAAI 2016
Respiratory and cardiovascular symptoms	Yes	Yes	Respiratory and cardiovascular symptoms	Yes	Yes
Urticaria if high risk factors and/or quality of life impairment present	Yes	Yes	Urticaria if high risk factors or quality of life impairment present	No	Yes
Large local	No ^a	No ^a	Large local	No	No
Unusual	No	No	Unusual	No	No

^a VIT could be considered a treatment option in patients with recurrent, troublesome large local reactions

Venom immunotherapy (VIT) is a highly effective treatment [3, 4], even in venom allergic patients with mastocytosis [5]. VIT is able to lessen the risk of a subsequent SR, prevent morbidity and improve health-related quality of life (HRQL), as demonstrated in yellow jacket-allergic patients [6]. In contrast, the self-injectable epinephrine is perceived as burdensome and an unsuitable definitive treatment by most venom allergic patients [7].

Adherence to VIT is reported to be high, possibly because of patients' perception of an unpredictable risk of life-threatening sting reactions [8]. This overview examines similarities and differences related to this treatment across the world.

Mechanisms

The underlying complex immunological mechanisms of VIT are continuously being elucidated.

In short, Th2 to Th1 shift occurs during VIT; an increase in interferon gamma (IFN- γ) levels is observed parallel to the decrease in allergen induced secretion of Th2 cytokines such as IL-4, and IL-13 [9–11]. An increase in Treg cell numbers and functions is also documented [11–13]. In particular, inducible regulatory T (iTreg) cells such as IL-10 producing Tr1 cells and transforming growth factor β (TGF- β) producing TH3 cells play an important role in the induction of tolerance [11, 13, 14]. The role of increased IL-10 levels has been demonstrated in the development of clinical and immunological tolerance in bee venom tolerant beekeepers as well as during VIT [11, 14].

Recently IL-10-secreting allergen-specific Breg cells have been identified in VIT administered patients [15].

The effects of VIT on venom-specific IgE and IgG antibodies are well documented, successful desensitization being accompanied by increases in both IgG4 and IgE-Inhibitory activity. However, the elevated specific IgG4 levels and IgE-facilitated antigen binding (FAB) inhibitory activity returned to baseline within months of discontinuation of VIT despite the prolonged protection [16], indicating that patients are probably protected by a mechanism independent from venom-specific IgG.

IL-10 also appears to counter-regulate synthesis of antigen-specific IgE and IgG4 antibodies, potentially

suppressing both total and allergen-specific IgE while simultaneously increasing IgG4 production [17, 18]. Therefore, IL-10 not only is involved in the suppression of allergen-specific T effector cells during VIT, but it also regulates specific isotype formation and skews the specific IgE response towards an IgG4-dominated phenotype.

Very early effects of VIT are also associated with an early decreased number and mediator release from mast cells and basophils, although the mechanisms that start desensitization are not fully understood. According to some authors, basophil sensitivity, the dose at which half of the maximum basophil response occurs, may be useful to monitor VIT [19].

Indications and contraindications

The indications for VIT are based on the history of a SR, a positive venom skin test and/or specific serum IgE tests and/or basophil activation test, the knowledge of the natural history and established risk factors for severe outcome [4, 20, 21]. The risk of a future allergic reaction, however, can only be expressed statistically since no available test can accurately predict the outcome of the next sting. This circumstance makes it difficult to specify what level of statistical risk justifies VIT.

While there is a good consensus that VIT is indicated for severe SRs, there has been over time less agreement on whether adults and especially children with cutaneous reactions are suitable candidates, as the prognosis in dermal reactors is usually good [22].

Though current opinion on providing patients with a history of a mild reaction with the self-injectable epinephrine differs among experts [23], its negative effect on HRQL could mean that treatment with auto-injectable adrenaline alone is probably inappropriate.

The 2005 European guidelines [24] stated that in patients (both adults and children) with a history of a cutaneous systemic reaction (urticaria, erythema, pruritus) VIT may be considered in the presence of additional risk factors including occupational issues, concomitant cardiovascular diseases, mastocytosis, remoteness from medical help, and seriously impaired HRQL. The same indication, but only for adults has

Table 2 Clinical contraindications to VIT ([29] modified)

Medical condition	Venom immunotherapy
Asthma (partially controlled)	R
Asthma (uncontrolled)	A
Autoimmune disorders in remission	R
Autoimmune disorders in active forms (nonresponding to treatment)	A
Malignant neoplasias	R
β -blocker	NO
ACE inhibitors	R
Cardiovascular diseases	NO
Pregnancy (initiation of VIT)	A
Pregnancy (continuation of well tolerated VIT)	NO
Mast cell diseases	NO
Children (<2 years of age)	A
Children (2–5 years of age)	R
A Absolute contraindication; R Relative contraindication; NO No contraindication	

been confirmed by the 2011 British guidelines [25] as well as by the 2018 European guidelines ([4]; Table 1).

The 2011 American practice parameter stated that patients older than 16 years who have experienced only cutaneous manifestations to an insect sting are generally considered candidates for VIT [26]. According to the 2016 update of the practice parameter, in a change from previous recommendations, VIT is generally not required in case of only cutaneous SRs both in children and adults, but may be considered in the presence of high-risk factors (frequent exposure, cardiovascular or respiratory conditions, or selected medications) or effects on HRQL [3].

Although subcutaneous VIT is capable of preventing large local reactions (LLRs) [27], it is not usually recommended in patients with such reactions due to the low risk of a subsequent SR, even though a recent paper on a large population shows that the risk of a SR, after a previous LLR, occur more frequently than that reported by previous literature [28]. VIT could be considered a treatment option in patients with recurrent, troublesome LLRs [4].

According to the European position paper [29] and a recent survey [30], some contraindications in VIT have been reconsidered [4]. Based on the risk/benefit profile, cardiovascular diseases *per se* are not a contraindication for VIT, but the underlying diseases should be stabilized before initiation. Moreover, treatment with β -blockers and/or ACE may be continued during VIT, but the patient should be informed about a potential increased severity of reactions (if they do occur) and for relapse during the treatment, respectively [4, 29, 31]. High-risk venom-allergic patients with cancer can be treated with VIT when malignant disease is stable or in remission [4, 29, 32]. VIT can be recommended in patients with organ-specific autoimmune disorders when the underlying disease

is stabilized, while it cannot be recommended in patients with active, multisystem autoimmune disorders [4, 29]. VIT should not be commenced during pregnancy, although well-tolerated maintenance VIT may be continued in order to prevent the risk of further SRs in the mother and protect the fetus ([29]; Table 2).

Effectiveness and duration

Subcutaneous VIT is reported to be effective in 77–84% of European patients treated with honeybee venom (HBV), and in 91–96% of those receiving vespid venom [4], demonstrating the higher protection rate of vespid VIT than honeybee VIT. The reasons for the lower efficacy of VIT with HBV are still unclear. Potential explanations might be the much larger and consistent venom amount delivered by a honeybee sting [24] and/or the broad sensitization profiles of HBV-allergic patient with different major HBV allergens [33], including those that might be underrepresented in certain therapeutic venom preparations [34, 35]. Other risk factors for reduced VIT effectiveness were identified into an ACE-inhibitor treatment, as demonstrated by a single work on 1532 patients using sting challenge [31], as well as adverse reactions to VIT ([24]; Table 3). In order to reduce this percentage of unsuccessful treatments, increased maintenance dosages of VIT, especially for HBV, might be suggested since the beginning, in addition to the proper management of comorbidities and concomitant drugs.

In Europe for the majority of patients, VIT with one venom may be recommended as sufficient for protection; in patients with a history of SRs to different insects or with severe initial reactions and clearly double positive tests, VIT with two venoms is recommended [4, 36].

As in the opinion of American experts all venoms eliciting positive test results should be included in the VIT regimen [3, 26], American patients often receive more than one venom, up to a total mixed maintenance dose of 300–400 μ g, which provides up to 98% protection [3]. Whole body extracts of most insects generally contain insufficient amounts of venom or salivary proteins to be of value for diagnosis or treatment; however, the protection rate reported in patients treated with imported fire ant whole body extract was good with an efficacy up to 98% [37], as it seems that it contains sufficient venom proteins to permit therapeutic use, although purified ant venom remains superior for both testing and treatment [37–39].

The protection rate of bumblebee VIT, demonstrated by sting challenge and by in field stings, has been estimated to be greater than 90% [40].

After an initial debate focused on the safety and efficacy profile of VIT in patients with mastocytosis [41], this treatment is now recognized as safe and efficacious [5].

Table 3 Risk factors for systemic reactions in HVA patients during and after discontinuation of VIT

Risk factors of reduced protection during VIT	Risk factors of adverse reactions during VIT	Risk factors of relapse after VIT discontinuation
Honeybee venom	Honeybee venom	Honeybee venom
Severity of pretreatment reactions	Build-up phase > maintenance phase	Severity of pretreatment reactions
Systemic adverse events during VIT	Dose increase schedule (ultrarush > rush > conventional)	Systemic adverse events during VIT
Clonal mast cell disorders and/or elevated baseline serum tryptase	Clonal mast cell disorders and/or elevated baseline serum tryptase (during the build-up phase) in vespid allergic patients	Clonal mast cell disorders
ACE inhibitor treatment (in one study)	–	Incomplete protection upon resting during VIT

The question of how long VIT should last in order to provide long-term protection after discontinuation is a long-standing issue [42]. VIT should be performed for 3–5 years [4], whereby most experts recommend 5 years [3, 21]. Three years of VIT may be sufficient in children [3]. Indeed, VIT with a minimum duration of 5 years is superior for long-term effectiveness and protects the majority of unselected patients [43, 44].

The optimal duration of fire ants immunotherapy is less well defined, most American allergists considering to stop VIT after 3–5 years [3].

One to five years after discontinuation of vespid VIT re-sting reaction rates of 0–10% have been reported [4]. There are only few old reports on the outcome following VIT withdrawal for more than 5 years, and there are no data for more than 10 years after discontinuing VIT. In two old studies, about 7% of patients treated with vespid venom relapsed after 7 to 10 years [44, 45], while 15.8% after stopping honeybee VIT had re-sting reactions [44]. Another study compared relapse rates after 4 and approximately 10 years and reported relapse rates of 10.2% and 16.2%, respectively [46]. The long-term outcome is superior in children compared to adults and in vespid allergic patients than in those allergic to HBV [4].

Moreover, it is likely that short- and long-term results are more favorable with the much higher total dose given in the US than with the standard 100 µg applied elsewhere. More European data on the discontinuation of VIT in HVA patients with 100 µg maintenance dose are needed.

A number of risk factors for the recurrence of a SR following Hymenoptera stings after stopping VIT have been identified and include HBV allergy, severity of pretreatment reactions, systemic side effects to VIT injections, incomplete protection upon re-sting during VIT, mast cell diseases ([3, 4, 24, 42]; Table 3). As a consequence, the recent European guideline state that lifelong therapy should be considered in patients with severe initial SR, systemic adverse events during VIT, and HBV-allergic patients with high risk of future honeybee stings. However, they do not consider mastocytosis as a strong general risk factor for relapse, except in those individuals with severe initial SR where VIT should be prolonged [4]. Due to the reporting of life-threatening and even fatal reactions to Hymenoptera stings after discontinuation of treat-

ment in mastocytosis patients, other authors suggest that VIT should be recommended probably with a life-long duration [21, 47].

In conclusion, the duration of VIT should be decided after a thorough patient–physician discussion based on the available evidence and patient's preference [3]. Moreover, some patients with low risk of relapse prefer to perform long-term VIT out of a sense of security and for improved HRQL. Presently, we do not know if an improvement in HRQL remains even after stopping VIT.

Selection of venom

Selection is based on the identification of the Hymenoptera species involved through an accurate diagnostic work-up (skin testing, sIgE detection), on geographical distribution of insects, and on venom cross-reactivity [20].

Several of the European species of the vespid family differ from those found in the US [48]. Furthermore, popular names for vespids in the US and Europe are different and may lead to confusion ([49]; Table 4).

Criteria for the selection of venom to be used in Europe for VIT were suggested [4, 24]. In particular, considering the incomplete cross-reactivity between Vespinae and Polistinae and the different geographical distribution of each species, treatment with *Vespula* venom alone is usually sufficient in the temperate European climate. In the Mediterranean area patients who test positive to both venoms should be treated with both, unless CAP inhibition reveals cross-reactivity [4, 36].

A weaker cross-reactivity between European and American paper wasps was demonstrated [50, 51]. The species *Polistes dominula* and *Polistes gallicus* are present in Europe, raising the need to use these extracts into clinical practice for diagnostic and therapeutic purposes, to replace the American *Polistes* species mixture presently being used [4, 51]. Honeybee and bumblebee venoms show marked cross-reactivity [20]; however the use of bumblebee venom, if available, would be preferable if the primary sensitization was induced by bumblebee stings [52].

In the US consensus data on which venoms to include for VIT are unavailable. Some authors believe it prudent to prescribe VIT with any venom which gives

Table 4 Vespid species in the USA and Europe

Genus	EUROPE		USA	
	Species	Popular Name	Species	Popular Name
<i>Polistes</i>	Gallicus Dominulus	Wasp	Annularis Fuscatus Exclamans	Paper wasp
<i>Vespula</i>	Vulgaris Germanica Rufa	Wasp	Vulgaris Germanica Maculifrons	Yellow jacket
<i>Dolicho- vespula</i>	Media Saxonica	Wasp	Maculata Arenaria	Hornet
<i>Vespa</i>	Crabro	European hornet	Crabro Orientalis	Hornet

a positive diagnostic result since there have been cases for which VIT was tailored towards the primary culprit insect, but the patients subsequently reacted to an insect to which they had previously been sensitized [3]. Of the 6 HV products marketed in the United States, three contain a single species (HB, yellow hornet, and white-faced hornet) and three are mixtures of species [48].

Cross-reactivity within stinging ant species and between ants' venom and HV is reported by recent studies, mostly related to the antigen 5, but data are limited [53, 54]. Imported fire ant with whole body extracts which contain sufficient venom allergens to provide reasonable clinical protection are available for *S. richterii* and *S. invicta* [48]. Immunotherapy for allergy to Australian Jack Jumper ants (genus *Myrmecia*) is performed using venom extract that is locally produced [38].

Preparation of venom

Venoms were the first standardized allergens introduced into clinical practice, and venom extracts are the only allergen extracts whose potency is measured in micrograms of allergen per milliliter, meaning that they are truly standardized [48]. However, Hymenoptera venom presents unique challenges in collection, processing, and stabilization of the venom extract product, which may influence the composition of the extracts.

In the last few years, increasing knowledge about the venom composition on a molecular basis and availability of component resolved diagnosis [55–57] allowed more precise analysis of therapeutic venom extracts, showing that different therapeutic HBV preparations can highly differ in the content of relevant allergens, particularly of those of low abundance such as Api m 10 [34, 35]. In the case of a patient predominantly sensitized to Api m 10, treated with an extract containing minimal amounts of Api m 10, the risk of VIT failure is increased [58]. Even though the current lack of results from prospective clinical studies makes it difficult to exclude other predominant sensitizations as risk factors for treatment failure in

specific patients, such information could in the future help to select the most suitable preparation in a personalized manner based on a patients' sensitization profile [4].

In Europe, purified and nonpurified aqueous venom extracts are commercially available for ultrarush, rush, clustered and maintenance phases, and purified aluminum hydroxide adsorbed (so-called depot) preparations for the conventional build-up and maintenance phases, with many European specialists switching to depot preparations after updosing [59]. Depot preparations seem to be associated with fewer local side-effects than aqueous preparations, but results may have been biased by the slower build-up phase with depot preparations [60]. Purified aqueous preparations cause smaller local reactions compared with nonpurified aqueous preparations [61]. Moreover, a comparative study in HBV-allergic patients indicates the superiority of the purified aqueous preparations over the corresponding nonpurified aqueous preparation under the same rush protocol in terms of SRs during the build-up phase [62]. Even though their efficacy is supported by studies using both sting challenge and “in-field” stings [59], these preparations are not approved by the US Food and Drug Administration and thereby unavailable to the US market [48].

Lastly, few years ago there was a disruption in venom supply for VIT, requiring a switch in manufacturer. The composition of the commercial venoms is similar, but because differences exist, dose adjustments were suggested [63]. A recent Italian multi-center prospective study reported that switching VIT from one manufacturer to another is a safe option, if necessary, in patients who had previously tolerated VIT, even without reducing the previous maintenance dose, in a proper medical setting staffed by experienced personnel [64]. In patients who experienced previous severe SRs during VIT, the treatment should be restarted with a rush/ultrarush protocol in centers experienced in hymenoptera venom allergy and VIT or with a conventional protocol in less experienced centers [21].

Treatment protocols and safety

The recommended maintenance dose of Hymenoptera venom is 100 µg in adults and children. According the last American practice parameter [3] children might be effectively treated with a maintenance dose of 50 µg. Indeed, a retrospective study showed that a 50 µg HB maintenance dose in children provided adequate protection from future Hymenoptera stings, but protection was based on the young participants' accounts of the reaction type [65]. Considering the lesser amount of venom delivered, 50 µg could be protective in the case of Vespid allergic children [66].

Table 5 Some examples of treatment protocols for VIT

Day	Hour	Conventional ^a	Cluster ^a	Rush ^a	Ultrarush ^a
1	0 0.5 1 1.5 2.5	0.01 0.1	0.001 0.01 0.1	0.01 0.1 1 2	0.1 1 10 20 30 40
2	0 1	–	–	4 8 10 20	–
3	0 1 2	–	–	40 60 80	–
4	0	–	–	100	–
8	0 1	1 2	1 5 10	100	–
15	0 1	4 8	20 30	100	50
22	0 1	10 20	50 50	–	100
29	–	40	100	100	–
36	–	60	100	–	–
43	–	80	–	100	100
50	–	100	–	–	–
57	–	100	–	–	–
64	–	–	100	–	–
71	–	100	–	100	100
85	–	100	–	–	–
92	–	–	100	–	–
99	–	–	–	100	100
106	–	–	100	–	–

^a Dose in μg of venom
Further injections of the maintenance dose of 100 μg —every 4 weeks during the first year, every 6 weeks in the second year

A dose of 200 μg is recommended when a SR follows an insect sting in spite of VIT with 100 μg [67] and in highly exposed populations such as beekeepers [68].

According to some authors, an elevated maintenance dose (usually 200 μg) from the start of VIT should be administered to HBV-allergic patients with concomitant mastocytosis and also considered in vespid venom-allergic subjects with additional risk factors [69].

To maximize protection, minimize side-effects and optimize patient convenience, slow to ultrarush induction protocols have been designed (Table 5). With rush and ultrarush protocols the time required to reach the maintenance dose takes a few days or only hours respectively, with subsequent boosters before initiating a monthly schedule (Table 6). This method is particularly useful in highly exposed subjects (e.g. beekeepers) or in patients referred to the specialist just prior to the start of the insect season, in order to reach the protective dosage as quickly as possible. In contrast with American procedures [3], rush VIT is a routinely used core treatment in Europe [21].

Table 6 An example of protocol of honeybee build-up rush phase [62]

Day	Dose	mL administered	μg administered	Concentration $\mu\text{g/mL}$
1	1	0.10	0.01	0.1
	2	0.10	0.1	1
	3	0.10	1	10
	4	0.20	2	10
2	5	0.30	3	10
	6	0.35	3.5	10
	7	0.35	3.5	10
3	8	0.10	10	100
	9	0.15	15	100
	10	0.15	15	100
4	11	0.20	20	100
	12	0.25	25	100
	13	0.25	25	100
5	14	0.30	30	100
	15	0.35	35	100
	16	0.35	35	100

Some studies show that VIT is protective immediately after the conventional maintenance dose has been reached, as demonstrated in HBV-allergic patients by sting challenges performed one week after reaching the maintenance dose, after a 3–5 day rush protocol [70, 71].

It may be recommended to give injections every 4 weeks in the first year of treatment, every 6 weeks in the second year, and in case of a 5 year treatment every 8 weeks from year 3–5 [4]. For patients who continue VIT for longer period, a 12 week interval is safe and effective [3], even though the studies assessing the feasibility of extending the maintenance interval up to 12 weeks included patients with mainly vespid allergy, or relied on reactions to field stings only.

The risk of side effects during VIT is highly variable, ranging from 8 to 20% [72–74], being more frequent during the build-up than in the maintenance phase and with rapid protocols (Table 3). It may be recommended that patients treated with bee venom and those on rapid up dosing protocols should be closely observed for side effects as they are at a higher risk of experiencing adverse events [73, 74]. However, some authors do not consider rush or ultrarush induction protocols to be dangerous, since they were able to demonstrate a low risk of systemic reactions and a safety profile equivalent to or even better than slower protocols [21].

The higher incidence of adverse reactions with honeybee VIT has been investigated using different approaches devised to improve safety, for example, pre-treatment with antihistamines, which may reduce the number/severity of large local reactions and mild systemic reactions [4].

Purified venom preparations can be recommended as they have a lower frequency of local and systemic adverse events than nonpurified aqueous prepara-

tions, especially in HBV allergic patients [62]. The safety profile of the purified aqueous and depot extract have been also confirmed in real life by Stovesandt et al. [75].

Side effects from VIT may be more frequent and severe in patients with elevated basal tryptase values, in patients allergic to vespids [74] and in those with mastocytosis [41]; however risk factors for adverse reactions in this patient population (e.g., type of mastocytosis, venom used for VIT, protocol) require further evaluation.

Unmet needs and future strategy

There is no doubt that subcutaneous VIT is the most effective treatment for Hymenoptera sting-induced SRs. VIT has an early, sustained and long-term efficacy and a disease modifying effect, and it can have a significant beneficial impact on HRQL.

However, there is still some gaps in evidence [4] that should be addressed in the near future. For instance, in children optimal duration of VIT should be identified, and the effect of VIT on HRQL should be investigated further. In adults, there is need for studies with sufficient power to evaluate risk factors for adverse effects during VIT or for treatment failure. In this context biomarkers to predict effectiveness of VIT and to identify treatment failure after stopping the treatment are urgently needed.

In addition, new VIT formulations and routes of administration would be helpful to make the therapy less invasive, potentially increasing the adherence and quality of life of patients. The use of sublingual immunotherapy (SLIT) has been already proposed for LLR due to bee stings, but further studies are needed to confirm the efficacy and the proper indications [76].

Finally, there is now a need to ensure that primary care healthcare professionals know which patients might benefit from VIT, that national healthcare providers understand that VIT is highly effective and is likely to be cost-effective, and that patients and patient support groups are aware of this approach [4].

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