

Quality of life in insect venom allergic patients

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Purpose of review

As re-sting rates and mortality in Hymenoptera allergy are generally low, health related quality of life is an important therapeutic target in the treatment of allergic patients. This review focuses on the impact of anaphylactic reactions and the effect of interventions in health related quality of life for Hymenoptera allergic patients.

Recent findings

Anaphylactic reactions following insect stings can have a great impact on the quality of life of insect sting allergic patients. Venom immunotherapy, with information about the risks and benefits of the treatment, was shown to improve health related quality of life. There were no patients whose health related quality of life was so severely impaired that they did not improve with venom immunotherapy. Treatment with an Epipen (ALK-Abello, Nieuwegein, The Netherlands) resulted in a deterioration in health related quality of life.

Summary

These findings suggest that patient education of these risks and benefits is as important as the treatment itself in order to achieve all the important therapeutic goals of venom immunotherapy. For most patients the Epipen is insufficient as definitive treatment from a quality of life point of view. Although the low mortality, morbidity and re-sting frequency in Hymenoptera allergic patients has led some authorities to conclude that many patients are treated unnecessarily, this conclusion is refuted by the fact that venom immunotherapy improves health related quality of life in the vast majority of patients receiving this treatment, even if they are not re-stung.

Keywords

insect venom allergy, quality of life, venom immunotherapy, Epipen, Hymenoptera, HRQL

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Abbreviations

HRQL health related quality of life
OPD outpatient department
VIT venom immunotherapy
VQLQ Vespid Allergy Quality of Life Questionnaire

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Introduction

Although insect stings can result in anaphylactic reactions, mortality is surprisingly low. Most patients who die of insect sting anaphylaxis did not have prior generalized allergic reactions [1,2]. Although allergy to Hymenoptera stings is common, morbidity is low due to the low re-sting frequency in most insect allergic patients [3,4]. Also, insect sting anaphylaxis has a variable risk of anaphylaxis following re-exposure with no recurrence of symptoms in many patients [5]. The life saving potential of venom immunotherapy (VIT) and its capacity to substantially reduce morbidity are therefore limited, despite being highly efficacious in preventing recurrent anaphylaxis.

This has led to criticism of VIT in the past [6,7]. Rubenstein [6] stated that allergists were scaremongers, and VIT was unnecessarily given to many patients. In his view, as physicians were not able to predict which patients are at risk for a serious reaction, it would be sufficient for patients to carry injectable epinephrine hydrochloride if they were frightened of being stung again.

These discussions did not consider the psychologically traumatic effect of an anaphylactic reaction. Allergic reactions following insect stings are frightening events and often affect emotional functioning of insect allergic patients. Reactions can also have an impact on patients' social and, in some cases, even professional functioning. Most Hymenoptera allergic patients therefore make efforts to avoid a recurrence following an anaphylactic reaction, sometimes even leading to a drastically altered style of living. Although these negative effects have been widely recognized, the impact of anaphylactic reaction following insect stings has never been the subject of systematic study, until recently.

Analysis of health related quality of life (HRQL) affords a methodology for studying the effect of an intervention in relation to outcomes which are important and relevant to patients. This is particularly informative in Hymenoptera allergy for which mortality and medical morbidity are low and thus insensitive to changes in health status.

In this article we will review the known effects of an anaphylactic reaction on the HRQL of different patient groups. The results of different treatments on quality of life will be discussed. The implications of these findings for clinical practice will be examined. We will conclude

by indicating where future research in this area could further improve our management of these patients.

The influence of untreated Hymenoptera allergy on quality of life

Studies concerning the impact of Hymenoptera allergy on quality of life have been very limited. An exploratory survey study in patients with insect venom allergy found that about one-third of the patients had debilitating beliefs concerning their allergy [8]. These patients believed that they should always be under medical surveillance. Over 12% of the patients were continuously preoccupied with the event, experiencing intrusive, disturbing thoughts, which they were unable to control. Patients felt restricted with regard to living in rural areas, going outdoors and especially in doing certain types of work. Some of them even felt vulnerable to diseases in general. The impact of these beliefs on patients' quality of life was not measured. Importantly, it is also unknown whether and how these patients were informed about the risks of their condition and the risks and benefits of treatment. However, the findings do indicate that the impact of an anaphylactic reaction can be very broad, and may even result in psychological symptoms which are unlikely to respond to treatment.

A systematic study of quality of life issues in Hymenoptera allergic patients was carried out when an instrument to study HRQL was developed for yellow jacket allergic patients [9**]. Nearly all patients indicated that many of the items in the 'emotions and feelings' domain were relevant and important. The impairment in quality of life was experienced in a broad range of activities such as work, mobility, social interactions and outdoor activities. However, there were no particular activities in which every patient felt limited. The most important issues were selected for with the Vespid Quality of Life Questionnaire (VQLQ).

The influence of clinical and demographic variables on health related quality of life

HRQL was measured at the start of the study. We examined whether this initial HRQL correlated with clinical and demographic variables.

Effect of severity of the anaphylactic reaction on HRQL in untreated patients

Intuitively it seems logical that the more severe the reaction the more the impact on quality of life. However, we found that VQLQ scores at the first outpatient department (OPD) visit did not correlate with the severity of the sting reaction (Fig. 1). It seems that independent of severity, a sting reaction results in uncertainty which results in an impaired quality of life. These results illustrate that patients' perception of risk is

not intuitively obvious and needs to be studied before conclusions may be drawn.

Effect of time after experiencing an anaphylactic reaction

Patients seen by a physician shortly after experiencing an anaphylactic reaction have almost no experience of living with the possibility of a re-sting and recurrent systemic reaction. The impact of an anaphylactic reaction on quality of life will initially be small in most cases.

This was confirmed in our study in which HRQL was more impaired in patients who had been stung more than a year before the first OPD visit than in those stung within a year of their visit (Table 1). This is in keeping with the experience of many physicians in this area that patients often do not present acutely following a sting event. This suggests that the passage of time alone is not accompanied by gradual improvement in HRQL and that the memory of the anaphylactic event either does not fade, or even if it does, that this does not significantly influence HRQL.

Effect of anxiety on quality of life

Although the study of Confino-Cohen [8] showed that many patients with remaining debilitating beliefs after VIT would probably need some form of psychological treatment, general anxiety was not measured in these patients. In our study general anxiety was measured with the Spielberger State-Trait Inventory DY2. We found that the higher the general anxiety the more impaired the HRQL ($r=0.37$; $P<0.001$; see Table 1). As will be discussed later, this did not preclude HRQL improvement in the anxious group.

Effect of demographic variables on quality of life

The HRQL of men was less impaired than the quality of life for women (Table 1). This was not due to a higher general anxiety level, a difference in time interval since the sting reaction, reaction severity or differences in age. Thus, experiencing an anaphylactic reaction results in a poorer HRQL in women than in men. Age does not influence quality of life: in both younger and older patients quality of life was impaired equally (Table 1).

Effects of treatment on health related quality of life of Hymenoptera allergic patients

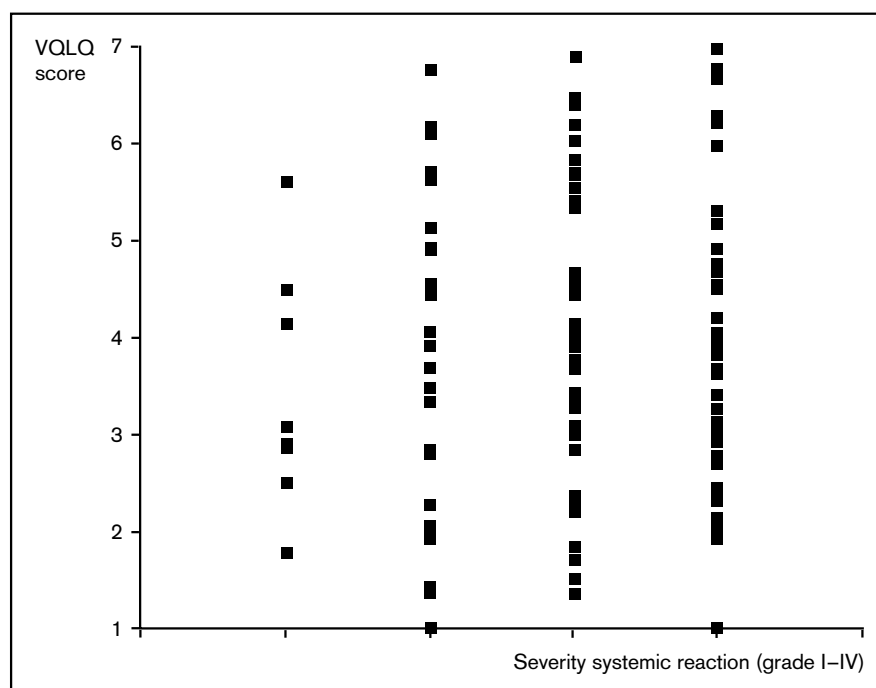
Having examined determinants of HRQL in Hymenoptera allergic patients, we will now examine whether patients with an impaired quality of life may benefit from interventions.

The effect of patient information

An assumption often made by clinicians is that once effective medical therapy has been given, patients' perceptions of benefit will improve correspondingly. In

Figure 1. Severity of the sting reaction before treatment

Severity, according to Müller, is shown in relation to the Vespid Allergy Quality of Life Questionnaire (VQLQ) score, ranging from no impairment in health related quality of life (score 1) to severe impairment (score 7) before treatment.

**Table 1. The influence of demographic variables on quality of life at first outpatient department visit**

		VQLQ	<i>n</i>	<i>P</i> -value
Gender	♂	3.47	61	NS
	♀	4.23	80	
Age		No correlation		
Anxiety	< 5 ^a	3.62	96	<i>P</i> < 0.001
	> 5	4.56	43	
		Correlation: <i>r</i> = 0.37; <i>P</i> < 0.0001		
Time interval	< 1 year ^b	3.58	73	<i>P</i> < 0.002
	> 1 year	4.42	68	
Severity		No correlation		

VQLQ, Vespid Allergy Quality of Life Questionnaire. ^aAnxiety measured with the Spielberger State-Trait Inventory DY2. ^bTime interval between allergic reaction and first outpatient department visit.

the case of VIT it is assumed that patients treated with VIT will no longer worry about insect stings. The study of Confino-Cohen [8] called this assumption into question. Despite immunotherapy, patients retained debilitating expectations, independent of the time on maintenance dose of immunotherapy (and even though these patients must have understood that VIT was being carried out to treat their insect allergy). In the accompanying editorial it was suggested that it is not sufficient for patients to know that a certain treatment is effective [10]. However, it is unknown whether these patients received any information and, if so, what kind of information and how it was given. As the medical treatment alone (VIT) did not achieve an improvement

in patients' debilitating beliefs, the authors suggested a need for better patient education but without indicating the requirements for this patient information. They suggested accompanying the information with a psychological evaluation. However, they did not indicate the character of this intervention. The author of the accompanying editorial suggests cognitive-behavioural therapy, together with rational discussion and information, to eventually achieve behavioural change. These are alarming observations, as most of these interventions are beyond the scope of the allergy specialist. Although the authors further considered the persistence of debilitating beliefs to be due to the lack of re-stings, they do not suggest offering these patients sting challenges.

The expectation of the outcome of a future sting and related quality of life is indeed largely determined by patients' perception of risks and benefits of the treatment. Patients' expectations may change if the clinician provides instruction about the therapy and what patients should expect in the future, and if they understand and remember the risks and benefits of the treatment. Expectations are not always under rational control, however, and even if the patient information is adequate one can imagine that this need not be effective for all patients.

In our study comparing the effects of VIT with those of the Epipen on HRQL, patients were educated with

standardized materials and procedures, approved by a committee [11••]. For an extensive description of procedure and materials see the article. All patients received written information specifying the chance of a systemic reaction after a future sting, as well as the possible severity of the reaction in the untreated situation. It also indicated the qualitative and quantitative risk reduction relating to VIT and the Epipen. This document was further explained by a trial technician and patients had the opportunity to ask questions. After receiving patient information participants were randomized to either VIT or Epipen. Patients were not screened for psychological or psychiatric abnormalities before inclusion in the study.

The results showed that VIT improved HRQL in all patient groups. We did not examine whether our patients had debilitating beliefs. Specifically, there were no patients whose HRQL was so severely impaired that they did not improve with VIT. This suggests that, if our patients had debilitating beliefs regarding their allergy, this did not significantly influence their HRQL improvement. Also the fact that only two out of 148 individuals were re-stung during the study period indicated that the protection that VIT provides does not have to be experienced directly in order for HRQL to improve.

Is providing correct information as to the risks of untreated Hymenoptera allergy alone sufficient to improve health related quality of life?

We did not study the provision of correct information about the risks of untreated Hymenoptera allergy directly because ethical considerations did not permit us to include a non-intervention group. However, in the Epipen arm of the study, HRQL deteriorated. Although this may have been due to deteriorative effects of the Epipen on HRQL, there was no suggestion that this may have been offset by possible HRQL improvements as a result of receiving correct information at the start of the study. Moreover, HRQL did not improve in patients choosing the Epipen as their only treatment. Even in these patients, who did not dislike the Epipen enough to prevent them from choosing this treatment, receiving correct information did not result in an improvement in HRQL. Furthermore, of patients provided with correct information, 49% refused to be randomized, of which 91% chose to be treated with VIT. Taken together, these results suggest that most patients are not reassured by correct information as to the risks of their allergy in the absence of VIT, and that receiving such information alone is not sufficient to improve HRQL.

The effect of treatment with the Epipen

In contrast to patients treated with VIT, patients randomized to treatment with an Epipen showed a

statistically significant deterioration in their HRQL [11••]. Anxious patients did not deteriorate more than the less anxious patients. Thus, injectable epinephrine in the absence of VIT is not adequate treatment from a HRQL point of view.

Although the percentage was small (9%), some patients chose the Epipen rather than starting VIT after receiving the patient information. In contrast to patients randomized to the Epipen, the HRQL of patients choosing this treatment did not change or deteriorate. For these patients the treatment might be appropriate. The reasons for preferring injectable epinephrine were diverse. Some were practical such as having no time for regular injections, some patients were afraid of the side effects of VIT, and some patients indicated that they felt VIT was not worth the effort after due consideration of the risks and benefits of both treatments.

In our centre, patients are advised to stop carrying their Epipen when they reach maintenance dose. We do not advise carrying an Epipen again after completion of VIT. The risk of a systemic reaction following a yellow jacket sting is low (<10%) and most of these reactions are also less severe [5,12,13]. However, not all allergists are willing to accept that risk, and some patients given full information will prefer to have an Epipen especially for activities such as camping and hiking. In our study we asked patients whether they would have preferred to carry the Epipen after starting VIT, and 12.4% indicated that they still carry their Epipen because they feel more safe with it. We were not able to study patient preference in this regard following discontinuation of VIT.

Overall, this means that policies concerning the Epipen differ between centres [14,15]. In our opinion an important reason to start VIT is to enable the patient to discontinue carrying the Epipen. It is inconvenient to carry an Epipen and it may act as an affirmation and reminder of the patient's risk and thus negatively influence the HRQL.

Although there is little direct information on HRQL in untreated patients, patients treated with an Epipen show a deterioration in their HRQL over time, and the treatment should only be considered as a temporary measure unless VIT is contraindicated, impossible or otherwise undesirable.

The effect of venom immunotherapy

VIT resulted in a clinically significant improvement of the HRQL of yellow jacket allergic patients [11••]. Subgroup analysis revealed no patient groups unresponsive to this treatment from a HRQL point of view.

Although women improved more than men, improvement was seen in men as well as women. Similarly, improvement was seen in all age groups, although it increased with age.

Even patients with high anxiety trait scores showed an improvement in HRQL after undergoing VIT. Thus, patients with higher levels of general anxiety are not refractory to treatment with VIT in terms of HRQL. The improvement was independent of the severity of the initial sting reaction. Even patients who experienced very severe anaphylactic reactions experienced an improvement in their HRQL.

The improvement was also seen in those stung recently as well as those stung more than a year before their OPD visit, although this was more so in patients who experienced an anaphylactic reaction more than a year before their OPD visit. Thus, VIT given many years after a sting reaction seems to be as effective on HRQL as when this treatment is given within a year of the last sting reaction. The mean final VQLQ scores of patients first randomized to Epipen before undergoing VIT for 1 year were comparable with the mean final VQLQ scores of patients who started immediately with VIT. Thus, a delay of 1 year in starting VIT does not result in a permanent (partial) impairment in HRQL.

Disadvantages of the treatment concerning quality of life

Some critics of VIT have maintained that this form of treatment is cumbersome, unpleasant and time-consuming for patients. We studied this using a burden of treatment measurement [11•]. Patients were asked to examine the balance of negative and positive effects of VIT on their overall wellbeing. The vast majority (94%) of the patients rated VIT as very to extremely positive, in contrast to patients treated with the Epipen, which only 30% rated as positive.

From the patient's perspective, therefore, the possible disadvantages of VIT do not detract from the advantages of the treatment. This is noteworthy, as the negative aspects of the treatment will be encountered immediately, in contrast to the protective effect, which was not experienced directly by most patients.

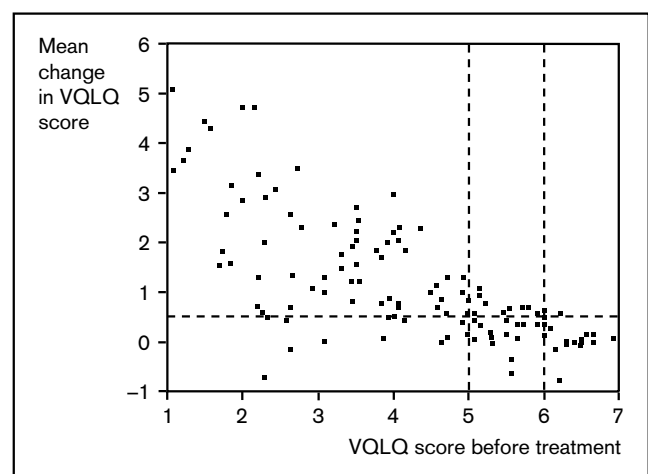
Can health related quality of life be used to select patients for treatment with venom immunotherapy?

Although some patient groups benefit more from VIT than others, we were not able to select patients for whom VIT was ineffective from a quality of life point of view. Some patients had little HRQL impairment before treatment, and therefore did not show improvement on VIT. However, this number of patients was small (Fig.

2), suggesting that initial HRQL measurements would not be an efficient way to select patients for having or not having VIT.

After being randomized to the Epipen, younger patients tended to prefer this treatment more often than older patients (Table 2), although many younger patients preferred VIT. Initial HRQL score and other demographic variables do not allow the clinician to select patients for this form of treatment. Moreover, HRQL generally deteriorates over time in untreated patients, so that although VIT could probably be postponed in some patients with initially unimpaired HRQL, it would probably be required in many of these cases eventually. We have seen adolescent patients sent by their parents for assessment, who refused VIT, only to present again after some years requesting VIT.

Figure 2. Vespid Allergy Quality of Life Questionnaire score versus mean change on the questionnaire



A score of 0.5 is the minimum clinically important difference. The higher the Vespid Allergy Quality of Life Questionnaire (VQLQ) scores before treatment, the lower the improvement on the VQLQ.

Table 2. Clinical and demographic variables of patients choosing to continue treatment with the Epipen after being randomized for 1 year to the Epipen as the only treatment

	VIT	Epipen	P-value
Age (years)	45.5	34.1	$P < 0.05$
Sex ♂:♀ (%)	44:56	33:67	NS
VQLQ score at $t=0$	3.34	3.73	NS
VQLQ score at $t=1$	2.89	3.80	NS
Mean change in VQLQ	-0.45	0.08	NS
Time interval (%): dermal vs. more than dermal	11:89	11:89	NS
Anxiety score	34.8	27.9	NS

VIT, venom immunotherapy; VQLQ, Vespid Allergy Quality of Life Questionnaire.

Areas for future research

In certain European centres [15] patients with dermal reactions or mild reactions with average exposure to insects are managed with the availability of emergency medication without VIT. Preliminary data show that HRQL is as impaired in dermal reactors as in patients with more extensive reactions, suggesting that an Epipen as sole treatment would be inappropriate. So far, however, we have not been able to study sufficient numbers of such patients to draw conclusions about this important subgroup.

The impact of anaphylactic reactions in children on their HRQL is unknown. Although most young children are very frightened of insect stings, it is not known whether children who experienced an allergic reaction have a more impaired HRQL than children who have been stung without experiencing such a reaction. The HRQL of parents may be more impaired than that of the children themselves. HRQL measurements have been undertaken in children and adolescents [16,17]. The impact of rhinitis on HRQL in adolescents was different from that on adults [16]. It would be of interest to study the HRQL of children and adolescents as the burden of the treatment (VIT) could have more of an impact (negatively) on their HRQL than the anaphylactic reaction itself.

HRQL is likely to be the most important factor causing the patient to seek medical attention for his or her allergy. From epidemiological data it is known that many individuals do not seek such medical attention despite having experienced systemic reactions to insect stings. A recent report from Australia showed that five out of seven victims of vespid sting fatalities were aware of their condition, but they were never treated with immunotherapy and did not carry epinephrine with them [18]. It would be of interest to know what the HRQL of individuals who do not seek medical attention is, what its determinants are, and whether HRQL or other factors are important in preventing these individuals from seeking help for their allergy.

Conclusion

A sting reaction, independent of its severity, may have a great impact on quality of life. It has been shown that providing VIT with correct information as to its efficacy is sufficient to improve both the expectation of the outcome of future stings as well as the resultant HRQL. No patients have been encountered whose HRQL was so severely impaired that they did not improve with VIT.

We therefore feel that if patients are given proper instruction in conjunction with VIT then they are unlikely to retain or develop debilitating beliefs

concerning their allergy which are extensive enough to prevent improvement in HRQL. As almost all patients in our study did not experience a re-sting and therefore did not experience the clinical protection, the improvement in quality of life is due to the knowledge that these patients have about the treatment. Therefore, patient education as to these risks and benefits is as important as the treatment itself in order to achieve all the important therapeutic goals of VIT.

In view of the negative effects on HRQL, the Epipen should only be considered as adjunct or definitive treatment in carefully selected cases. As VIT given many years after a sting reaction seems to be as effective on HRQL as when this treatment is given within a year of the last sting reaction, even patients who have carried an Epipen for years may be offered VIT to improve their HRQL.

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