

Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom

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Background: Venom immunotherapy (VIT) is effective in preventing anaphylactic reactions after insect stings. The effect of VIT on health-related quality of life (HRQL) was studied to evaluate whether this treatment is of importance to patients. **Objective:** We compared HRQL outcomes measured with a disease-specific instrument (Vespid Allergy Quality-of-Life Questionnaire [VQLQ]) in patients allergic to yellow jacket venom treated with VIT or with an adrenalin self-administration device (EpiPen) in an open-label, randomized, controlled trial. **Methods:** Consenting patients were block randomized to either VIT or EpiPen. Patients received uniform, standardized information, which specified the risk of their condition and the risks and benefits of both treatment options. HRQL measures took place before and after 1 year of treatment with VIT or EpiPen.

Results: Seventy-four patients agreed to be randomized, of whom 36 received VIT and 38 an EpiPen. The mean change in VQLQ score in the group randomized to VIT was 1.07 (95% CI, 0.68-1.46), and this improvement was statistically significant ($P < .0001$) compared with that seen in the group randomized to the EpiPen, in which this change was -0.43 (95% CI, -0.71 to -0.16). These differences were seen in both men and women, persons with more or less general anxiety, and those stung recently and those stung more than a year before their outpatient department visit. The overall proportion of patients receiving benefit from VIT is 0.72, generating a number needed to treat of 1.4.

Conclusions: VIT results in a clinically important improvement in HRQL in patients allergic to yellow jacket venom in all subgroups studied. Of every 3 patients treated with VIT, 2 patients experience an important improvement in their quality of life. (*J Allergy Clin Immunol* 2002;110:174-82.)

Key words: Venom immunotherapy, EpiPen, quality of life, Hymenoptera allergy, insect allergy, yellow jacket allergy, number needed to treat, minimal important difference, Vespid Allergy Quality-of-Life Questionnaire

Abbreviations used

HRQL:	Health-related quality of life
MID:	Minimal important difference
NNT:	Number needed to treat
NR-VIT:	Nonrandomized immunotherapy
NR-EPI:	Nonrandomized EpiPen
OPD:	Outpatient department
R-EPI:	Randomized EpiPen
R-VIT:	Randomized immunotherapy
STAI:	Spielberger State-Trait Anxiety Inventory
VIT:	Venom immunotherapy
VQLQ:	Vespid Allergy Quality-of-Life Questionnaire

Although venom immunotherapy (VIT) has established efficacy for the prevention of anaphylactic reactions to Hymenoptera stings,^{1,2} the merits of this treatment have been questioned by some authorities. Critics of immunotherapy have pointed out that the chance of being stung again is low in the majority of patients and that even if a re-sting occurs, the chance of severe or fatal reactions is low in many, if not most, patients.³ Indeed, because many fatalities from Hymenoptera stings occur in patients not previously known to be allergic,^{4,5} it has been difficult to maintain that VIT should have an effect on fatality rates. However, clinicians treating patients allergic to Hymenoptera venom have argued that an anaphylactic reaction after a Hymenoptera sting is a frightening experience that often affects emotional, social, and, in some cases, professional functioning. Although these negative effects of untreated Hymenoptera allergy have been widely recognized, they have never been studied systematically.

Analysis of health-related quality of life (HRQL) affords a methodology for studying the effects of an intervention in relation to outcomes that are important and relevant to patients. A disease-specific questionnaire, the Vespid Allergy Quality-of-Life Questionnaire (VQLQ), was developed and validated for assessing HRQL in patients with anaphylactic responses after yellow jacket stings.⁶ We used this instrument to assess VQLQ outcomes in an open-label, randomized, controlled trial in patients treated with either immunotherapy with yellow jacket venom or an epinephrine HCL self-administration device (EpiPen, ALK-Abelló, Hørsholm, Denmark).

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METHODS

Patient selection

Patients were recruited from the allergy outpatient department (OPD). Consenting patients aged 18 to 65 years were included if they had experienced one or more anaphylactic reactions after yellow jacket stings and were sensitized to yellow jacket venom (ie, positive skin test response with a histamine equivalent wheal size of at least 0.7 at a concentration no greater than 0.1 µg/mL, which represents clear-cut sensitization^{7,8}; positive Pharmacia CAP-RAST result of at least class 2; or both). Patients were excluded if there were contraindications for VIT, including pregnancy, β-blocker therapy, mastocytosis, or serious medical or surgical illness, or if there was a need to carry an EpiPen for other reasons.

At the first OPD visit, every patient was instructed in how to use the EpiPen. Patients receiving VIT all started during winter with a modified semirush protocol,⁹ reaching the maintenance dose (and relinquishing their EpiPen) well before the next summer, during which measures took place.

Patient information

Because the expectation of the outcome of future stings and related quality of life is largely determined by patients' perception of risk and benefits of the treatment, materials and procedures used for patient education were standardized and subjected to expert review. A patient information document relating to the risk-benefit issues was generated on the basis of 36 peer-reviewed publications. This document was approved by a committee consisting of a general physician, an allergologist, an epidemiologist, a government health care representative, and a psychologist. The document specifies 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 indicates the qualitative and quantitative risk reduction relating to VIT and EpiPen. The document is presented in English translation as Appendix A. A trial technician was trained to present and explain the document to patients in an objective and uniform manner. Patients received this information after completing the VQLQ and had the opportunity to ask questions before deciding whether to be randomized. The trial technician also obtained written informed consent.

Instruments

The VQLQ, a disease-specific instrument for measurement of HRQL in patients allergic to yellow jacket venom was developed and cross-sectionally validated, as described elsewhere.⁶

To study the influence of general anxiety levels on HRQL, general anxiety levels were measured with the Dutch adaptation of the Spielberger State-Trait Anxiety Inventory (STAI), from which the anxiety trait was used (the STAI version DY-2).¹⁰ This measurement was carried out before the intervention. Anxiety disposition levels range from 1 through 10. A score of less than or equal to 5 was defined as a low anxiety level, and a score of greater than 5 was defined as a high anxiety level. Sensitivity analysis of this cut-off score was carried out by calculating relevant outcomes with cut-off scores of 3 and 7.

Before and 1 year after receiving the patient information, 2 questions reflecting the expectation of outcome were added to analyze patients' perception of risk and benefits of the treatment: the Expectation of Outcome questionnaire.

A question reflecting burden of treatment was added to the questionnaire at the end of the study period to examine the balance of negative and positive effects of immunotherapy on the overall well-being of patients. Patients who received VIT were asked to consider possible negative effects of this treatment, including side effects, discomfort, inconvenience, and personal expense, and to weigh these against possible positive effects, such as reduction of anxiety

or greater personal freedom. Positive versus negative effects were scored with 7 response options, of which 3 were positive response options from "slightly positive" to "extremely positive," 1 indicated equivalence of the positive and negative aspects of treatment, and 3 were negative response options ranging from "slightly negative" to "extremely negative."

Study design

Patients visiting the OPD who had experienced a systemic reaction after a yellow jacket sting were given a set of measures before physician contact. These measures consisted of the specific HRQL instrument, the Expectation of Outcome questionnaire, and the STAI. Measures took place during summer, when insect exposure was highest. After completing the measures, patients were seen by a physician for a medical history and standard physical examination. Physicians were instructed not to discuss patients' risk of a resting reaction or the benefits of treatment because these issues would be subsequently explained by the trial technician. Possible candidates for VIT were then given the written information described above, as well as an informed consent document explaining the study. Both information documents were further explained by the trial technician, who then inquired whether patients consented to be randomized. Patients consenting to randomization were allocated to one of the 2 open-label study arms, namely VIT for 1 year or carrying an EpiPen for the same time period, by using a minimization computer program. The 2 groups were stratified for factors that might influence HRQL, namely time interval since last reaction (>1 year or <1 year), anxiety level (high or low, as measured with the STAI), and severity of the reaction according to the method of Mueller¹¹ (grade I vs grades II-IV).

If patients refused randomization, they were asked to participate in a nonrandomized longitudinal study with either VIT or EpiPen. Enrollment took place over 2 years to mitigate seasonal differences in yellow jacket exposure in successive years. After 1 year of treatment with either VIT or an EpiPen, the set of measures was readministered, as well as the burden of treatment questions.

VIT was given with a semirush regimen and started up in our hospital. The maintenance dose was generally achieved in 6 weeks. Further maintenance therapy was administered by the patients' family physician.

After completing the study, patients in the randomized EpiPen (R-EPI) group were asked whether they wanted to start VIT, and the VIT of the randomized VIT (R-VIT) group was continued. All patients participating in the study provided written informed consent. The study was approved by the medical ethics committee of University Hospital Groningen. Patients did not pay for their venom (all patients had health insurance). Patients were not compensated for travel or other expenses.

Statistics and calculations

Overall VQLQ score was calculated from the mean of all 14 items, with a range from 1 (severe impairment in HRQL) through 7 (no impairment in HRQL). Mean change in VQLQ score was calculated for each treatment group (R-VIT and R-EPI) from the mean VQLQ score after 1 year of treatment minus the mean pretreatment VQLQ score.

SPSS version 10.0 for Windows was used for statistical analysis. The VQLQ scores and change in VQLQ scores were analyzed with the paired Student *t* test, and VQLQ measures between groups were analyzed with the unpaired *t* test. Multiple linear regression analysis was used to assess the influence of age, sex, severity of the reaction, anxiety, and time interval since the last sting reaction on VQLQ scores. Crosstabs and Kruskal-Wallis testing were used to compare the severity of the reactions, age, sex, general anxiety, and time interval between sting and OPD visit between different treat-

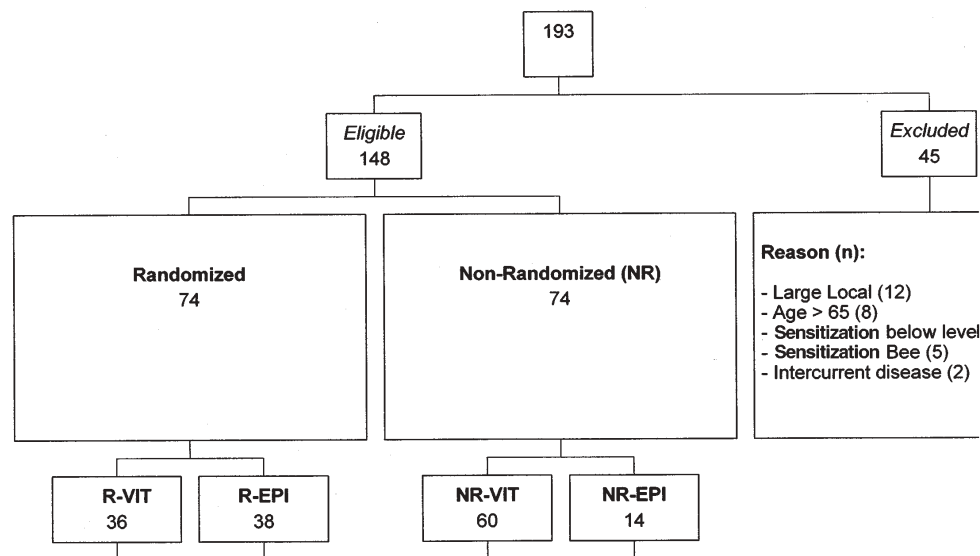


FIG 1. Enrollment (during 1996 and 1997) and follow-up (from 1997 to 1998) of patients. Of 148 eligible patients, 74 agreed to be randomized (36 to VIT and 38 to EpiPen). The other 74 patients chose their own treatment. After a 1-year follow-up, the results of 135 of 148 patients could be analyzed.

ment groups. The χ^2 and Kruskal-Wallis tests were used to compare the range of reaction severities, age, sex, and anxiety between the different treatment groups to examine possible selection bias.

The minimal important difference (MID) is defined as the change in VQLQ score that patients perceive to be important and that would justify a change in treatment in the absence of adverse effects or excessive costs.¹² Use of HRQL instruments for different diseases by using 7-point response options have estimated the MID to be 0.5 when used to examine changes within the same patients.¹³⁻¹⁵ Hence the percentages of patients in the R-VIT and R-EPI groups with an MID greater than 0.5 (important improvement of HRQL), between -0.5 and 0.5 (unchanged), and less than -0.5 (important deterioration) were calculated.

From the proportion of patients with improved scores, scores that remained the same, or scores that deteriorated relative to baseline status in both the VIT and EpiPen groups, the proportion of patients who fared better receiving VIT compared with those receiving EpiPen and patients who fared better receiving EpiPen compared with those receiving VIT were calculated (for further explanation, see Appendix B). The overall proportion of patients who received benefit from VIT is the difference of both above-mentioned proportions.

The number needed to treat (NNT; defined as the number of patients who need to be treated with the intervention for one patient to have a clinically important improvement over and above that which he or she would have experienced with the control intervention) was calculated according to the methodology for parallel-group studies.¹⁶ The NNT is the reciprocal of the proportion of patients who show an important improvement on each of the treatments.

RESULTS

Patient population

Patients were enrolled during the summer of 1996 and 1997. A total of 193 patients were seen in the OPD. Forty-five patients were excluded for reasons such as large local reaction only ($n = 12$), age older than 65 years ($n = 8$), sensitization at less than the level specified in the

inclusion criteria ($n = 17$), clinical reactions to honey bee venom ($n = 5$), intercurrent diseases ($n = 2$), or inability to understand the questionnaire ($n = 1$; Fig 1).

Of the 148 patients who were eligible for the study, 74 agreed to be randomized: 36 received VIT (R-VIT group), and 38 received an EpiPen (R-EPI group). The remaining 74 patients refused to be randomized and preferred to choose their own treatment (60 VIT and 14 EpiPen). All 74 patients agreed to a follow-up assessment.

The measurements after 1 year of treatment took place in the summers of 1997 and 1998. A total of 148 patients (74 randomized and 74 nonrandomized) were given or sent the second questionnaire. Of these 148 questionnaires, a total of 135 questionnaires could be analyzed (34 in the R-VIT group, 35 in the R-EPI group, 54 in the nonrandomized VIT [NR-VIT] group, and 12 in the nonrandomized EpiPen [NR-EPI] group). Of the 13 subjects who dropped out, 2 discontinued VIT because of intercurrent diseases and 2 because of side effects, 2 could not be located and were lost to follow-up, 2 had not reached the maintenance dose before summer, and 5 did not return their questionnaire (Fig 1). The overall response was 96.6%. The baseline patient characteristics are given in Table I.

Re-sting rates

Only 2 of 148 individuals were re-stung during the follow-up period. The patient in the VIT group who was stung did not experience a systemic reaction. One person in the R-EPI group required EpiPen for a systemic reaction.

Comparison of VQLQ outcomes of the randomized groups

There was no difference in the year of recruitment between patients assigned to the R-VIT and R-EPI groups (data not shown). Baseline VQLQ scores in each treat-

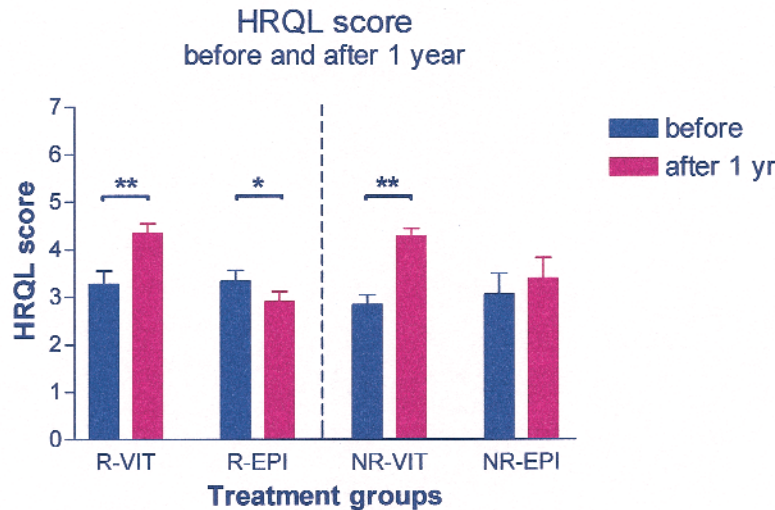


FIG 2. Histogram showing the VQLQ scores before and after 1 year of therapy for the R-VIT group, the R-EPI group, the NR-VIT group, and the NR-EPI group. * $P < .003$, ** $P < .0001$.

TABLE I. Summary of the patient baseline characteristics for the different treatment groups

Characteristic	Treatment group				Total, n (%)
	R-VIT, n (%)	R-EPI, n (%)	NR-VIT, n (%)	NR-EPI, n (%)	
No. of patients	34	35	54	12	135
Sex					
Male	16 (47.1)	18 (51.4)	24 (44.4)	3 (25.0)	61 (45.2)
Female	18 (52.9)	17 (48.6)	30 (55.6)	9 (75.0)	74 (54.8)
Severity of reaction					
Grade I	—	5 (14.3)	3 (5.6)	1 (8.3)	8 (5.9)
Grade II	11 (32.4)	8 (22.6)	11 (20.4)	2 (16.7)	32 (23.7)
Grade III	9 (26.5)	11 (31.4)	24 (44.4)	4 (33.3)	48 (35.6)
Grade IV	14 (41.1)	11 (31.4)	16 (29.6)	5 (41.7)	46 (34.1)
Age, mean $\pm$ SD (y)	43.38 $\pm$ 11.09	41.23 $\pm$ 11.21	42.91 $\pm$ 12.96	36.08 $\pm$ 10.87	41.99 $\pm$ 11.93

Severity of the reactions was graded according to the method of Mueller.¹¹

ment group were similar (mean $\pm$ SD, 3.28 ± 1.62 for the R-VIT group and 3.34 ± 1.37 for the R-EPI group).

After 1 year, VQLQ scores improved in patients treated with VIT (mean VQLQ score improved from 3.28 to 4.35, $P < .0001$) in contrast to the EpiPen group (mean VQLQ score decreased from 3.34 to 2.90, $P < .003$; Fig 2). The mean change in VQLQ score in the R-VIT group was 1.07 (95% CI, 0.68-1.46) and improved significantly ($P < .0001$) compared with that in the R-EPI group, in which this change was -0.43 (95% CI, -0.71 to -0.16), resulting in a mean difference between the 2 groups of 1.51 (95% CI, 1.04-1.98; Fig 3).

Comparison of VQLQ outcomes of the nonrandomized groups

There were no differences in general anxiety level, severity of reaction, and time interval between sting and OPD visit between nonrandomized groups, although these variables were not matched. Baseline VQLQ scores

in both nonrandomized treatment groups were similar: The mean $\pm$ SD was 2.84 ± 1.53 in the NR-VIT group and 3.05 ± 1.54 in the NR-EPI group.

After 1 year, VQLQ score improved in the NR-VIT group (from 2.84 to 4.29, $P < .0001$). VQLQ scores showed no significant change in the NR-EPI group (Fig 2).

Expectation of outcome

There were no differences in mean pretreatment expectation of outcome scores, indicating that the expectation of the outcome of future stings was similar in all groups. After 1 year of treatment, the expectation of outcome scores changed in both patient groups treated with VIT ($P < .0001$): from 5.66 to 2.88 in the R-VIT group and from 5.45 to 2.88 in the L-VIT group. Thus patients treated with VIT had a better sting outcome expectation than before treatment, which is in contrast with results in the randomized and longitudinal EpiPen groups, in which the expectation of outcome scores did not change.

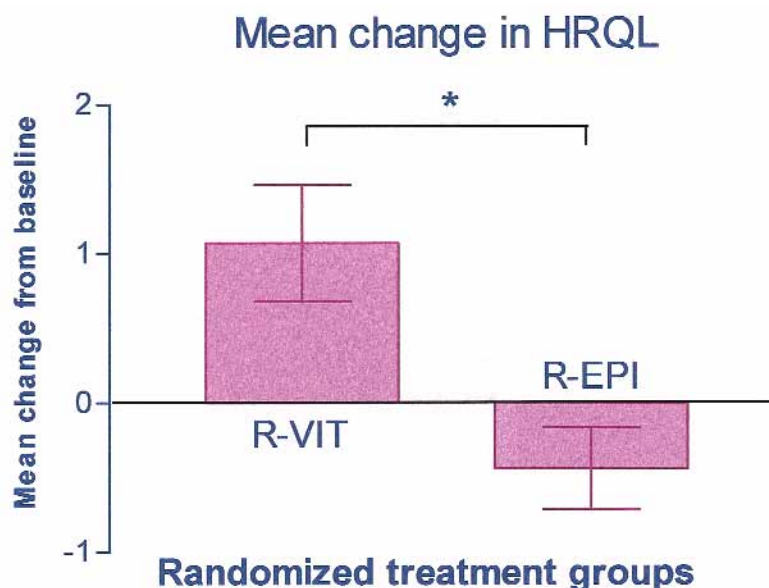


FIG 3. Histogram showing the mean change in VQLQ score from baseline for the R-VIT and R-EPI groups.
* $P < .0001$, R-VIT versus R-EPI group.

TABLE II. Treatment comparison of VIT versus EpiPen comparing the proportion of patients faring better with VIT and the proportion of patients faring better with EpiPen

Treatment comparison	Difference between groups		Proportion better with VIT	Proportion better with EpiPen	Proportion benefiting with VIT	NNT for a single patient to benefit
	Mean	<i>P</i> value				
VIT vs EpiPen	1.51	.0001	0.74	0.02	0.72	1.4

Analysis of subgroups

The number of men and women in the patient population was equal, as was the case in the different treatment groups. Of the 148 patients, 43 had a high general anxiety level as measured by the STAI using a cut-off value of 5. These were equally distributed between the different treatment groups. The distribution in time interval between sting and OPD visit (<1 year or >1 year) and in severity of the reactions was the same for the whole population as for all different treatment groups.

Pretreatment VQLQ score was more impaired in women ($P < .005$) and in the more anxious patients ($P < .005$). Initial VQLQ score was not influenced by the age of the patient, the interval between sting and OPD visit, or the severity of the reaction.

After 1 year of treatment, VQLQ score improved in all subgroups independent of age, sex, or interval between sting and OPD visit but remained more impaired in the more anxious patients. It also improved in all patients with a more than dermal reaction (grade II-IV). Because of the small number of the exclusively dermal reactors, further analysis of this subgroup was not possible. The mean change in VQLQ score was comparable in all subgroups (data not shown).

Sensitivity analysis with respect to the chosen cut-off anxiety score of 5 was performed, in which a low anxiety level was defined as a score lower than or equal to 3 or, alternatively, as a score lower than or equal to 7. Although this affected the *P* values slightly, all the differences above remained significant.

MID, NNT, and burden of treatment

The percentage of patients with an improvement in VQLQ score of greater than 0.5 was 74% in the R-VIT and 9% in the R-EPI group; 26% in the R-VIT and 65% in the R-EPI group had a difference in VQLQ score of between -0.5 and 0.5 . No patient's score deteriorated in the R-VIT group in contrast to 26% in the R-EPI group (deterioration in VQLQ score < -0.5). Therefore the proportion of patients who fared better receiving VIT compared with those receiving EpiPen is 0.74, and the proportion of patients who fared better receiving EpiPen compared with those receiving VIT is 0.02 (see Appendix B), resulting in an overall proportion of patients benefiting from VIT of 0.72. This corresponds to an NNT of 1.4 (Table II).

In response to the burden of treatment question, the percentage of patients who rated VIT as very to extremely positive when weighing the positive versus the negative effects of this treatment was 94% in the R-VIT group

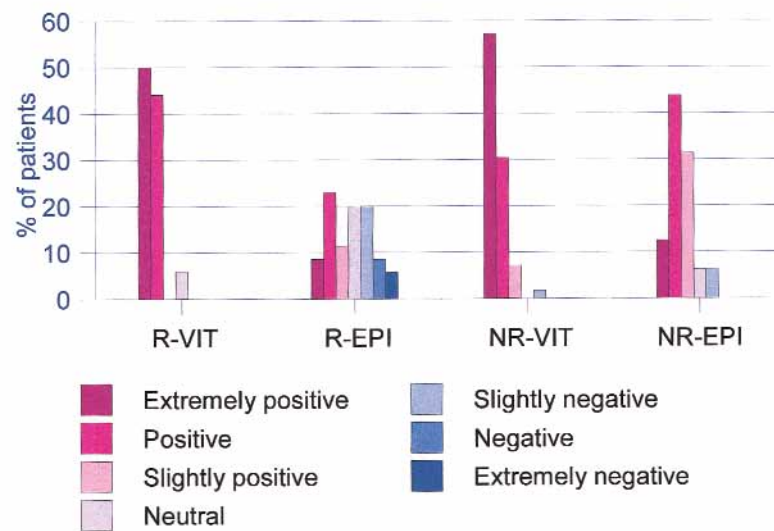


FIG 4. Histogram showing results of the burden of treatment evaluation for each of the different treatment groups.

(50% extremely positive) and 98% in the NR-VIT group (57.1% extremely positive; Fig 4).

DISCUSSION

Although the efficacy of VIT in the prevention of recurrent anaphylactic reactions after Hymenoptera stings is undisputed, our data show that this treatment also results in a clinically significant improvement in HRQL in these patients. This improvement is evident at the end of the first year of treatment, is seen in both men and women, is seen in persons with greater or less general anxiety, and is seen both in those stung recently and in those stung more than a year before their OPD visit. The fact that only 2 of 148 individuals were re-stung during the study period indicates that the protection that VIT provides does not have to be experienced directly for HRQL to improve. Providing the treatment and 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.

After providing all patients with the patient information, half of them refused randomization, of whom most (80%) preferred to start VIT. Although half of the patients refused randomization, this did not result in selection bias: pretreatment VQLQ scores were identical for both randomized and nonrandomized patients, and there were no differences in anxiety score, severity of the reaction, age, sex, and interval between sting and OPD visit. In fact, patients choosing VIT had even more score improvement than those randomized to this treatment, indicating that the randomization procedure would tend to underestimate the improvement of the VQLQ score obtained with VIT in unselected patients.

The clinical relevance or interpretability of the improvement in VQLQ scores measured in patients treat-

ed with VIT was assessed to ascertain whether the improvement in VQLQ was also meaningful to patients. This method generated an NNT of 1.4, which is the number of patients who need to be treated with VIT to give at least one patient a meaningful improvement in VQLQ. This NNT compares favorably with that found in other studies in which HRQL was also the outcome of interest.^{16,17} These data indicate that the improvement in HRQL that VIT provides is clinically important and relevant to patients.

Despite the documented medical safety of VIT,^{18,19} critics have claimed that this treatment remains cumbersome, unpleasant, and time-consuming for the patient. We therefore undertook to objectify the overall effect of VIT from the perspective of the patient by means of a burden of treatment question, which attempts to capture medical and nonmedical negative aspects of treatment and weigh them against the positive aspects of such treatment. Patients participating in the study were treated in the same way as patients not participating and did not receive any form of compensation. Almost all patients who had experienced immunotherapy for 1 year believed that the positive aspects of their treatment outweighed the negative aspects, with the majority of patients indicating that the advantage of VIT was considerable. These data show that VIT was well tolerated in the perception of patients and had a high patient acceptance.

Patients randomized to treatment with EpiPen showed a statistically significant deterioration in VQLQ score. It is presently unclear whether carrying an EpiPen actually contributes to progressive deterioration of the VQLQ score in the absence of VIT because there was no nonintervention group included in this study for ethical reasons. Although the EpiPen might provide some measure of assurance to the patient, it is also conceivable that it might act as an affirmation and reminder of the patient's risk and

thus negatively influence HRQL. In the group choosing an EpiPen, although this group was small (14 individuals), no deterioration in HRQL was seen. For this latter group, even though the treatment with an EpiPen might not be desirable for other reasons, such as unacceptable medical risk, this treatment might be appropriate from an HRQL point of view. For the majority of patients, however, these results demonstrate that the assurance of prompt treatment with an EpiPen is neither sufficient nor satisfactory, as has been contended in the past.²⁰

The improvement in HRQL after VIT was not influenced by age, sex, general anxiety, time interval between last sting and OPD visit, or reaction severity. The pre-treatment VQLQ scores were lower in patients with a high anxiety score compared with those seen in patients with a low anxiety score, and this difference remained after 1 year of treatment. However, patients with both high and low 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. Similarly, both remotely and recently stung patients benefited from VIT. Although there was a trend toward improvement in HRQL in exclusively dermal reactors receiving VIT, there were not enough of these patients to allow for meaningful analysis.

Our study addressed the question of the effect of VIT and associated patient education in relation to EpiPen and its associated information on HRQL in a group of patients, the overwhelming majority of whom were not re-stung and who did not undergo sting challenge tests. Our study was not powered to address the effect on those who are re-stung, and we did not conduct sting challenge tests. Thus one could question the generalizability of our findings to populations with a high sting rate or to a clinical setting in which sting challenge tests are part of routine practice. However, given the established efficacy of VIT in preventing reactions, the results of studies in these other settings would, in all likelihood, be similar to our findings in this study.

In summary, VIT resulted in a clinically important improvement in HRQL in patients allergic to yellow jacket venom, and treatment was well tolerated and had a high patient acceptance. This improvement was not influenced by age, sex, general anxiety, time interval between last sting and OPD visit, and reaction severity and occurred even when patients were not re-stung. The HRQL response rate to VIT is high: Of every 3 patients treated with VIT, 2 patients experienced an important improvement in their HRQL. Treatment with an EpiPen in the absence of VIT is not sufficient to prevent deterioration of HRQL.

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APPENDIX A

Yellow jacket allergy

Patient information document (18-65 years)

Introduction

Anyone might become allergic to yellow jackets. The risk of developing an allergy is greater when stung more often.

How many people have an allergy for yellow jackets?

Probably between 10% and 20% of the population have abnormal reactions to stings by yellow jackets. Most of these persons will experience only a moderate to large local swelling, such as a

swollen hand or arm after being stung in the finger. Although this reaction might be very unpleasant, it is almost never dangerous, unless the sting occurs in the throat. However, about 1 in 100 persons might have a generalized allergic reaction. For example, they might experience serious asthmatic symptoms, swelling of the throat, or shock. It has been estimated that in the Netherlands almost 5 persons a year die as a result of an allergic reaction to a honeybee or yellow jacket sting. Older persons and persons with cardiovascular diseases (hardening of the arteries) are at greater risk for dying.

What might happen during an allergic reaction to a yellow jacket sting?

The allergic symptoms after a yellow jacket sting might be different for different people. For example, hives might develop distant from the site of the sting, or severe itching, swelling of the whole body, difficulties with breathing or swallowing, nausea, vomiting, dizziness, lightheadedness, or loss of consciousness might develop. These symptoms might develop very quickly, sometimes within a few minutes after the sting.

What is the chance of an allergic reaction after a future sting?

An allergic person will not have an allergic reaction every time he or she is stung. The chance of an allergic reaction is about 50%. This means that a person with an allergy for yellow jackets will react to approximately half of the yellow jacket stings that he or she will experience.

Do people get the same allergic symptoms every time they react?

If you react to a subsequent sting, you have the greatest chance of experiencing symptoms similar to those you had after previous stings. If, in the past, you have had symptoms limited to the skin, the chance of a more serious reaction is low, but it is possible.

Can the allergy disappear?

A yellow jacket allergy probably lasts for life. The chance of a serious reaction will diminish during the years but will remain greater than in the general population.

For which individuals is treatment recommended?

Adults who experienced an extensive allergic reaction need to be treated.

What kind of treatments are possible?

The autoinjector (EpiPen). The autoinjector is appropriate for all individuals who have experienced an extensive allergic reaction after a yellow jacket sting.

The autoinjector is a large pen, which contains a syringe filled with adrenalin. A safety cap is located on the top of the pen. If you remove the safety cap and firmly apply the pen to the outside of the thigh, the syringe is activated, and the adrenalin is injected automatically.

After a sting, you might or might not have an allergic reaction. However, an allergic reaction, if it does occur, might start within minutes. You therefore need to carry the autoinjector with you at all times. Immediately after a sting, you should remove the safety cap from the autoinjector and wait for a possible reaction.

If a reaction occurs at the site of the sting or symptoms limited to the skin occur, you do not have to use the autoinjector. If, however, you experience shortness of breath or you believe that you are going to lose consciousness, you should apply the autoinjector to your

outer thigh, and the adrenalin will be injected. If you are in doubt as to whether to use the pen or not, it is generally best to be on the safe side and use it. After using the pen, you should alert a physician as quickly as possible because further treatment might be necessary.

Thus using an autoinjector does not prevent an allergic reaction, but it does prevent severe symptoms from developing.

Does the autoinjector have side effects? Side effects can occur. Possible side effects are palpitations, increase in blood pressure, anxiety, restlessness, headache, pallor, and tremor. Also, disturbances of the heart rhythm or angina pectoris (cardiac chest pain) might occur, especially in persons who already have heart disease. When the effects of the autoinjector have worn off, the side effects also stop.

Immunotherapy (desensitization). Immunotherapy refers to a course of injections or shots of pure yellow jacket venom given over a period of time. Another word for immunotherapy is desensitization. The goal is to achieve a state of unresponsiveness to the venom of yellow jackets.

The treatment regimen consists of a phase during which the dosage is gradually increased (incremental phase) and a maintenance phase. In Groningen the incremental phase always takes place in the hospital. This requires an admission of 1 day and 1 night. On the first day, you will receive 6 injections, which are given at half hour intervals. The next morning, you will receive an injection, after which you are allowed to leave hospital. Thereafter, you will receive an in-hospital injection every week containing gradually increasing amounts of yellow jacket venom. After every injection, you must wait half an hour before leaving the hospital.

As soon as you reach maintenance phase, the risk of an allergic reaction might be compared with the risk of the general population. The chance of an allergic reaction has then been reduced from 50% to 3%, or from a chance of reacting to 1 of every 2 stings to 1 of every 30 stings. If reactions develop, they are usually confined to the skin.

Does immunotherapy have side effects? Minor side effects might occur at the site of the injection. Some patients experience minor swelling, redness, or warmth of the skin at the injection site, especially at the beginning of the treatment. Others feel a bit uncomfortable during the day of the injection. These symptoms usually diminish during treatment and do not generally cause treatment delays. Generalized allergic reactions after injections might occur in less than 10% of patients. These reactions are usually mild. The dosing schedule is then adjusted to prevent serious side effects. There have been no reported deaths caused by immunotherapy with yellow jacket venom.

Why 3 years of treatment? It takes at least 3 years of treatment to build up lasting protection. In the past, treatment was considered necessary for life. However, recent results show that in most cases 3 years of treatment is enough.

Do you need the autoinjector during immunotherapy? After the incremental phase, usually about 6 to 12 weeks after the start of the treatment, you are adequately protected from reactions to yellow jacket stings. The autoinjector is then no longer necessary.

Is treatment possible during pregnancy? The incremental phase should not take place during pregnancy. When the maintenance dose has been reached without side effects or problems, pregnancy is no longer an issue. The venom injections have no known harmful effects on the fetus.

What can you do if you are stung?

- The most important thing is to take your autoinjector and make it ready for use. Keep calm and wait to see if a reaction occurs.
- Try to remove the stinger as soon as possible. Lift it from the skin with a sharp object (nail, paperclip, or knife). Do not pull the stinger with your fingers because this will squeeze more venom into the skin.

- You can suck out the place where the stinger enters the skin or ask someone else to do this. A small vacuum extractor (Aspivenom) might be bought at a pharmacy or drug store. Presumably, these devices prevent further release of venom. However, the benefit of such devices has not been studied scientifically.

How can you avoid being stung?

None of the following measures have been studied scientifically. The following recommendations are based on common sense.

- Yellow jackets are attracted by scents. This might be relevant for the following things or situations: all kinds of cosmetics, such as deodorants, perfumes, hairsprays, suntan lotions, and after shaves; food; garbage cans and rubbish bins; flowers; and overripe fruit.
- Sweat also attracts yellow jackets. If necessary, use an unperfumed deodorant.

- Yellow jackets and bees sting when they feel cornered, literally or figuratively. Therefore wearing loosely fitting clothes, into which yellow jackets might easily fly, increases the risk of being stung. Yellow jackets and bees might be attracted to black or floral-patterned clothes.
- Yellow jackets and bees might be found on the ground or in lawns. Walking barefoot is therefore not without risk.
- Although you cannot watch out for insects when you are asleep, you can prevent yellow jackets from entering your bedroom by keeping the windows closed or using screens.
- Yellow jacket nests in your immediate vicinity will increase your exposure to these insects. These nests should therefore be removed by an exterminator.

APPENDIX B. Calculating the proportion of patients who benefited from receiving VIT compared with patients randomized to an EpiPen

Randomized EpiPen	Randomized VIT		
	Proportion better with VIT (0.74) (x)	Proportion showing no change with VIT (0.26) (y)	Proportion worse with VIT (0) (z)
Proportion better with EpiPen (0.09) (a)	0.07 (ax)	0.02 (ay)	0 (az)
Proportion showing no change with EpiPen (0.65) (b)	0.48 (bx)	0.17 (by)	0 (bz)
Proportion worse with EpiPen (0.26) (c)	0.19 (cx)	0.07 (cy)	0 (cz)

Patients who fared better receiving VIT (bx + cx + cy): 0.48 + 0.19 + 0.07 = 0.74. Patients who fared better receiving EpiPen (ay + az + bz): 0.02. Cells ax, by, and cz represent patients whose outcomes are the same, irrespective of treatment.