

Original article

Generic or disease-specific quality of life scales to characterize health status in allergic rhinitis?

Background: In patients with allergic rhinitis (AR), various instruments have been validated for the measurement of quality of life (QOL), which may be greatly reduced. However, it is not clear which QOL instruments should be used for the different types of AR and whether they are sensitive to treatment.

Methods: The QOL of patients suffering from symptomatic seasonal AR (sSAR) (before and during treatment with a topical or systemic antihistamine), symptomatic perennial AR (sPAR), and asymptomatic seasonal AR (aSAR) was determined with the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) as disease specific and with the Munich Life Dimension List (MLDL) and the Visual Analogue Scale for Quality of Life (VAS-QOL) as generic QOL instruments.

Results: The different forms of AR were associated with typical QOL patterns. In sSAR, we found severe limitation of the global QOL, reduced global life satisfaction, high ranking of practical problems, high limitation of activity, and a high degree of disturbance in all subscales of the RQLQ. In sPAR, there were moderate limitation of the global QOL, normal global life satisfaction, high ranking of practical problems, moderate limitation of activity, and a high degree of disturbance by common symptoms. Under antihistamine treatment, both systemic and nasal, a significant improvement of QOL parameters was found, reaching the levels of patients with aSAR after 2 weeks.

Conclusions: QOL instruments can distinguish the impairment resulting from sSAR from that of sPAR and are sensitive to treatment with topical and systemic antihistamines. However, as the RQLQ was not designed to measure the short-term variations of disease status that appear in SAR, it may not demonstrate the rapid improvement of QOL under antihistamine treatment.

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Allergic rhinitis (AR), although common, is not a trivial disease. Besides the immediate physical symptoms of the affected organ, it can lead to mental disorders, disturbance of social activity, and the inability to function in everyday life, all of these factors possibly leading to a reduced quality of life (QOL) (1–3). However, the typical symptom scores do not reflect these elements. Moreover, sequelae of AR, such as bronchial asthma or polyposis nasi, are only poorly expressed through symptom scores, although they result in significant variations in a QOL survey. Various instruments have been validated for the measurement of QOL in AR. These include the disease-specific Rhinitis Quality of Life Questionnaire (RQLQ) (1), as well as generic questionnaires such as the SF-36 Health Status Questionnaire (2), the Munich Life Dimension List (MLDL), and the Visual Analogue Scale for Quality of Life (VAS-QOL) (4–8). There is no doubt today that for assessment of new therapies not

only the symptoms, but also the functional, emotional, and psychosocial effects of an illness, as well as the physical side-effects of the treatment, have to be taken into account. Yet, there is a lack of systematic examination of the corresponding parameters of the various forms of AR with its various stages and multiple treatments. We have set up a QOL profile for the different forms of AR and documented the course of the QOL under topical and systemic therapy.

Material and methods

QOL questionnaires

A disease-specific questionnaire, the German version of the RQLQ, according to Juniper & Guyatt (1) in its validated German form (3), was used. The assessment period applied to the week preceding the study. The RQLQ queried the extent of subjective disturbance in terms of various rhinitis symptoms and their emotional and practical effects. We considered 28 symptoms, which made up the final evaluation and were divided into seven subgroups: “nasal symp-

toms", "ocular symptoms", "general symptoms", "sleeping disorders", "practical problems", "limitations of activity", and "emotional disorders". The evaluation was on a scale from 0 (nonexistent) to 6 (maximum). The overall QOL was calculated from the mean values of the 28 symptoms. A linear transformation was performed for the subscale scores of the RQLQ, transforming each subscale into a 0–100% scale of discomfort. The score of the RQLQ was inverted, so that a 0 value of overall discomfort was transformed to 100% of QOL. This was done to correlate these scales better with the other QOL scales that generically use a 0–100% grading.

Two generic QOL questionnaires were used. The MLDL, a questionnaire assessing a patient's enjoyment of life, has been validated for Germany by Heinisch et al. (4) and comprises 19 items divided into four subgroups: "physis", "psyche", "social life", and "everyday life". The evaluation ranged from 0 (absolutely dissatisfied) to 10 (absolutely satisfied). The total enjoyment-of-life value was determined by the mean value of the 19 items. The results from the MLDL were converted to a scale of 0–100, high values being equivalent to a high degree of life enjoyment. The VAS-QOL is a classical 100-mm scale for global assessment of the present QOL. It was validated in 1974 by Huskisson as an instrument for pain determination (5). It ranges from 0 on the left – "my QOL could not be worse" – to 100 on the right – "my QOL could not be better."

Study design

We conducted three studies. In the first, a cross-sectional multicenter study, we determined the QOL of 279 untreated patients with symptomatic seasonal AR (sSAR) during pollen allergen exposure in the spring and summer, of 103 patients with symptomatic perennial AR (sPAR) during increased symptom strain in the autumn and winter, and of 104 patients with asymptomatic seasonal AR (aSAR) during the symptom-free phase in the autumn and winter. PAR was excluded in all sSAR and aSAR patients, and SAR was excluded in all sPAR patients. The demographic data are presented in Table 1. Enrollment criteria were as follows: age 18–65 years; a positive medical history of SAR or PAR; antiallergic pretreatment during a previous season; positive RAST for serum-specific IgE or positive skin prick test for tree and/or grass and/or weed pollen in the seasonal allergic group and for house-dust mite and/or animal allergens in the perennial allergic group; the presence of at least two symptoms of AR being of at least moderate strength in the symptomatic groups and a positive history of such complaints in the asymptomatic group with at the most one mild symptom of AR at present; for women of childbearing age, proof of an effective contraceptive measure; and, in all cases, written proof of consent. Exclusion criteria were as follows: the presence of forms of rhinitis other than sSAR, sPAR, and aSAR; the ingestion of interfering medications (any nasal decongestants, anticholinergics, sympathomimetics, theophylline preparations, long-acting sedatives, or neuroleptics); the presence of certain illnesses, such as asthma, psychiatric diseases, or severe common diseases; pregnancy, nursing, or insufficient contraception; drug or alcohol addiction; history (current or past) of hyposensitization and narrow-angle glaucoma.

Antiallergic therapy before the start of the study, depending on the respective pharmacokinetics, was not allowed for the sSAR patients. In the sPAR group, 34% of the patients had therapy-resistant symptoms not allowing them to stop antiallergic treatment. All of the sPAR patients that were treated had complaints not sufficiently responsive to treatment and at least two symptoms of AR of at least moderate strength. Due to symptoms caused by aspecific hyper-reactivity, 10% of the patients of the aSAR group had continued their antiallergic treatment postseasonally, all having at the most one mild symptom of AR. The possible symptoms were rhinorrhea, itching, sneezing, and congestion. Upon inclusion in the study, all patients filled out three questionnaires, the disease-specific RQLQ and the generic MLDL and VAS-QOL.

In the second study, the course of the QOL of patients with sSAR

under treatment with a topical antihistamine (one puff of 0.14 mg dimetindene maleate [DMM] 0.1% nasal spray per nostril twice daily) was tested. A total of 157 patients were included in this clinical multicenter trial, 76 of whom received DMM while the other 81 patients used the placebo (saline) nasal spray. Table 2 shows the demographic patient data. The study period lasted 2 weeks. The selection criteria were the same as in the first trial; however, additional criteria were sufficient reliability and compliance by the patients with the prescribed treatment.

In the third study (Table 3), the course of the QOL of patients with sSAR who were being treated topically and that of those treated systemically with an antihistamine were compared. This was done as a follow-up study in a multicenter, randomized, double-blind study by the double-dummy technique, including 326 patients in two parallel groups. Group 1 (165 patients) received one puff of 0.14 mg azelastine nasal spray per nostril twice daily as well as one placebo pill in the morning. Group 2 (161 patients) received one puff of a placebo-nasal spray per nostril twice daily as well as a loratadine capsule of 10 mg in the morning. The effectiveness of azelastine nasal spray has already been proven in several studies (9–12) and was therefore not tested against placebo. The effectiveness of loratadine tablets has also been proven in numerous studies (9–14) and was therefore not tested against placebo. The inclusion and exclusion criteria remained the same as in the previous studies. The RQLQ, MLDL, and VAS-QOL again served as QOL questionnaires. In addition to QOL, common symptom scores were also registered in this study. The monitored symptoms were runny nose, sneezing, and nasal congestion. They were specified from 0 (no symptoms) to 3 (severe symptoms) and documented in a patient diary every morning and night. Upon conclusion of the treatment, patients judged their condition on a scale ranging from 0 (extremely tired) to 100 (wide awake).

Ethical-legal aspects

The study was performed in compliance with the declaration of the 18th Conference of the World Physicians' Association in Helsinki and its revisions. Furthermore, the "Methodological principles of the Work Group of Medical Ethics Committees in the Federal Republic of Germany, including Berlin (West)" (Cologne, 1987) and the recommendations of the "Good clinical practice for trials on medicinal products in the European Community" (Brussels, 1990) were taken into account. The ethical review board of the local medical faculty had approved the study protocol before the study was initiated. Each patient gave written consent for their participation.

Statistical analysis

The data input and statistical analysis was done with the PC-SAS® program (SAS Procedure Guide, 1988). Pairwise nonparametric comparisons between treatment (patient) groups were performed by the Mann-Whitney-U-test for the first study. Intragroup comparisons for the score profiles were done with Friedmann's rank test and the pairwise signed Wilcoxon test.

Results

All test groups contained patients with a similar distribution with regard to age, sex, height, and weight (Table 1). We found significant differences with all QOL measuring devices ($P < 0.01$) for the different groups of patients with AR (sSAR, sPAR, and aSAR). Both the global assessment of QOL on the VAS-QOL and the MLDL and the disease-related assessment on the RQLQ showed that symptomatic patients with sSAR or sPAR judged their QOL to be

Table 1. Demographic patient data

Study 1	Total	Men	Women	Age (years)
sSAR	279	40.1%	59.9%	31.9 ± 10.4
sPAR	103	37.9%	62.1%	36.0 ± 12.2
aSAR	104	48.1%	51.9%	32.7 ± 12.9

significantly worse than did asymptomatic patients (aSAR), and that patients with sSAR judged their QOL to be significantly worse than did patients with sPAR (Fig. 1). There were highly significant discrepancies ($P < 0.0001$) between the asymptomatic group and both symptomatic groups for all subscales of the RQLQ (nasal, eye, and common symptoms; sleep disorders; practical problems; limited activity; and emotional disturbances) (Fig. 2). This shows that subscales which did not strictly concern rhinitis symptoms were also affected. Again, patients with sSAR judged QOL to be significantly worse than did patients with sPAR on all subscales. In both symptomatic groups, there was a remarkably high rating of practical problems. Compared to the other subscales, the limited activity was relatively more disturbing to patients with sSAR than to patients from the other groups, and general symptoms were relatively more disturbing to patients with sPAR. The results of the generic MLDL showed that the global life satisfaction was reduced only for sSAR, and not for sPAR and aSAR. The results of the subscales showed that social life and everyday life were only minimally or not at all affected compared to "physis" or "psyche" (Fig. 3).

The results of the second study obtained before therapy began for the RQLQ, MLDL, and VAS-QOL for patients with sSAR compared well with the results obtained from the patients with sSAR from the first study. During therapy with a topical antihistamine, there was a highly significant improvement of QOL on all scales during the 14-day treatment ($P < 0.001$) (Fig. 4). The results of patients with sSAR after therapy corresponded for the most part with the results of patients with aSAR of the first examination.

In the third study, we once again used the RQLQ, MLDL, and VAS-QOL as well as symptom scores, for the comparison between topical and systemic therapies. Before the study began, there were no significant distinctions between the two treatment groups. The treatment effects proved to be significant in all QOL tests ($P < 0.0001$) (Fig. 5–7). As expected, the largest improvements were achieved within the first week of treatment. Here as well, the final results corresponded

Table 2. Demographic data

Study 2	Total	Men	Women	Age (years)	Height (cm)	Weight (kg)
Topical antihistamines	76	44.7%	55.3%	32.2 ± 11.3	173 ± 7.9	71.0 ± 12.7
Placebo	81	42.0%	58.0%	34.5 ± 12.3	172 ± 7.8	69.5 ± 13.0

Table 3. Demographic data

Study 3	Total	Men	Women	Age (years)	Height (cm)	Weight (kg)
Topical antihistamines	165	44.2%	55.8%	31.0 ± 10	172.3 ± 11.3	67.8 ± 12.7
Systemic antihistamines	161	36.0%	64.0%	33.0 ± 10	171.2 ± 8.8	68.0 ± 11.5

with those of the first examination of patients with aSAR. The improvement of the condition of patients as determined by the QOL questionnaires was reflected in the symptom score. The nasal symptom scores changed during both treatments from an initial value of 5.32 (maximum: 9) to final values of 2.23 (topical) and 2.13 (systemic) (Fig. 8). The condition stated by the patients on a visual analog scale of 0–100 corresponded well with the results stated in the VAS-QOL (Fig. 9).

Discussion

QOL has been determined in most recently published clinical trials in AR. The rationale for this is that there are no "hard endpoints", as AR is not a life-threatening disease, nor are there generally accepted objective criteria by which the severity of the condition can easily be measured. However, although the RQLQ, a disease-specific QOL scale, was introduced by Juniper & Guyatt some 10 years ago (1), it is still not clear whether it truly reflects the impairment caused by the different facets of the condition (seasonal/perennial or, in more recent terminology, intermittent/persistent). It must also be doubted that the RQLQ is sensitive to the amelioration of the patient's condition. In two recent clinical trials in SAR (15, 16), the RQLQ could not distinguish the improvement under loratadine from that

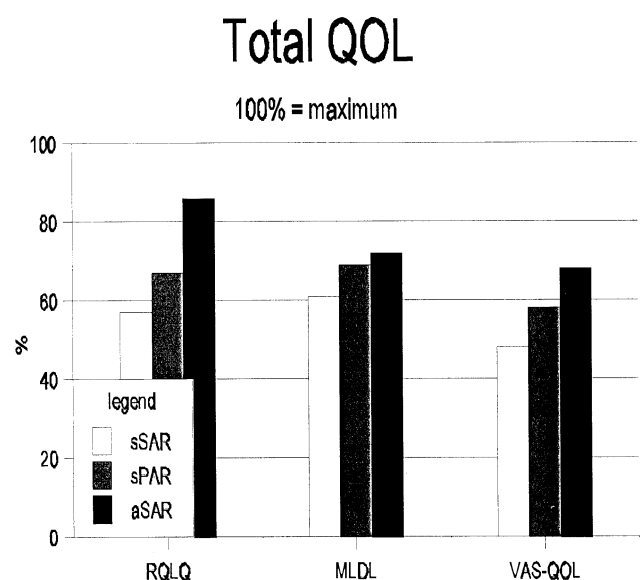


Figure 1. Quality of life (QOL) in RQLQ, MLDL, and VAS-QOL with sSAR ($n = 279$), sPAR ($n = 103$), and aSAR ($n = 104$) (first study).

RQLQ

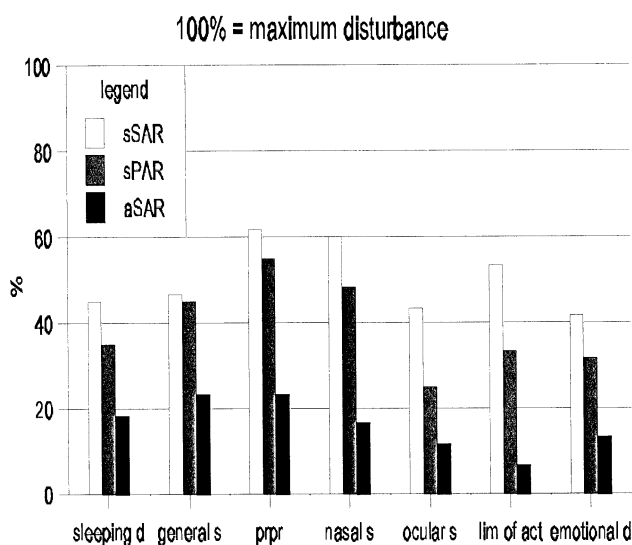


Figure 2. Subscales sleeping disorders (sleeping d), general symptoms (general s), practical problems (prpr), nasal symptoms (nasal s), ocular symptoms (ocular s), limitation of activity (lim of act), and emotional disorders (emotional d) of RQLQ with sSAR ($n=279$), sPAR ($n=103$), and aSAR ($n=104$) (first study).

under placebo, although in all published trials loratadine was significantly superior to placebo in control of nasal symptoms.

Do generic QOL scales as used by Bousquet et al. (2) better reflect the patient's status? To answer this question, we set up a series of clinical studies in

MLDL

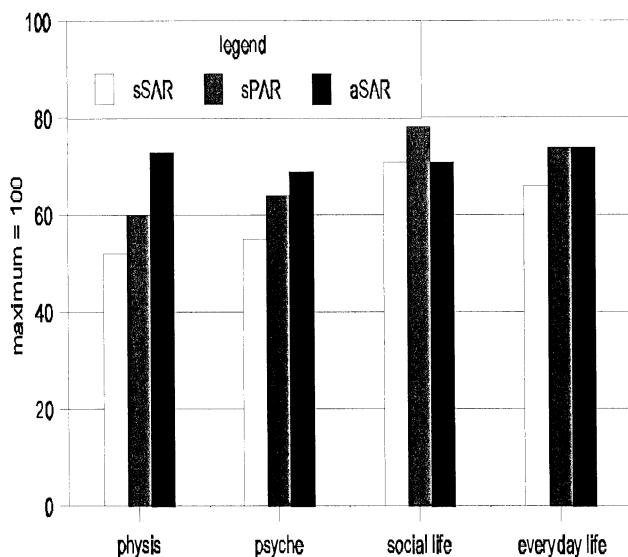


Figure 3. Subscales physis, psyche, social life, and everyday life in MLDL with sSAR ($n=279$), sPAR ($n=103$), and aSAR ($n=104$) (first study).

QOL (topical therapy)

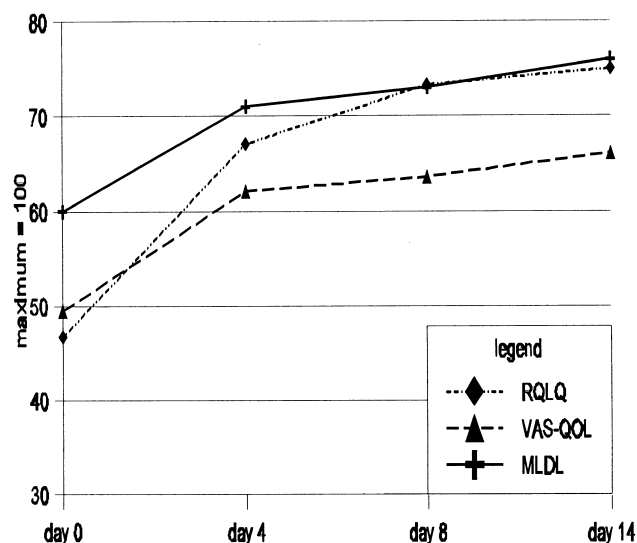


Figure 4. Course of QOL in RQLQ, MLDL, and VAS-QOL under topical antihistamine therapy ($n=76$) (second study).

which we used both types of QOL scales, generic as in the MLDL and the VAS-QOL, and the German version of the disease-specific RQLQ that we validated in 1991. Our investigation has proven that patients with SAR or PAR have a greatly reduced QOL. The general QOL was significantly lower in patients with sSAR than those with sPAR, whose QOL, in turn, was much lower than that of patients with aSAR. Previous research has found PAR to be more disturbing than SAR (2, 16).

MLDL

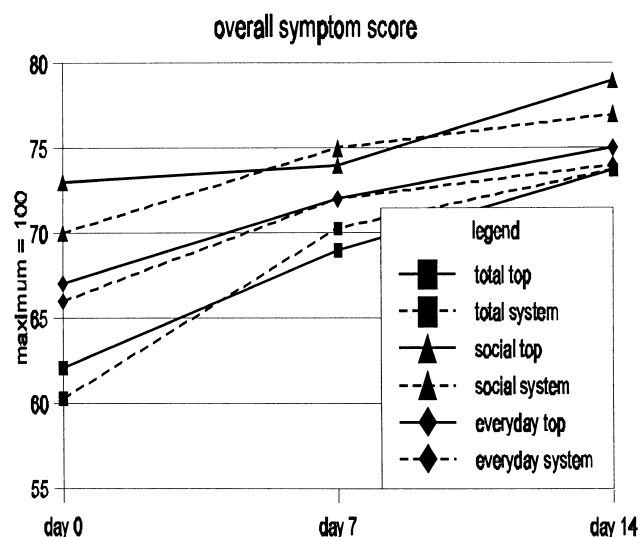


Figure 5. Course of total QOL (total) and subscales social life (social) and everyday life (everyday) in MLDL from day 0 to day 14 under therapy with topical antihistamine (top) ($n=165$) and systemic antihistamine (system) ($n=161$) (third study).

VAS-QOL

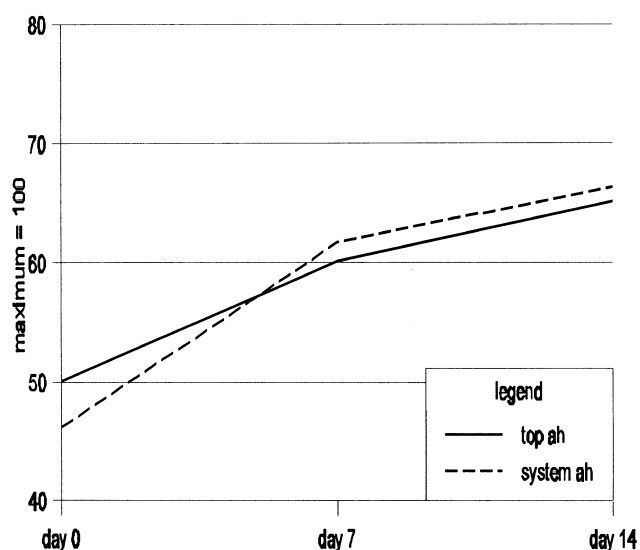


Figure 6. Course of total QOL in VAS-QOL from day 0 to day 14 under therapy with topical antihistamine (top ah) ($n=165$) and systemic antihistamine (system ah) ($n=161$) (third study).

However, despite the fact that sPAR appears to create less overall disturbance within the 2- or 1-week time period that these QOL instruments refer to, sPAR is a year-round illness and the QOL instruments cannot capture this disturbance over the entire year. From the clinical point of view, it is doubtful whether a patient would prefer 12 months of continuous symptoms (even less disturbing) to 1 month of more disturbing ones. In

Nasal symptom score

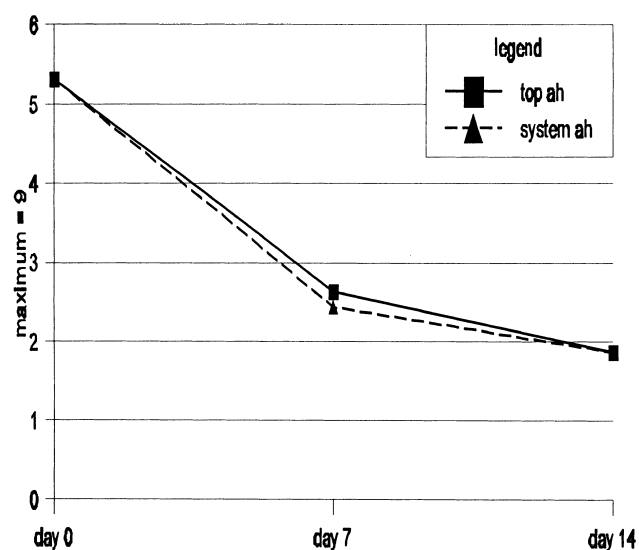


Figure 8. Course of nasal symptom score according to patient opinion from day 0 to day 14 with topical antihistamine (top ah) ($n=165$) and systemic antihistamine (system ah) ($n=161$) (third study).

addition, the prevailing symptom of PAR is nasal obstruction and there is little hope that the patients can overcome this problem other than by taking nasal steroids. Only one out of three patients is willing to accept these as long-term treatment. The others dissimulate and rate their symptoms as minor. In SAR, with the onset of mostly H_1 -mediated symptoms such as secretion, itching, and sneezing at the start of the season,

RQLQ

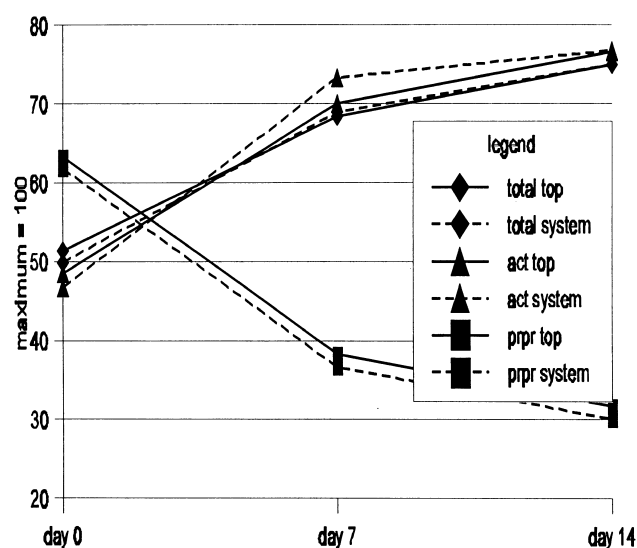


Figure 7. Course of total QOL (total) and subscales practical problems (prpr) and activity (act) in RQLQ from day 0 to day 14 under therapy with topical antihistamine (top) ($n=165$) and systemic antihistamine (system) ($n=161$) (third study).

State of health

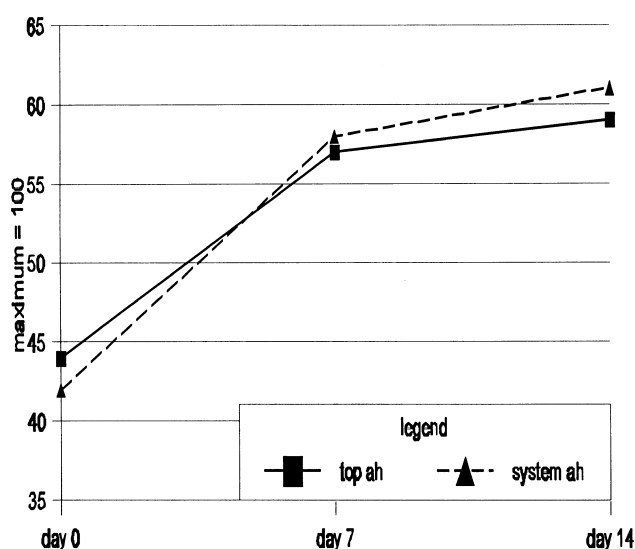


Figure 9. Course of state of health according to patient opinion from day 0 to day 14 with topical antihistamine (top ah) ($n=165$) and systemic antihistamine (system ah) ($n=161$) (third study).

patients suddenly become aware that their problem still exists and therefore they experience a much deeper suffering.

Especially striking was the importance attributed to the practical problems associated with AR, a finding which confirms the special meaning which QOL evaluations possess in studies concerning AR. The limited activity was relatively more bothersome to patients with sSAR than to those in other groups. The similarity of areas and changes of the RQLQ "general symptoms" and the MLDL "physis" was also prominent. The improvement of sleep corresponded with improved alertness during the day. Emotional disturbances seemed comparably less distinct than physical problems. Furthermore, it was obvious in the RQLQ that patients with sPAR showed a high degree of disturbance caused by common symptoms and practical problems. This could indeed be caused by a high symptom strain but also by an elevated degree of disturbance by chronically affecting symptoms. It is difficult to adjust to some symptoms which typically appear with atopic illnesses (e.g., itching).

The detailed analysis of the scales showed that allergic rhinoconjunctivitis, which is most troublesome due to nasal and eye symptoms and the practical problems caused by them, limits life satisfaction (MLDL) mainly in the areas of "physis" and "psyche". The social, or rather interhuman, field and the ability to function in everyday life were far less affected. However, especially with acute hay fever, life satisfaction and QOL are definitely globally limited.

Whether the additional use of the SF-36 Health Status Questionnaire has given some additional information is uncertain. The items which are not specific for AR (general symptoms, sleeping disorders, practical problems, limitations of activity, and emotional disorders in the RQLQ in comparison with general perception of health, energy/fatigue, physical functioning, role limitations attributed to physical problems, and role limitations attributed to emotional problems in the SF-36) are similar in the RQLQ and the SF-36, and some investigations have shown similar results for the RQLQ and the SF-36 in different patient groups (18, 19). Investigations comparing the SF-36 and the VAS in patients with chronic fatigue syndrome and in patients with HIV showed moderate to strong correlations (20, 21). To our knowledge, there have been no comparisons between the SF-36 and the VAS-QOL in patients with AR until now.

In the therapy study before treatment began, values were found which corresponded with those of the group of untreated patients selected by the same inclusion criteria as the untreated patients of the first study. This indicates the reliability of all the questionnaires used. It was furthermore proven that the indices for QOL under treatment with a topical or systemic antihistamine improved in a similar way as symptom scores. After a 2-week treatment period, the QOL scores of patients

with sSAR reached the values of patients with aSAR. This corresponds with the reduction of symptom scores to normal levels, as was shown not only in our study, but also in several other studies after several weeks of treatment. QOL evaluation can increase the possibility of interpreting clinical results, since psychological and social effects are also monitored in addition to physical effects. Progression of the illness (e.g., toward allergic asthma) will have a lasting influence on QOL scores, while the (nasal) symptom scores may even improve after the nasal symptoms have been alleviated. There may be also treatment effects with a negative influence on QOL opposing the general improvement of symptom scores. A more precise examination of these aspects should be the subject of further investigations.

The measuring devices mentioned for QOL are suitable for determining the status of AR. The different forms of rhinitis can be associated with typical QOL patterns (for example, sSAR causes greater limitation of the global QOL in the RQLQ, a high score on practical problems, a relatively high limitation of activity, and a high degree of disturbance in all areas of the RQLQ; sPAR causes moderate limitation of the global QOL in the RQLQ, a high assessment of practical problems, less pronounced limitation of activity, and a high degree of disturbance by common symptoms and practical problems in the RQLQ). Therapy monitoring is possible with these scales.

However, a considerable disadvantage of recording the QOL for the purpose of therapy control in AR is the lack of sensitivity to rapid changes in the patient's condition, changes that often occur particularly in SAR. The RQLQ, for example, inquires about the patient's condition in the last week before testing, a limitation which does not do justice to the rapid changes in SAR due to variation of pollen concentrations as they often occur in central Europe. Moreover, quick benefits due to therapy (modern antihistamines have a rapid onset of action within the first hour after intake) are not recorded by measuring QOL with the RQLQ. In some pharmacologic studies, QOL in SAR was checked for the first time 14 days after the beginning of treatment (22), a practice which, in our opinion, leads not only to the disregard of pollen count-dependent fluctuations, but also to a complete disregard of the onset of action, and thus does not do justice to the realistic needs of the patient.

As expected, we found significant improvement of the symptom scores within the first two treatment days under topical as well as under systemic treatment with an antihistamine. These improvements could not be, or at least not so clearly, recorded by means of the RQLQ, in which the topical antihistamine was not clearly superior to its placebo spray after 1 week of treatment. However, significant differences were found when asking the patient on a daily basis for the limitations of daily activities caused by the disease. For example,

the question, "Did your symptoms allow you to spend time outdoors today?" distinguished well between the drug and placebo and could constitute, in our opinion, an addition to the sole recording of symptom scores, as well as to the QOL scores. Recording can take place daily in a diary or even at several fixed time points per day with a handheld computer (23) and is therefore suited to the rapid changes of allergen exposure and consequent changes in health status. QOL as determined by overall RQLQ, in our opinion, is only partially suitable for therapy monitoring in SAR and should be supplemented by additional parameters.

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