ORIGINAL ARTICLE

Tolerated Sting Challenge in Patients on Hymenoptera Venom Immunotherapy Improves Health-Related Quality of Life

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Abstract

Background: Sting challenge with a live insect remains the best test for proving the efficacy of immunotherapy in Hymenoptera allergy.
Objective: We studied the impact of tolerated sting challenge on quality of life.
Patients and Methods: In this prospective study, data were collected via self-report questionnaires completed by consenting patients with Hymenoptera venom allergy on venom immunotherapy before and after a sting challenge.
Results: The study population comprised 100 adult patients (82 with yellow jacket allergy and 18 with honeybee allergy) who participated between September 2009 and November 2010. After the sting challenge, the score on the Vespid Allergy Quality of Life Questionnaire revealed a statistically significant improvement (mean [SD] change, 0.73 [0.98]; *P*<.0001; 95% CI, 0.52-0.94). This improvement was independent of the patients' gender and age and the severity of the initial anaphylactic reaction. A statistically significant improvement was documented in 2 subgroups of the Short Form 36 Health Survey (physical functioning, mean change, –5.78 [25.23]; *P*=.038; 95%CI, –11.22 to –0.34; vitality, mean change –4.29 [12.49]; *P*=.002; 95% CI, –7.02 to –1.57).
Conclusions: Sting challenge results in a significant improvement in disease-specific quality of life and subgroups of general quality of life in patients allergic to Hymenoptera venom receiving established venom immunotherapy.

Key words: Hymenoptera. Immunotherapy insect. Quality of life. Sting challenge.

Resumen

Antecedentes: La prueba de repicadura con insecto vivo continúa siendo la exploración más adecuada para determinar la eficacia de la inmunoterapia en la alergia a himenópteros.
Objetivo: Estudiar el impacto que produce sobre la calidad de vida relacionada con la salud, una prueba de repicadura bien tolerada.
Métodos: Se trata de un estudio prospectivo, en el que una muestra consecutiva de pacientes alérgicos a himenópteros y en tratamiento con inmunoterapia, respondieron un conjunto de cuestionarios auto-administrados antes y después de la prueba de repicadura.
Resultados: Un total de cien pacientes con alergia a himenópteros (82 avispa y 18 abeja) participaron en el estudio, que se realizó entre septiembre del 2009 y noviembre del 2010. La puntuación del cuestionario VQLQ mejoró de forma significativa tras la prueba de repicadura (media del cambio 0.73, SD 0.98, p < 0.0001, 95% IC: 0.52-0.94). Esta mejoría era independiente del sexo, edad o de la gravedad de la reacción anafiláctica inicial por la que se instauró el tratamiento. También se observó una mejoría significativa en dos de los dominios del cuestionario genérico SF 36 (función física, media del cambio -5.78, SD 25.23, p = 0.038, 95% IC: -11.22- -0.34; vitalidad, media del cambio -4.29, SD 12.49, p = 0.002, 95% IC: -7.02- -1.57).
Conclusiones: La prueba de repicadura bien tolerada se asoció a un incremento de la calidad de vida de los pacientes con alergia a himenópteros, y en tratamiento con inmunoterapia. La mejoría se documentó tanto por un cuestionario específico para la enfermedad (VQLQ) como en algunos dominios del cuestionario genérico SF-36.

Palabras clave: Himenóptero. Inmunoterapia con insecto. Calidad de vida. Prueba de repicadura.

Introduction

Venom immunotherapy (VIT) is a highly effective treatment for patients with a history of systemic reaction and IgE-mediated hypersensitivity to venom allergens [1]. Sting challenge tests with living insects are recommended for patients with Hymenoptera venom allergy on maintenance VIT to identify those who are not yet protected [2]. Using this diagnostic tool, failure of VIT can be detected in up to 22% of allergic patients [3].

Ours is the first study to evaluate the impact of sting challenge on quality of life in patients with Hymenoptera venom allergy on maintenance VIT.

Patients and Methods

Patients

Patients were recruited from the allergy unit of the Fachkrankenhaus Coswig, Coswig, Germany from September 2009 through November 2010. All the patients had a history of a systemic anaphylactic reaction (SAR) after a yellow jacket or bee sting, with IgE-mediated sensitization to yellow jacket or bee venom. Severity was graded 1 to 4 according to Ring and Messmer [4]. Patients underwent ultrarush VIT for 2 days with yellow jacket or bee venom preparations (ALK Abelló) until a maintenance dose of 100 µg was reached. For at least the first year, the maintenance dose was administered every 4 weeks by an attending allergologist.

All patients gave their written informed consent to participate in the study. The Medical Ethics Committee of the Carl Gustav Carus University in Dresden approved the study.

Sting Challenge Tests

For many years, patients at our institution were offered a standard procedure of a sting challenge with a live insect, usually during the first year after reaching the maintenance dose, regardless of the severity of the initial SAR. The sting challenge was performed according to a published procedure and with the patient's written informed consent. After insertion of an intravenous line with a drip infusion and continuous monitoring of heart rate, blood pressure, and oxygen saturation, an open-ended plastic syringe containing the insect was applied to the volar side of the patient's arm. The plunger was depressed in order to push the insect against the patient's skin until a sting was felt by the patient [5].

Instruments

To study the influence of depressiveness and anxiety on health-related quality of life (HRQOL), we applied the Hospital Anxiety and Depression Scale (HADS) [6], a widely used 14-item self-report scale designed to quickly measure current anxiety and depressive symptoms in nonpsychiatric hospital patients.

The General Severity Index of the Brief Symptom Inventory (BSI) was used to measure subjective impairment due to physical and psychological symptoms, particularly depression and anxiety [7,8].

Assessment of HRQOL was completed using the Short Form 36 Health Survey (SF-36), which is a generic questionnaire describing 8 subscales (physical functioning, social functioning, role-physical, role-emotional, mental health, vitality, bodily pain, and general health) [9] and the Lebenszufriedenheitsfragebogen [LEZU, Life Satisfaction Questionnaire]), which is an instrument for measuring overall quality of life, particularly physical condition [10].

Specific HRQOL was measured with the Vespid Allergy Quality of Life Questionnaire (VQLQ), a disease-specific instrument for measuring HRQOL in patients allergic to yellow jacket venom [11]. VQLQ scores range from 1 (severe impairment in HRQOL) through 7 (no impairment in HRQOL). The VQLQ score was calculated from the mean of all 14 items. First, the questions were translated into German and then retranslated into English by 2 independent persons (a physician and a psychologist). In cases of failed consensus, the items were discussed and a single common solution was found. The reliability of the questionnaire was determined by internal consistency, which in the present study was high (Cronbach α=0.98).

Construct validity was verified using principal component analysis. A scree test was used as the stopping criterion. The result was a main factor with an explained variance of 78.5%, on which all questions loaded high (all loads >0.69). As a further determination of construct validity and for the purpose of external measurement, the questionnaire was correlated with the SF-36 and its subscales using a bivariate Pearson correlation (Table 1). The mental summary scale correlated with the total VQLQ value (r=0.36; *P*=.004). Using the subscales of the SF-36, a correlation was detected for vitality, social functioning, and mental health. Furthermore, the total VQLQ value correlated with that of the anxiety scale of the HADS (r=0.22; *P*=.04), but not with that of the depression scale. Additionally, specific questions associated with fear

Table 1. Pearson Correlations Between VQLQ, HADS, and SF-36

		HADS Anxiety	HADS Depression	SF-36 Physical Summary Scale	SF-36 Mental Summary Scale	SF-36 Physical Functioning	SF-36 Role Limitation Physical	SF-36 Bodily Pain	SF-36 Vitality	SF-36 General Health	SF-36 Role Limitation Emotional	SF-36 Social Functioning	SF-36 Mental Health
VQLQ	R	0.216	0.114	–0.001	0.321	0.116	0.093	0.127	0.249	0.033	0.162	0.272	0.334
	P	.035	.272	.991	.004	.274	.385	.222	.019	.769	.133	.008	.001
	N	95	95	77	77	90	89	94	89	84	88	95	89

Abbreviations: HADS, Hospital Anxiety and Depression Scale; VQLQ, Vespid Allergy Quality of Life Questionnaire; SF-36, Short Form 36 Health Survey.

Table 2. Pearson Correlation Between VQLQ and BSI items

		Feeling Afraid in Open Spaces	Feeling Fearful	Feeling Afraid to Travel on Buses, Subways, or Trains	Having to Avoid Certain Things, Places or Activities, Because They Frighten You	Feeling Tense or Keyed up	Spells of Terror or Panic
VQLQ	r	–0.100	–0.076	0.031	–0.231	–0.228	–0.119
	p	0.210	0.272	0.404	0.030	0.032	0.170
	n	67	67	66	67	67	67

Abbreviations: BSI, Brief Symptom Inventory; VQLQ, Vespid Allergy Quality of Life Questionnaire.

Table 3. Characteristics of Patients Enrolled in the Study (N=100)

Age (years)	
Mean (SD)	53.13 (11.55)
Range	19-74
Gender	
Male	45
Female	55
Causative insect	
Yellow jacket	82
Honeybee	18
Severity of the initial anaphylactic reaction (Ring and Messmer)	
Grade 1	6
Grade 2	65
Grade 3	27
Grade 4	2

Table 4. Results of the Questionnaires Before and After the Sting Challenge Test[a]

Instrument	Prechallenge	Postchallenge	*P* Value
VQLQ	4.49 (1.54)	5.27 (1.51)	<.0001
HADS			
Depression	9.80 (1.59)	9.94 (1.67)	NS
Anxiety	12.85 (1.95)	13.10 (2.25)	NS
BSI			
General	0.27 (0.31)	0.27 (0.35)	NS
Depression	0.17 (0.39)	0.21 (0.49)	.027
Anxiety	0.33 (0.044)	0.31 (0.44)	NS
Phobic anxiety	0.19 (0.39)	0.17 (0.37)	NS
SF-36			
General	50.05 (8.29)	51.16 (8.11)	NS
General health	66.78 (17.66)	68.48 (18.14)	NS
Vitality	63.84 (15.93)	68.13 (15.32)	.002
Physical functioning	82.61 (23.99)	84.64 (20.88)	NS
Role limitations (physical)	82.45 (34.09)	88.24 (26.89)	.038
Bodily pain	74.20 (26.58)	76.08 (24.82)	NS
Social functioning,	89.89 (15.58)	89.23 (18.93)	NS
Role limitations (emotional)	88.89 (26.87)	91.36 (27.27)	NS
Mental health	75.77 (15.70)	77.83 (15.80)	NS
LEZU	5.21 (1.26)	5.07 (1.32)	NS

Abbreviations: BSI, Brief Symptom Inventory; HADS, Hospital Anxiety and Depression Scale; HRQOL, health-related quality of life; LEZU, Lebenszufriedenheitsfragebogen (Life Satisfaction Questionnaire); NS, nonsignificant; SF-36, Short Form 36 Health Survey.
[a]Data are presented as mean (SD)

of insects were selected in the BSI. Data for the Pearson correlation are presented in Table 2.

The questionnaires were completed the morning before and around 4-6 weeks after the sting challenge. Patients with a systemic reaction after the sting challenge were excluded from the study and did not complete a second questionnaire.

Statistical Analysis

SPSS version 19 for Mac (IBM Corp) was used for the statistical analysis. The mean differences of t1 and t2 were tested using 1- or 2-factor analysis of variance with repeated measures or the paired *t* test. The Wilcoxon test was used to test positive and negative changes in HRQOL. Subgroup analysis of patients with grade 4 severity was not performed because of the small sample size.

Results

Patients

A sting challenge test was offered to 105 consecutive patients who were on VIT with a maintenance dose of 100 µg. Two patients refused to participate in the study, and 3 patients were excluded because of a systemic reaction after the sting challenge test. Patient data and characteristics are outlined in Table 3.

Overall Outcomes

The results of the questionnaires before and after the sting challenge test are presented in Table 4. VQLQ improved significantly after the sting challenge ($P<.0001$).

A definite shift was recorded in the rank order of patients. Forty patients improved, 4 worsened, and 42 remain unchanged ($P=.0001$) after the sting challenge.

Neither the physical nor the psychological SF-36 score changed significantly after the sting challenge, although a significant improvement was documented in the SF-36 subgroups of vitality ($P=.002$) and physical role ($P=.038$).

No significant differences in pre-sting and post-sting challenge were observed for the overall BSI-GSI score or the BSI score for anxiety or phobic anxiety, although the BSI score for depression increased significantly ($P=.027$).

No significant changes were documented for the HADS score (anxiety and depression) or for the LEZU score (overall quality of life and physical condition) before or after the sting challenge.

Outcomes in Patient Subgroups

No differences in the baseline values of VQLQ, HADS, BSI, SF-36, or LEZU were recorded according to gender, age, and initial severity of the SAR (grade 4 severity was not assessed because of the small subgroup size).

VQLQ improved after the sting challenge independently of age or gender and the initial severity of the allergic reaction.

VQLQ improved significantly more in patients allergic to yellow jacket venom than in those allergic to bee venom (P=.04). In the SF-36 subgroup of physical role function, a stronger improvement was documented in patients allergic to bee venom than in those allergic to yellow jacket venom (P=.01). The changes over time in the BSI, HADS, and LEZU were not affected by the causative insect.

Discussion

Our findings show that patients on VIT because of Hymenoptera venom allergy have improved specific HRQOL after a tolerated sting challenge. Furthermore, a significant improvement was documented in the SF-36 subgroups of vitality and physical role.

Even though VIT significantly reduced the risk of systemic reaction to an insect sting and all our patients were informed about efficacy before starting VIT, at control visits we observed that some patients were still frightened of re-sting to the extent that it had a significant impact on quality of life (eg, avoiding outdoor activities). Only after a tolerated sting challenge do many patients trust in their therapy. Therefore, we performed this prospective study to further analyze this clinical observation.

HRQOL in allergic patients, particularly those with Hymenoptera allergy, has received increasing attention in allergological research in recent years. In 1999, Confino-Cohen et al [12] reported on the enduring adverse psychological consequences and perceived impairment in quality of life caused by systemic reaction to Hymenoptera stings. One-third of the study patients with VIT still reported impaired HRQOL or held self-imposed debilitating beliefs. Oude Elberink et al [13] demonstrated that VIT improves HRQOL in patients allergic to yellow jacket venom, even in those with mild systemic reactions [14], and that an adrenaline autoinjector is an unsuitable definitive treatment for patients with venom allergy because it is perceived as burdensome by most patients [15]. In a prospective trial, Confino-Cohen et al [16] demonstrated that VIT was followed by a significant reduction in medically unfounded debilitating beliefs and preoccupation with the systemic reaction and an increase in allergy-related quality of life. Therefore, in patients with long-lasting dysfunctional beliefs and impaired quality of life, the authors recommended offering a sting challenge, because the mostly negative result would be able to further improve these debilitating beliefs [16].

Although we demonstrated an improvement in quality of life after performing a sting challenge, we also observed an increase in the BSI score for depression. As in other diseases, anxiety and depression are closely correlated [18]. One possible explanation for this unexpected outcome is that depression may initially be masked by anxiety; when anxiety decreases, depression becomes more prominent.

A few limitations to our investigation should be noted. The VQLQ questionnaire was developed and validated to investigate patients with yellow jacket venom allergy [6]. Although the vast majority of our study population had yellow jacket venom allergy (82%), we also used this questionnaire for patients who were allergic to bee venom. Two patients with bee venom allergy were beekeepers and were stung during their work. Beekeepers may cope with an anaphylactic reaction differently: their passion for their work can reduce the impact of such an experience. Therefore, the results for the bee venom allergy group should be interpreted with caution, although we believe that all 14 items are relevant for the vast majority of these patients. Thus, our data demonstrated that VQLQ in patients allergic to bee venom also improved significantly after a sting challenge test.

At the beginning of our study, no validated German version of the VQLQ questionnaire existed; therefore, all questions were translated into German and retranslated into English. This German version of the VQLQ questionnaire proved very reliable: internal consistency was high, and construct validity was verified by a principal component analysis and external measures (correlations with the items included in SF-36, HADS, and BSI). Since we performed our challenge test, another German version of the VQLQ questionnaire has been published (18).

In conclusion, to our knowledge, the present study is the first to show that sting challenge with a live insect to confirm the efficacy of established VIT in patients who are allergic to Hymenoptera venom results in a significant improvement in disease-specific quality of life and in subgroups of general quality of life. A sting challenge should therefore be recommended for all patients with Hymenoptera venom allergy.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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