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Development, validation, and initial results of the Angioedema Activity Score

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Abstract

Background: Recurrent angioedema (RecA) is a frequent clinical problem characterized by suddenly occurring cutaneous and/or mucosal swellings. Depending on their location, RecA may be painful, hindering, disfiguring, or even life-threatening. The assessment of disease activity in affected patients is important to guide treatment decisions. Currently, however, there is no standardized and validated outcome measure available to do so.

Objective: To develop and validate the first specific patient-reported outcome instrument to assess disease activity in RecA patients, the Angioedema Activity Score (AAS).

Methods: After a set of potential AAS items was developed, item evaluation and reduction were performed by means of impact analysis, factor analysis, regression analysis, and by checking for face validity. In addition, the items of the final AAS questionnaire were tested for their validity and reliability during a 12-week validation study.

Results: In total, data from 110 and 80 RecA patients were used during the AAS item evaluation and validation phase, respectively. The resulting AAS consisted of five items and was found to have a one-dimensional structure and excellent internal consistency. It correlated well with other measures of disease activity and quality-of-life impairment, thus demonstrating its convergent validity. In addition, the known-groups validity and test–retest reliability of the AAS were found to be good.

Conclusions: The AAS is the first validated and reliable tool to determine disease activity in RecA patients, and it may serve as a valuable instrument in future clinical studies and routine patient care.

Recurrent angioedema (RecA) is characterized by relapsing nonpruritic, nonpitting swellings of deeper cutaneous and mucosal tissues (1). It is either mast cell mediator induced, for example, in patients with chronic spontaneous urticaria (csU), or bradykinin mediated (2), for example, in patients with hereditary angioedema (HAE) due to C1-inhibitor deficiency or defects (HAE1&2). CsU is frequent with 0.5–1.0% of the total population affected (3), while HAE1&2 are orphan diseases (estimated prevalence of 1:10 000–1:50 000) (4, 5). All HAE1&2 patients and one to two of three csU patients exhibit RecA (3). Most csU patients with RecA also have wheals (hives). However, there is a csU subgroup with isolated RecA without wheals (3). It is generally not possible to distinguish between bradykinin- and mast cell-mediated angioedema based on the clinical picture. Thus, additional information (clinical, laboratory, patient history) is always needed to identify the type of RecA.

Although RecA is an important and common clinical problem, research is currently hindered by the lack of specific and validated outcome instruments. A missing consensus how to best measure angioedema activity also makes it difficult to compare data across clinical trials. Therefore, the need of a simplified angioedema disease-scoring instrument has been discussed already (6). Recently, we developed and

used the first symptom-specific tool to measure quality-of-life impairment in these patients, the Angioedema Quality of Life Questionnaire (AE-QoL) (7). In contrast, a validated and reliable instrument to measure and follow disease activity in RecA patients has not been reported yet. This is required to enhance the quality as well as the comparability of future clinical research projects and would be ideal to complement the AE-QoL. In addition, it may help with treatment decisions in routine care. Here, we report the development of such a tool, the Angioedema Activity Score (AAS), which was designed as a prospective, diary-type instrument, intended for use in adult RecA patients.

Methods

AAS item and instrument development

Angioedema Activity Score (AAS) item generation was performed by following current recommendations for patient-reported outcome (PRO) development (8): In addition to the involvement of experts, we performed a literature search for existing PRO instruments and collected published information on disease activity of angioedema patients. This was complemented by exploratory, semi-structured interviews with ten affected HAE and csU patients.

The AAS instrument deployed in the evaluation and validation phase consisted of 13 items that each referred to the previous 24 h. It was designed as a daily diary with an opening question followed by further AAS items. The opening question asked the patients if angioedema occurred during the past 24 h. The patients were only asked to complete the additional items if the answer to the opening question was positive. Questions on the location of angioedema, on the occurrence of dyspnea, and on the applied treatment were among the items administered to the patients, but were not included in the later analysis to ensure content and face validity of the resulting instrument. Although answers to these questions give valuable information on characteristics of single swellings and the observed population, these are not suited to measuring the construct of disease activity that can be understood as a combination of symptom severity and frequency.

Data collection

Patients receiving care from one of two angioedema specialist centers, the Department of Dermatology and Allergy of the Charité – Universitätsmedizin Berlin and the Department of Dermatology of the University Medical Center Mainz, were recruited to participate in the AAS item evaluation and validation phase between April 2011 and January 2012. Each site's local ethics committee approved the study, and all participants had to sign a written informed consent. In total, 110 and 80 patients were included in the analysis of the item evaluation and the AAS validation phase, respectively. Prerequisite for inclusion into each phase was age 18 and older, a current diagnosis of RecA (HAE1&2, csU) as well as being literate in German.

While the patients of the item evaluation phase had to complete an evaluation form once, the participants of the validation phase were asked to complete all intended AAS items once daily for 12 weeks. In addition, once every week, the patients were requested to globally self-rate their angioedema activity [patients' global assessment (PGA)] over the previous 7 days on a 10-cm visual analogue scale (PGA-VAS) and a 5-point Likert scale (PGA-LS, answer options: 'none', 'mild', 'moderate', 'severe', 'very severe'). At week 4 and week 12, all patients also completed the AE-QoL as well as the SF-36, a generic quality-of-life measure.

Item reduction and internal consistency

Impact analysis

In the item evaluation form, the participants were asked which of the problems indicated in the potential AAS items they had experienced during the last year (response options: yes or no) as well as to rate the importance of each item (response options: 1 = not important to 5 = extremely important). The results were expressed as 'frequency' of patients (proportion who had experienced the problem indicated in the respective item) and as 'importance' (mean importance of each item). The 'impact' of each item was then computed as the product of 'frequency' and 'importance'. The aim of this analysis was to exclude all items with a low impact score. In addition, the patients were asked to rate the comprehensibility and completeness of items.

Factor analysis/internal consistency

An exploratory factor analysis was performed on the completed items of the AAS validation phase to determine the dimensionality (domain structure) of the AAS, its internal consistency as well as to further reduce the number of items. The approach employed was a principal component analysis with varimax rotation and Kaiser normalization. The criterion chosen to retain domains (factors) was an eigenvalue 1. Individual items loading onto a domain with a factor loading ≥ 0.5 were assigned to that domain.

Internal consistency measures the homogeneity of an instrument's domain. It was tested by computing Cronbach's α-coefficient. The commonly suggested interpretation of its values is <0.60 unacceptable, 0.60–0.65 undesirable, 0.65–0.70 minimally acceptable, 0.70–0.80 respectable, 0.80–0.90 excellent, and >0.90 excessive consistency (9).

Regression analysis

For item reduction, a regression analysis was performed with all potential AAS items as independent and the factors as dependent variables. In fact, this was done for only one factor as it turned out that the instrument was one-dimensional.

AAS computation

Each AAS item was scored between 0 and 3 points, that is, the minimum and maximum daily AASs were 0 and 15 points. The daily AASs were summed up to 7-day scores (AAS7), 4-week scores (AAS28), and 12-week scores

(AAS84). Missing values were not replaced. The only exception was the computation of the AAS84. Due to an, in this case, otherwise problematic adding up of missing values to $n = 25$, we decided to replace a maximum of one missing AAS7 with the mean AAS7 value of the remaining eleven available AAS7 of that patient ($n = 13$). In case more than one AAS7 value was missing, the data of that patient were excluded ($n = 12$).

Convergent validity

Convergent validity tests whether items, scales, or total instruments that should theoretically be related are related. To determine the convergent validity of the AAS, we correlated its scores with different anchors: the related PGA-VAS, the number of angioedema affected days, the AE-QoL total scores as well as the SF-36 scores (Spearman correlation). The AE-QoL is the first validated symptom-specific health-related quality-of-life measure designed for all patients with RecA (7). It consists of 17 items that can be summed up to a total score. The SF-36 is a generic instrument that has been used extensively to detect and compare health-related quality-of-life impairment in dermatologic and nondermatologic diseases (10–14). It is composed of 36 items that are related to 8 domains and two composite scores, the 'physical component summary' and the 'mental component summary'. The calculation of the SF-36 scores included the recoding and recalibration of items, the computation of raw domain/composite scores, and the conversion of the latter to a 1–100 scale and was performed using the SF-36 analysis software provided by the Hogrefe-Verlag (Hogrefe-Verlag, Göttingen, Germany).

Known-groups validity

One important criterion for validity is that an instrument is able to distinguish patient groups that are assumed to differ. Known-groups validity of the AAS was examined by determining whether it yielded different results in case of different PGA-LS ratings. To this end, all available AAS7 were classified according to their related PGA-LS rating (the PGA-LS rating of the same time period in the same patient) into five different groups ('none' to 'very severe') and the related mean and median AAS7 were computed. Subsequently, the scores were compared using an ANOVA trend test followed by the unpaired Student's *t*-test.

Test–retest reliability

Test–retest reliability investigates whether an instrument has the ability to yield stable results in patients with stable disease. To investigate the test–retest reliability of the AAS, each patient's AAS7 of the first week of the validation phase was compared with the AAS7 of the same patient in the closest subsequent week where he/she reported an identical PGA-LS using the paired Student's *t*-test. In addition, the AAS7 results were compared by computing the intraclass correlation coefficient (ICC). An ICC of 0.5–0.7 was considered to be indicative of a moderate to good reproducibility and >0.7 to demonstrate excellent reproducibility (15).

Minimal important difference

To determine the minimal important difference (MID) (16) of the AAS7, we applied two different approaches, one anchor based and one distributional criterion approach. The anchor-based approach was applied by computing the mean intra-individual differences of AAS7 between weeks with a different PGA-LS (defined as a change in one step in the PGA-LS, for example, from mild to moderate or moderate to severe). In case more than 1 week was available with an identical PGA-LS rating in the same patient, only the AAS7 of the closest subsequent week to week 1 of the validation phase was included in the analysis.

The distributional criterion approach was based on the work of Norman et al. (17) who found that one half of the SD of an instrument's results may represent a good approximation of its MID. In our study, the combined results of all available AAS7 were used to calculate the half SD.

Statistical analysis

All statistical analyses were performed using SPSS (IBM SPSS Statistics version 19; IBM Corporation, Armonk, NY, USA). $P \leq 0.05$ was considered as statistically significant. In case of repeated measurements per subject, standard errors were corrected for dependency of data using generalized estimating equations.

Results

Patient sample characteristics

A total of 110 and 80 RecA patients were included in the analysis of the item evaluation and AAS validation phase, respectively. The sociodemographic and clinical characteristics of these populations are shown in Table 1. The mean disease duration ± SD was 115 ± 140 months (median: 60) and 117 ± 145 months (median: 60), respectively. Most patients of the AAS validation phase also took part in the item evaluation.

AAS item generation and impact analysis

During the item generation phase, eight items possibly relevant to patients with RecA were identified. The impact analysis did not clearly suggest any of them to be removed from the final AAS because all items scored high (all scored ≥ 2.5 in terms of their impact) (Table 2).

Factor analysis, regression analysis, and internal consistency

All eight items were subjected to an exploratory factor analysis, which identified a one-dimensional structure (Table 3). The additional regression analysis suggested the removal of four items (items 1, 3, 7, 8). However, for face validity

Table 1 Patient sample characteristics

	AAS item evaluation phase *n* (%)	AAS validation phase *n* (%)
Gender		
Female	72 (65.5)	52 (65.0)
Male	38 (34.5)	28 (35.0)
Age (years)		
18–40	28 (25.5)	17 (21.3)
41–60	46 (41.8)	30 (37.5)
61–80	34 (30.9)	31 (38.8)
>80	2 (1.8)	2 (2.5)
Disease duration (years)		
0–2	37 (33.6)	26 (32.5)
2–10	37 (33.6)	27 (33.8)
>10	31 (28.2)	24 (30.0)
Unknown	5 (4.5)	3 (3.8)
School education (years)		
9	17 (15.5)	13 (16.3)
10	48 (43.6)	32 (40.0)
12–13	42 (40.9)	32 (40.0)
Unknown	3 (2.7)	3 (3.8)
Diagnosis		
HAE1&2	22 (20.0)	17 (21.3)
CsU (patients with wheals and recurrent angioedma)	54 (49.1)	43 (53.8)
CsU (patients with isolated recurrent angioedma)	34 (30.9)	20 (25.0)

HAE, hereditary angioedema; csU, chronic spontaneous urticaria.

reasons, we decided to keep item eight in the final AAS instrument in order to retain a global assessment of severity of the angioedema episodes. The internal consistency of the final 5-item solution was found to be excellent with a Cronbach's α value of 0.90.

AAS computation

The mean AAS7 $\pm$ SD obtained in the AAS validation phase was 5.8 ± 9.5 (median: 0, range: 0–63). In addition, the AAS28 and AAS84 were computed and are shown in Table 4. The AAS values were broad ranging, thus indicating a considerable variation of angioedema activity in the included patient population.

Convergent validity

Correlations were computed between the AAS values and other markers of disease activity and quality-of-life impairment to test its convergent validity. The correlation coefficient for the relation of all available AAS7 to its corresponding PGA-VAS was $r = 0.714$ ($P < 0.001$, $n = 867$), thus demonstrating a strong correlation ($r > 0.7$). Similar results were seen for the correlation of the AAS7 with the number of angioedema affected days during the corresponding weeks ($r = 0.914$, $P < 0.001$, $n = 912$). In addition, correlations were computed for all available AAS28 and the corresponding PGA-VAS, the number of angioedema affected days, and quality-of-life impairment (AE-QoL scores and SF-36 component summary values) (Table 5). All correlations were in the expected direction. The correlations with the SF-36 are negative, because, in contrast to the other measures, lower scores in this instrument represent a stronger QoL impairment.

Known-groups validity

Known-groups validity of the AAS was tested by investigating whether the AAS7 yielded different results in weeks with a different disease activity as measured by PGA-LS. As expected, we found a good linear trend of the mean AAS7 values with the PGA-LS from 'none' to 'very severe' (Table 6 and Fig. 1). The comparison of the mean AAS7 values related to different PGA-LS was significant for AAS7 values corresponding to 'none' *vs* 'mild', 'mild' *vs* moderate', and 'moderate' *vs* severe ($P < 0.001$ ANOVA trend test, $P < 0.001$ for each comparison with the unpaired Student's *t*-test). Only the comparison of 'severe' *vs* 'very severe' showed no significant difference ($P = 0.188$) probably due to the limited number of 'very severe' PGA-LS ratings. An alternative or additional possibility is that the PGA-LS is not good in discriminating patient with 'severe' and 'very severe' disease.

Test–retest reliability

The mean AAS7 $\pm$ SD of the participants of week 1 and a closest subsequent week with an identical disease activity

Table 2 Item impact analysis

Item	Item name	Frequency (%)	Importance (mean)	Impact
1	Occurrence of angioedema during the last 24 h	Not applicable	3.98	Not applicable
2	Number of angioedema affected 8-h periods	0.98	3.60	3.53
3	Size (diameter) of angioedema	0.97	3.33	3.23
4	Severity of physical discomfort caused by angioedema	0.87	3.96	3.45
5	Ability to perform daily activities during presence of angioedema	0.75	3.61	2.71
6	Cosmetic disfigurement caused by angioedema	0.76	3.29	2.50
7	Global assessment of impairment caused by angioedema	0.94	3.80	3.57
8	Global assessment of severity caused by angioedema	Not applicable	3.80	Not applicable

Table 3 Exploratory factor analysis and internal consistency (item factor loadings and Cronbach's α)

Item no.	Item	Factor loadings 8 items	Factor loadings 5 items
1	Occurrence of angioedema during the last 24 h	0.93	
2	Number of angioedema affected 8-h periods	0.89	0.87
3	Size of angioedema	0.89	
4	Severity of physical discomfort caused by angioedema	0.96	0.95
5	Ability to perform daily activities during presence of angioedema	0.88	0.90
6	Cosmetic disfigurement caused by angioedema	0.83	0.81
7	Global assessment of impairment caused by angioedema	0.93	
8	Global assessment of severity caused by angioedema	0.95	0.96
Cronbach's α		0.95	0.90

Table 4 Results of the AAS. All available AAS7, AAS28, and AAS84 of $n = 80$ patients were included in the analysis

	n	Mean	SD	Median
AAS7 (pooled scores)	912	5.8	9.5	0
AAS28 (pooled scores)	198	20.3	26.9	11.5
AAS84 (week 1–12)	68	59.2	62.9	38.5

AAS, Angioedema Activity Score.

(PGA-LS) as a surrogate for stable disease was found to be not different (7.6 ± 9.5 *vs* 7.4 ± 9.6, $P = 0.850$). In addition, the ICC was 0.65, indicating good reproducibility. In total, ten of the 80 patients were excluded from the analysis because they either had a missing AAS7 value in week 1 or showed no subsequent week with an identical PGA-LS rating as in the first week.

Minimal important difference

The mean intra-individual differences of AAS7 values between weeks with different disease activity (PGA-LS) are shown in Table 7. These range from 6.6 to 8.8 points when not considering the differences between weeks rated to be 'severe' and 'very severe'. In case of the latter, the high SD indicates an imprecision of the results, probably due to the very low number of available information ($n = 4$). The combined intra-individual AAS7 differences were found to be 7.8 points. In contrast, the AAS7 mean change in case of a stable disease activity (nonchanging PGA-LS) was only 0.2 ± 8.2 points. Therefore, our results indicate a MID of the AAS7 of around eight points.

For the distributional criterion approach, the SD of all available AAS7 values (9.5, see Table 4) was divided by two. Here, the result even suggests a MID of 4.7 (one half of the SD criterion). However, because the latter approach is indirect, we regard the results of the anchor-based approach as more convincing.

Discussion

The assessment of disease activity in RecA patients is important to guide treatment decisions but also to monitor

Table 5 Convergent validity of the AAS. Correlations were computed between the AAS28 and the indicated measures. While the available AAS28 and the PGA-VAS data were included for all three 4-week periods of the 12-week validation study (week 1–4, week 5–8, and week 9–12), the AE-QoL and SF-36 were applied only twice (at weeks 4 and 12) each time covering the previous 4 weeks. Therefore, the correlation between the AAS28 and both quality-of-life measures could only be computed for a lower *n* as compared to the other correlations

	AAS28		
	Spearman's rho (correlation coefficient)	*P*-value	*n*
Number of angioedema affected days	0.958	<0.001	198
Patients' mean global self-rated disease activity (PGA-VAS)	0.825	<0.001	180
AE-QoL total score	0.528	<0.001	132
SF-36 physical component summary	−0.309	0.001	123
SF-36 mental component summary	−0.294	0.001	123

AAS, Angioedema Activity Score; PGA, patients' global assessment; VAS, visual analogue scale; AE-QoL, Angioedema Quality of Life Questionnaire.

Table 6 Known-groups validity. The results are expressed as all available AAS7 in relation to the patients' global self-rated disease activity during the corresponding weeks (PGA-LS)

Patients' global self-rated disease activity (PGA-LS)	AAS7			
	n	Mean	SD	Median
None	462	0.2	1.9	0
Mild	241	6.5	6.9	5
Moderate	133	15.4	10.1	14
Severe	61	21.2	11.3	20
Very severe	7	28.0	23.0	17

AAS, Angioedema Activity Score; PGA, patients' global assessment; LS, Likert scale.

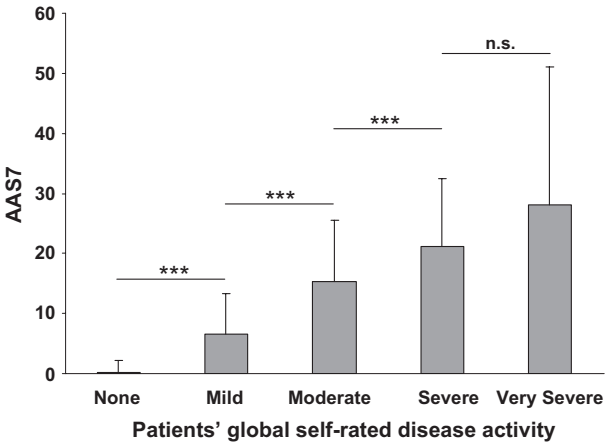

Figure 1 Known-groups validity. The results are expressed as all available AAS7 from $n = 80$ recurrent angioedema (RecA) patients in relation to the patients' global self-rated disease activity (Likert scale rating from 'none' to 'very severe', PGA-LS) during the corresponding weeks (mean AAS7 ± Standard Deviation (SD). ***$P < 0.001$, n.s., not significant.

Table 7 Intra-individual AAS7 differences in case of a change in patients' global self-rated disease activity (PGA-LS)

Intra-individual difference in patients' global self-rated disease activity (PGA-LS)	Intra-individual AAS7 differences			
	n	Mean	SD	Median
Mild–none	56	6.6	7.6	4.5
Moderate–mild	45	8.8	11.1	6.0
Severe–moderate	28	8.2	11.7	5.5
Very severe–severe	4	14.3	21.9	4.0
Pooled differences	157	7.8	10.2	5.0

AAS, Angioedema Activity Score; PGA, patients' global assessment; LS, Likert scale.

response in clinical trials. We here report the development of the first specific tool for this purpose, the AAS.

The AAS was designed as a prospective diary-type tool for all RecA patients. As expected, it was found to have a one-dimensional structure during exploratory factor analysis. In addition, we were able to reduce the number of AAS items to only five, which makes it a simple tool that can be completed within <1 min.

The validity of the final five-item AAS (Data S1) was established by demonstrating significant increases in the AAS values with rising disease activity as measured by the PGA-LS (known-groups validity). Furthermore, the observed AAS values correlated well with other markers of disease activity (number of angioedema affected days, PGA-VAS) and quality-of-life impairment (AE-QoL and SF-36 results). In accordance with previous studies (18–20), the correlation of disease activity (AAS28) with the quality-of-life results was found to be moderate ($r > 0.3$) to good ($r > 0.5$) and to be lower as compared to the applied measures of disease activity ($r > 0.7$), that is, the number of angioedema affected days and PGA-VAS. This was expected, because it is well established that other factors in addition to disease activity, for example, psychiatric comorbidities (21), may also influence the patients' quality-of-life perception. These other factors are not well characterized for RecA patients but need to be identified in future research projects. Of note, the results of the angioedema-specific AE-QoL showed a higher correlation with disease activity as compared to the component summaries of the SF-36. This indicates a higher sensitivity of the symptom-specific AE-QoL when testing for angioedema-related quality-of-life impairment as compared to the generic SF-36. In addition, this is in line with earlier results obtained in other settings (19) and supports the use of AE-QoL in RecA patients.

The internal consistency reliability of the AAS was supported by a Cronbach's alpha coefficient of 0.90, which is generally interpreted as excellent. In addition, the test–retest reliability of the AAS was found to be good with an ICC of 0.65.

In addition to validity and reliability, it is important to test a PRO instrument for its MID, because a mean difference of a PRO instrument's result, for example, derived before and after treatment adjustment, could be statistically significant, but may not necessarily reflect a clinically relevant change for individual patients. This is of particular importance when working with large sample sizes. Therefore, the AAS MID as a measure for intra-individual clinically meaningful changes was determined by applying different approaches. Our results suggest a MID of around eight points for the AAS7, which should help to interpret future results obtained with this instrument.

A major strength of this investigation is that most age-groups (except minors), educational classes, subjects of both genders, and the major types of RecA patients were included. Accordingly, the AAS will be suitable for a broad audience. Moreover, multiple methods and measures were applied during the AAS development to increase its quality and performance. For example, during item selection and reduction impact analysis, factor analysis and regression analysis were combined. In addition, different anchors for validity and reliability were used during the AAS validation phase.

Before the development of the AAS, there was no specific tool available to measure disease activity in patients with RecA. However, for patients with csU, the Urticaria Activity Score (UAS) exists since many years. The UAS has been proven to be a valid outcome measure (19) and is recommended by the current EAACI/GA²LEN/EDF/WAO guidelines for urticaria (22) but its use is limited by the fact that it only covers wheals and pruritus but not angioedema. Depending on the aim of a disease activity measurement and depending on the observed patient populations, it is advisable to either use the UAS, the AAS, or both. While only the AAS is suitable for csU patients with isolated angioedema and HAE1&2, the UAS and AAS may be used to complement each other in csU patients with wheals and angioedema.

Limitations of this work include that the AAS was not tested in children. Therefore, it is currently not possible to

predict its performance in this group. In addition, the patients were recruited in specialized centers and we cannot exclude that the reported AASs might be different in other patient collectives. Finally, to this point, it is not clear how efficient this tool can detect treatment effects, because this was a noninterventional study. However, we expect from our results on the known-groups validity that the AAS should have this property.

In conclusion, the AAS was found to be a valid and reliable tool to determine disease activity in RecA patients. It was designed as a diary-type tool for clinical studies but may also be used during regular care, because it is easy to administer and fast to complete. Together with the recently published AE-QoL it may help to improve, standardize, and stimulate clinical research in the field of RecA.

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Author contributions

K. Weller substantially contributed to conception and design, acquisition of data, analysis and interpretation of data; drafted the article; and gave final approval of the version to be published. A. Groffik and P. Staubach made substantial contributions to acquisition and interpretation of data, reviewed the article critically for important intellectual content, and gave final approval of the version to be published. M. Magerl substantially contributed to conception and design, acquisition of data, and interpretation of data; reviewed the article critically for important intellectual content; and gave final approval of the version to be published. N. Tohme made substantial contributions to acquisition of data, reviewed the article critically for important intellectual content, and gave final approval of the version to be published. P. Martus and M. Maurer substantially contributed to conception and design, analysis and interpretation of data; reviewed the article critically for important intellectual content; and gave final approval of the version to be published. K. Krause and M. Metz made substantial contributions to acquisition and interpretation of data, reviewed the article critically for important intellectual content, and gave final approval of the version to be published.

Conflict of interest

K. Weller and M. Metz recently are or were speakers for Novartis, Shire, UCB, MSD, Uriach, and are scientific advisors for Moxie. A. Groffik, N. Tohme, P. Martus, and P. Staubach declare that there is no conflict of interest. M. Magerl is a consultant, speaker, and/or study coordinator for CSL, Sobi, Novartis, Shire, Viropharma, and is a scientific advisor for Moxie. K. Krause recently is or was a speaker for Novartis, Shire, Dr. Pfleger, and is a scientific advisor for Moxie. M. Maurer is a consultant, speaker, and/or study coordinator for Genentech, Novartis, Shire, Viropharma, FAES, UCB, Uriach, and is a scientific advisor for Moxie.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. AAS – validated German version.

References

1. Banerji A, Sheffer AL. The spectrum of chronic angioedema. *Allergy Asthma Proc* 2009;**30**:11–16.
2. Maurer M, Bader M, Bas M, Bossi F, Cicardi M, Cugno M et al. New topics in bradykinin research. *Allergy* 2011;**66**:1397–1406.
3. Maurer M, Weller K, Bindslev-Jensen C, Gimenez-Arnau A, Bousquet PJ, Bousquet J et al. Unmet clinical needs in chronic spontaneous urticaria. A GA(2)LEN task force report. *Allergy* 2011;**66**:317–330.
4. Maurer M, Magerl M. Hereditary angioedema: an update on available therapeutic options. *J Dtsch Dermatol Ges* 2010;**8**:663–672.
5. Zanichelli A, Vacchini R, Badini M, Penna V, Cicardi M. Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: a 21-month prospective study in a cohort of 103 patients. *Allergy* 2011;**66**:192–196.
6. Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy* 2012;**67**:147–157.
7. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K et al. Development and construct validation of the angioedema quality of life questionnaire (AE-QoL). *Allergy* 2012;**67**:1289–1298.
8. Baiardini I, Bousquet PJ, Brzoza Z, Canonica GW, Compalati E, Fiocchi A et al. Recommendations for assessing patient-reported outcomes and health-related quality of life in clinical trials on allergy: a GA(2) LEN taskforce position paper. *Allergy* 2010;**65**:290–295.
9. Kocaturk E, Weller K, Martus P, Aktas S, Kavala M, Sarigul S et al. Turkish version of the chronic urticaria quality of life questionnaire: cultural adaptation, assessment of reliability and validity. *Acta Derm Venereol* 2012;**92**:419–425.
10. Baiardini I, Pasquali M, Braido F, Fumagalli F, Guerra L, Compalati E et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). *Allergy* 2005;**60**:1073–1078.
11. Bronsard V, Paul C, Prey S, Puzenat E, Gourraud PA, Aractingi S et al. What are the best outcome measures for assessing quality of life in plaque type psoriasis? A systematic review of the literature. *J Eur Acad Dermatol Venereol* 2010;**24**(Suppl 2):17–22.
12. Budzynski J, Pulkowski G, Suppan K, Fabisiak J, Majer M, Klopocka M et al. Improvement in health-related quality of life after therapy with omeprazole in patients with coronary artery disease and recurrent angina-like chest pain. A double-blind, placebo-controlled trial of the SF-36 survey. *Health Qual Life Outcomes* 2011;**9**:77.

13. Stuck BA, Czajkowski J, Hagner AE, Klimek L, Verse T, Hormann K et al. Changes in daytime sleepiness, quality of life, and objective sleep patterns in seasonal allergic rhinitis: a controlled clinical trial. *J Allergy Clin Immunol* 2004;**113**:663–668.
14. Yarlas AS, White MK, Yang M, Saris-Baglama RN, Bech PG, Christensen T. Measuring the health status burden in hemodialysis patients using the SF-36(R) health survey. *Qual Life Res* 2011;**20**:383–389.
15. Allen MH, Daniel DG, Revicki DA, Canuso CM, Turkoz I, Fu DJ et al. Development and psychometric evaluation of a clinical global impression for schizoaffective disorder scale. *Innov Clin Neurosci* 2012;**9**:15–24.
16. Juniper EF. Quality of life questionnaires: does statistically significant = clinically important? *J Allergy Clin Immunol* 1998;**102**:16–17.
17. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003;**41**:582–592.
18. Haeck IM, ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA, Knol MJ. Moderate correlation between quality of life and disease activity in adult patients with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2012;**26**:236–241.
19. Mlynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? *Allergy* 2008;**63**:777–780.
20. Weller K, Church MK, Kalogeromitros D, Krause K, Magerl M, Metz M et al. Chronic spontaneous urticaria: how to assess quality of life in patients receiving treatment. *Arch Dermatol* 2011;**147**:1221–1223.
21. Staubach P, Eckhardt-Henn A, Dechene M, Vonend A, Metz M, Magerl M et al. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *Br J Dermatol* 2006;**154**:294–298.
22. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Gimenez-Arnau A et al. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009;**64**:1417–1426.