



Impaired quality of life in patients with insect venom allergy

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Received: 6 December 2016 / Accepted: 26 January 2017 / Published online: 14 March 2017
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Abstract

Background Although documented fatalities following insect stings are only rarely reported, insect venom allergy is a potentially life-threatening disease. Experiencing anaphylaxis due to an insect sting represents a threatening event for patients.

Methods A presentation and discussion of the published data on the importance of quality of life among insect venom allergy patients.

Results It is well established today that affected individuals experience anxiety, practice avoidance behavior, and restrict outdoor physical activities as a result of insect stings, thereby impacting their quality of life as a whole. Using a specially developed quality-of-life questionnaire among individuals allergic to wasp venom, it was possible to show that performing specific Hymenoptera venom immunotherapy (VIT) results in improved quality of life, despite the occurrence of an initial and mild systemic sting reaction with manifestations restricted to the skin. Solely carrying an adrenaline autoinjector does not show this effect. This improved quality of life due to VIT was demonstrated not only in adults, but also in children with insect venom allergy, as well as in their parents. It was also shown that the tolerated sting challenge as a method of monitoring treatment efficacy under on-going VIT likewise results in increased quality of life in patients. The fact that the patient experiences a “problem-free,” controlled sting by the disease-causing insect confirms the good efficacy of VIT described

in the patient information and has measurable effects on patients' quality of life and behavior.

Conclusions Therefore, particularly with regard to quality of life, it is important to ensure that all insect venom allergy patients are referred to an allergist, the indication for VIT is verified, treatment is initiated where appropriate, and sting challenge is performed during maintenance treatment.

Keywords Immunotherapy · Insect venom allergy · Quality of life · Sting challenge

Abbreviations

VIT	Hymenoptera venom immunotherapy
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
QUALY	Quality-adjusted life years
SF-36	Short-Form 36
SIT	Specific immunotherapy
UK	United Kingdom
VQLQ	Vespid Quality of Life Questionnaire

Introduction

Data on treatment efficacy are playing an ever greater role when it comes to the allocation of healthcare resources. In Great Britain (UK), the National Institute for Health and Care Excellence (NICE) commissions systematic literature reviews and analyses of treatments with the aim of determining the efficacy of various treatment forms, primarily on the basis of cost-effectiveness ratios (costs per QUALY). QUALYs (quality-adjusted life years) refers to the mean number of years at a particular quality of life gained by a certain treatment, e. g., compared with placebo. On the basis of cost–QUALY ratios, NICE then decides which treat-

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ment forms are to be approved in the UK or whether the related treatment costs can be reimbursed.

As part of a review of the efficacy of specific immunotherapy using Hymenoptera venom (VIT), NICE recently determined that VIT would generate per-QALY costs of around £ 7.6 million (over € 9 million; exchange rate as of 12/2016) compared with an intervention comprising solely of avoidance measures [1]; this cost–QALY ratio exceeds the currently acceptable limit for treatment reimbursement (£ 30,000/QALY). Only by taking into account data on quality of life was it possible to arrive at a cost–effectiveness ratio acceptable in the UK.

In Germany, a different algorithm is currently used for the approval or cost reimbursement of treatments: for a treatment to be approved, only—and, in principle, irrespective of cost in the first instance—evidence of effectiveness is required. Data on quality of life most certainly play a role here, e. g., when it concerns pricing drugs or treatments, as well as when evidence of an additional benefit is required to achieve a positive evaluation or to agree a particular fee with the health insurance funds.

Awareness of how a treatment restores a patient's quality of life also plays a crucial role for the physician active in the field of allergology. This primarily applies to establishing the indication for VIT, as well as to recommending particular diagnostic techniques, such as sting challenge for instance.

General quality of life with insect venom allergy

Experiencing a systemic allergic reaction to a sting reduces the quality of life of those affected. For example, a nonstandardized questionnaire used on a group of 97 insect venom-allergic individuals was able to show for the first time that around a third of patients held persistent debilitating beliefs as a result of the stinging event, were preoccupied with insect sting anaphylaxis, and felt emotionally impaired as a result [2]. The debilitating beliefs and anxieties about their allergy manifested in particular as concerns about outdoor activities, occupational restrictions, living in a rural environment, and fear of repeat insect sting anaphylaxis. This often had a negative impact on their social and, at times, also their professional, lives.

On the whole, quality of life is impaired to a greater extent among wasp venom-allergic individuals compared with individuals allergic to bee venom [3]. This may be due to the fact that wasps exhibit more aggressive behavior than bees and are, thus, perceived as more of a threat. On the other hand, one regularly encounters bee venom-allergic beekeepers whose passion for beekeeping supersedes their health concerns and fears.

An initial severe allergic reaction can be associated with more pronounced symptoms of anxiety [4]. However, it can be said as a whole that even a history of milder systemic reactions can impair patients' quality

of life; thus, the severity of the sting reaction did not correlate with the quality-of-life index score [5].

There have been no studies as yet to investigate whether, alongside drug therapy in the form of VIT and targeted patient information, specific behavioral therapy to decondition patients from the above-mentioned anxieties and debilitating beliefs would be beneficial [6].

Instruments for measuring quality of life in insect venom allergy

The development and validation of a suitable measuring instrument in the form of a standardized questionnaire, designed to determine quality of life in this specific patient group, formed an essential basis for the scientific investigation of quality of life in insect venom-allergic individuals. Oude Elberink et al. first published a standardized questionnaire in 2002 to measure the specific and health-related quality of life in individuals with insect venom-allergy (VQLQ, Vespil Quality of Life Questionnaire) [7]. Altogether, the questionnaire comprises 14 questions relating to symptoms of anxiety, stress situations, and emotional distress in insect venom-allergic individuals. Each question can be answered on a scale of 1 (very high impact on quality of life) to 7 (no impact on quality of life). The questionnaire can be easily completed by patients within 10 min. Since the VQLQ was validated in Dutch and US patients, it was initially only available in Dutch and English.

The questionnaire has since been translated into German (VQLQ-d), Spanish (HRQLHA), Polish, and Turkish (VQLQ-T), and provision has been made in each case for further modifications [8–11].

Although the original questionnaire by Oude Elberink et al. was developed and validated only for wasp venom-allergic individuals, it was later also used in bee venom-allergic individuals [9, 11, 12]. For instance, the Spanish questionnaire also includes patients allergic to paper wasps (Polistinae) and not only those allergic to true wasps (Vespinae) [9].

Specific questionnaires have also been developed to measure quality of life in children and adolescents with insect venom allergy, as well as in their parents [13, 14].

Specific immunotherapy and quality of life in insect venom allergy

VIT represents the most significant treatment approach for insect venom-allergic individuals and is associated with high success rates. Therefore, the question of whether VIT resulted in a change in quality of life among affected patients was at the focus of investigations on quality of life in insect venom-allergic individuals. It could be shown that VIT significantly improved health-related quality of life among wasp venom-allergic patients, whereby two out of three

Table 1 The most relevant studies into the impact on quality of life among insect venom-allergic individuals

Study/year	Patients (<i>n</i> = case number)	Objective/comparison	Result
[15]/2002	Wasp venom-allergic patients (<i>n</i> = 74)	Health-related quality of life under VIT or adrenaline autoinjector	VIT improves health-related quality of life
[16]/2006	Wasp venom-allergic patients (<i>n</i> = 193)	Effects of an adrenaline autoinjector on quality of life compared with VIT	Solely carrying an adrenaline autoinjector impairs quality of life
[17]/2009	Wasp venom-allergic patients (<i>n</i> = 55)	Health-related quality of life under VIT or adrenaline autoinjector in the case of systemic skin reactions only	VIT also improves health-related quality of life in the case of systemic skin reactions only
[19]/2009	Insect venom-allergic patients ^a (<i>n</i> = 34)	Health-related quality of life under VIT	VIT improves health-related quality of life and reduces subjectively debilitating beliefs and anxieties
[18]/2014	Bee venom-allergic patients (<i>n</i> = 90)	Anxiety and depression in patients under VIT, adrenaline autoinjector, or without treatment	Solely carrying an adrenaline autoinjector has the highest anxiety and depression values, VIT the lowest
[20]/2013	Wasp venom-allergic patients (<i>n</i> = 57)	Effects of sting challenge during VIT on health-related quality of life	Tolerated sting challenge improves health-related quality of life
[12]/2014	Wasp and bee venom-allergic patients (<i>n</i> = 100)	Effects of sting challenge during VIT on health-related quality of life	Tolerated sting challenge improves health-related quality of life
[21]/2015	Wasp and bee venom-allergic patients (<i>n</i> = 50)	Effects of sting challenge during VIT on health-related quality of life	Tolerated sting challenge improves health-related quality of life

VIT specific Hymenoptera venom immunotherapy
^aNo data on whether wasp and/or bee venom-allergic patients

patients benefited from the treatment. In contrast, specific quality of life remained unchanged or even worsened in the control group, which was supplied solely with adrenaline autoinjectors for emergency medication [15]. The authors concluded that solely prescribing an adrenaline autoinjector represented an inadequate treatment option from the perspective of health-related quality of life. A follow-up study even showed that prescribing solely an adrenaline autoinjector without simultaneously performing VIT was not only associated with a reduction in specific quality of life, but was also perceived by patients as emotionally distressful [16].

Under VIT, quality of life improved even in wasp venom-allergic patients who had experienced only mild systemic reactions restricted to the skin [17]. This effect was not seen in patients randomized to receive only an adrenaline autoinjector for emergency medication; indeed, a further worsening of health-related quality of life was observed in this group. Established VIT is deemed nonburdensome and superior to an adrenaline autoinjector even by those patients who originally experienced only mild systemic reactions.

Also among bee venom-allergic individuals, the provision of an adrenaline autoinjector as the sole treatment measure was associated with poorer quality of life (measured using a depression and anxiety questionnaire) compared with the performance of VIT [18].

The clinical significance of the impact of VIT on specific quality of life in insect venom-allergic individuals is also reflected in the calculated number of treatments needed (NNT, number needed to treat). For example, if insect venom-allergic individuals exhibit only dermal manifestations upon sting reaction, one needs to treat 1.7 patients to achieve a significant

effect in terms of improved quality of life and, indeed, only 1.4 patients if anaphylaxis severity is greater [15, 17].

Another prospective study showed that VIT improves not only health-related quality of life, it also reduces subjectively debilitating beliefs and allergy-related anxiety [19]. Despite VIT's positive effect, almost a third of patients nevertheless reported continued debilitating beliefs and anxiety, which, although medically unfounded, caused considerable impairment to their everyday lives. The authors therefore recommended performing sting challenges particularly in these patients, in order that a further improvement to quality of life could be achieved by virtue of the fact that the patients would—in all likelihood—tolerate the sting challenge.

Sting challenge and quality of life in insect venom allergy

In clinical routine, patients with insect venom allergy often report that, despite extensive information on the high efficacy of VIT, they are only able to gain confidence in the treatment after tolerating a sting challenge. This clinical observation has been evidenced by three prospective studies.

The first study investigated 57 wasp venom-allergic patients before and after sting challenge performed during on-going VIT in relation to their general and health-related quality of life (using the German version of the VQLQ) [20]. Although the tolerated sting challenge had no effect on general quality of life, it significantly improved the specific quality of life of patients after sting challenge, particularly if there had been a marked impairment to quality of life prior to challenge.

The second study on 100 (82 wasp venom-allergic and 18 bee venom-allergic) patients also showed that the tolerated sting challenge resulted in a significant improvement in health-related quality of life, irrespective of age and gender, as well as the severity of the systemic anaphylactic reaction experienced at the initial stinging event [12]. Once again, it showed no effect on general quality of life as such, but a significant improvement was seen in the subgroups “vitality” and “physical role function” in the SF-36 questionnaire (short-form 36). This suggests that patients exhibit less avoidance behavior and, e. g., undertake more outdoor activities following a tolerated sting challenge, which serves as tangible evidence of treatment efficacy. What was also striking here was that quality of life was more markedly improved among wasp venom allergic individuals compared with those allergic to bee venom.

The third study performed a longitudinal comparison of two groups, each comprising 25 insect venom allergic patients (wasp and bee venom allergies) with established VIT; one group underwent sting challenge, while the other did not [21]. Only those patients who underwent sting challenge showed an improvement in specific quality of life over time. This conclusively demonstrates that sting challenge under established VIT results in an improvement of quality of life among insect venom-allergic individuals.

Conclusion

Insect venom allergy is unequivocally associated with a marked impairment to health-related quality of life, given that a considerable proportion of patients live in fear a repeat sting event, feel emotionally debilitated as a result, and potentially modify their behavior. Performing VIT is not only highly effective in relation to avoiding a recurrence of sting anaphylaxis, it also improves patients' quality of life in a clinically relevant manner. Solely prescribing an adrenaline autoinjector as emergency medication is not an alternative in this respect, but is associated instead with a reduction in quality of life. Performing sting challenge under ongoing VIT also improves quality of life among insect venom-allergic patients by providing patients with evidence of VIT's efficacy. Table 1 provides a summary of the current data. Therefore, insect venom allergy patients who have experienced a systemic allergic reaction should undergo VIT, as well as sting challenge during the course of treatment, not least from a quality-of-life perspective.

Conflict of interest D. Koschel declares that he has no competing interests.

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