

Short communication

How to assess disease activity in patients with chronic urticaria?

Background: The current EAACI/GA²LEN/EDF guidelines recommend assessing disease activity in chronic urticaria (CU) by using an established and well-defined symptom score, i.e. the urticaria activity score (UAS), which combines daily wheal numbers and pruritus intensity. However, this UAS has never been formally tested for its suitability in assessing CU activity.

Aim: To determine the UAS correlation with quality of life (QoL) in CU patients and to compare the UAS to other symptom scores.

Methods: Chronic urticaria symptoms (wheals, erythema, angioedema, pruritus) were assessed on seven consecutive days in 111 CU patients for their numbers, duration, size, and/or intensity. Quality of life was assessed by using the Dermatology Life Quality Index. Both, urticaria activity and QoL were determined before and after a 3-week period, in which the patients followed a pseudoallergen-low diet.

Results: Urticaria activity score values correlated positively, albeit weakly, with QoL impairment in CU patients ($r^2 = 0.31$, $P < 0.05$). Also, changes in QoL following a pseudoallergen-low diet were reflected by the changes observed in the UAS ($r^2 = 0.30$, $P < 0.05$). No significant differences were found comparing the QoL correlation of the UAS and other symptom scores combining up to four CU symptom qualities. Quality of life correlation with UAS values increased with the number of days the UAS was assessed and plateaued starting from the fourth consecutive day.

Conclusions: Our findings back the current guideline recommendations to use the UAS for monitoring disease activity in CU patients. Urticaria activity score mean values of at least four consecutive days should be used.

A. Młynek^{1,2*}, A. Zalewska-Janowska^{2*}, P. Martus³, P. Staubach⁴, T. Zuberbier^{1*}, M. Maurer^{1*}

¹Department of Dermatology and Allergy, Charité-Universitätsmedizin Berlin, Berlin, Germany; ²Psychodermatology Department, Medical University, Łódź, Poland; ³Institute of Biometry and Clinical Epidemiology, Charité-Universitätsmedizin Berlin, Berlin, Germany; ⁴Department of Dermatology, University Hospital Mainz, Mainz, Germany

Key words: chronic urticaria; disease activity; mast cells; urticaria score.

Marcus Maurer, MD
Department of Dermatology and Allergy
Allergie-Centrum-Charité
Charité – Universitätsmedizin Berlin
Charitéplatz 1
10117 Berlin
Germany

*Member of GA²LEN

Accepted for publication 26 February 2008

Chronic urticaria (CU) is a common skin disorder characterized by the recurrent appearance of wheals and/or angioedema for more than 6 weeks. Wheals are preceded by erythema formation and they are typically associated with intense pruritus. As of yet, reliable biomarkers for diagnosing CU and monitoring its activity remain to be identified (1–3). Therefore, the assessment of CU activity in CU relies on the patients' documentation of their symptoms and of what effects these symptoms have on their quality of life (QoL) (4–8).

In the past, many different symptom scores for assessing CU activity have been used, which had made it difficult to compare the results of clinical trials as well as of epidemiological investigations (9–11). Because of this, the recent EAACI/GA²LEN/EDF guidelines recommend using a straightforward and well established symptom score, i.e. the urticaria activity score (UAS). Daily UAS values can range from 0 to 6 points, depending on the number of wheals (0–3 points) and the intensity of pruritus (0–3 points) present on that day.

The UAS has been used in numerous controlled trials and is frequently used in routine clinical practice to monitor the course of CU and the efficiency of its treatment (2, 3). As of yet, however, there are no studies that have tested the UAS for its suitability in measuring and monitoring CU activity. Also, there is virtually no information on how the UAS compares with other symptom scores in this respect.

Here, we have assessed QoL impairment in CU patients by using the Dermatology Life Quality Index (DLQI). This outcome parameter has repeatedly been shown to reflect disease activity in CU patients, and its changes are positively correlated to spontaneous as well as therapy-induced changes in CU activity (9). Next, we assessed the correlation of DLQI and UAS as well as the correlation of their changes following therapeutic intervention to test the UAS for its suitability in monitoring CU activity. Finally, we compared the UAS with other symptom scores and we characterized the optimal UAS scoring duration.

Materials and methods

Patients

Chronic urticaria symptoms and QoL were documented by 111 CU outpatients (79 women and 32 men) treated at the Clinic of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Germany (68 patients, 19 men) and at the Universitäts-Hautklinik, Johannes Gutenberg-Universität, Mainz, Germany (43 patients, 13 men) in 2005 and 2006. The age of the patients ranged from 18 to 83 years (mean 43.7 ± 15.4) and duration of CU was from 4 to 444 months (mean 68.4 ± 95). Diagnosis of CU was based on a detailed history and physical examination.

Assessment and calculation of CU symptom scores including UAS

Chronic urticaria patients were required to document their CU symptoms once daily for 4 weeks using a diary. During this 28-day observation period, CU patients documented both their wheals and erythemas in terms of numbers [none (=0 points) <10 (=1 point), 10–50 (=2 points), or >50 per day (=3 points)], duration [none (=0 points), <1 h (=1 point), 1–3 h (=2 points), or >3 h per day (=3 points)], and size [none (=0 points), <1 cm (=1 point), 1–3 cm (=2 points), or >3 cm per day (=3 points)]. Chronic urticaria patients also quantified their numbers of angioedemas [none (=0 points), 1 (=1 point), 2–3 (=2 points), or >3 (=3 points) per day], and the intensity of their pruritus [(=0 points), mild (=1 point), moderate (=2 points), severe (=3 points)]. On the basis of this data, we calculated different values of various symptom scores daily including those of the UAS. For example, daily UAS values (0–6 points/day) were calculated by adding the score value for number of wheals (0–3) and for pruritus intensity (0–3). Score values were calculated from the data obtained in week 1 (before the patients started to adhere to a diet low in pseudoallergens) and in week 4 (the third week on a pseudoallergen-low diet) (12–15).

Quality of life measurement

The DLQI was used at the end of week 1 and at the end of week 4 to assess the levels of QoL impairment. The DLQI is a simple 10-question validated QoL questionnaire used for patients with skin diseases that was shown to be a valid, reliable, and clinically useful outcome measure for assessing health-related QoL in CU patients (7). The DLQI contains six main items: symptoms and feelings (questions 1 and 2), daily activities (questions 3 and 4), leisure (questions 5 and 6), work and school (question 7), personal relationships (questions 8 and 9), and treatment (question 10). All questions are related to the week prior to testing, and response categories include 'not at all', 'a little', 'a lot', and 'very much' with corresponding scores 0, 1, 2, and 3, respectively; the response 'not relevant' was scored as 0. The summing of all responses gave a total index score. The minimum index scoring was from 0 to 1 (no effect at all on patients' life) and the maximum from 21 to 30 (extremely large effect on patients' life).

Data management and statistical analyses

The primary aim of the analysis was to assess several CU symptom scores using the established QoL instrument DLQI as a reference for cross-sectional analysis and responsiveness after 3 weeks (end of week 4 vs end of week 1). To this end, the established UAS and other combinations of up to four different symptoms were evaluated. In addition to the number of symptoms experienced, evaluation was performed with respect to the number of days on which these symptoms were recorded. To assess the validity of symptom scores, adjusted r^2 (Pearson) values, which quantify the proportion of variance of the DLQI explained by these scores, were calculated.

The appearance of missing values was handled as follows: a recorded day was classified as completely missing if more than three symptom qualities were not quantified in the diary for this day. Missing values for specific symptoms were replaced by information from the preceding or the following day, if available. Subsequently,

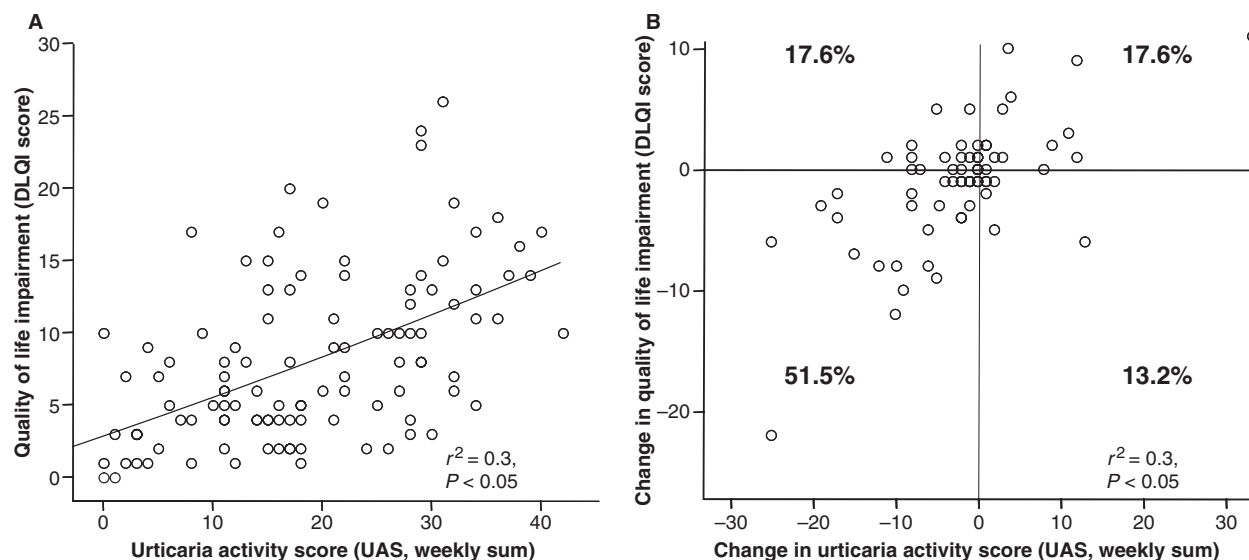


Figure 1. UAS values (and their changes) reflect CU patients' quality of life impairment (and its changes). Correlation between UAS sum from the 1st week and the total DLQI for the same period of time in chronic urticaria patients (A, $n = 111$). (B) Correlation of changes of UAS weekly total values between weeks 1 and 4 and changes of DLQI scores between the same weeks in CU patients ($n = 68$).

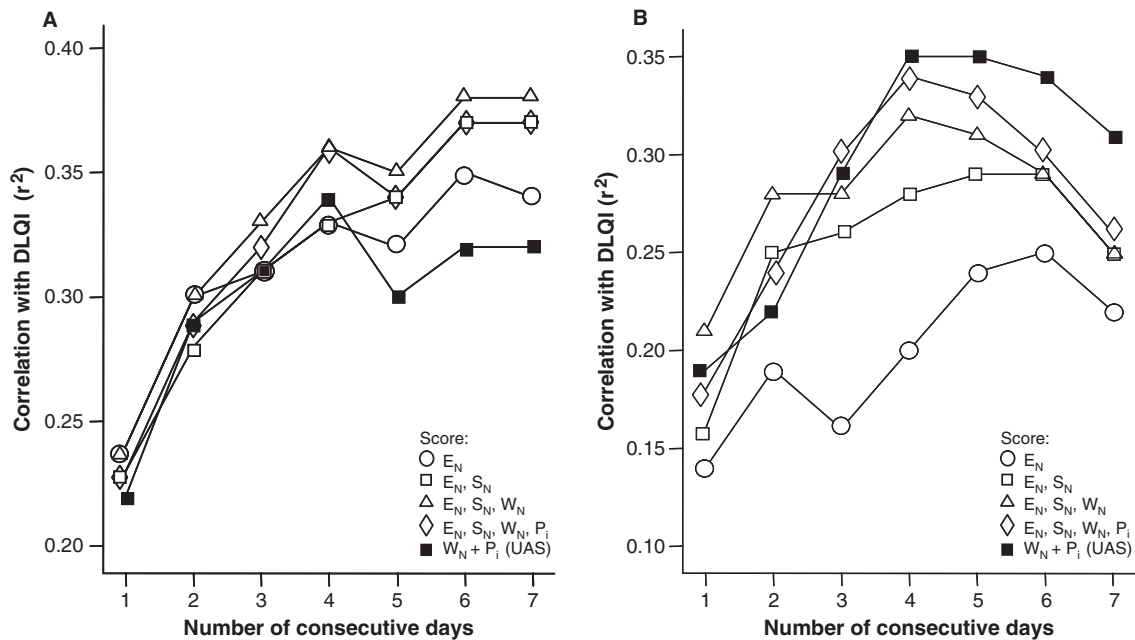


Figure 2. Differences in the correlation with DLQI scores of different CU symptom scores. (A) Subgroup analyses for 'compliant' patients (<5% missing data); ($n = 68$). (B) Subgroup analyses for 'non-compliant' patients ($\geq 5\%$ missing data). E_N -erythema number; P_i -pruritus intensity; S_N -swelling number; W_N , wheal number; UAS, urticaria activity score.

average scores were computed for each day and for the entire week. This procedure leads to the practice of missing single symptom values being replaced by the average of available symptom values for each day. Only diaries with five or more completed days for every of 2 weeks were included in study. In the end, two groups of patients were defined: The compliant subgroup ($n = 68$ patients), with a maximum of 5% missing data and the non compliant subgroup ($n = 43$) with more than 5% missing data.

Note that this was an explorative analysis, no adjustment for multiple testing was applied. Thus, reported significances (level 0.05, two-sided) are not confirmatory. All analyses were implemented by using SPSS 13.0.

Results

Weekly UAS and DLQI values in week 1 ranged from 0 to 42 (mean $\pm$ SEM = 18.6 ± 11.0) and from 0 to 26 (mean $\pm$ SEM = 7.97 ± 5.8), respectively. UAS values were found to correlate positively and significantly with DLQI values ($r^2 = 0.31$, $P < 0.05$, Fig. 1A). In addition, therapy-associated changes in UAS values were positively correlated with the changes observed in QoL index scores during the same period of time, e.g. 79.6% of the patients that reported QoL improvement also exhibited reduced UAS values in week 4 as compared to week 1 ($r^2 = 0.30$, $P < 0.05$, Fig. 1B).

To test whether other CU symptom scores are as good as or better than the UAS for measuring disease activity and changes thereof, we compared the correlation of the UAS with DLQI scores with that of the best 1-item score

Table 1. Preference of chronic urticaria patients for reporting symptom qualities

Skin symptom	Symptom quality	Number of missing data*
Wheal	Number	31
Pruritus	Intensity	34
Wheal	Size	51
Wheal	Duration	56
Erythema	Number	86
Swelling	Number	90
Erythema	Duration	94
Erythema	Size	98

*540 data entries (out of 12432) were missing.

(number of erythemas; 0–3 points), 2-item score (number of erythemas and number of angioedemas, 0–6 points), 3-item score (number of erythema + number angioedemas + number of wheals; 0–9 points), and 4-item score (number of erythema + number angioedemas + number of wheals + pruritus intensity; 0–12 points). These analyses revealed three independent and most interesting findings: (i) there was no statistical difference between any of these symptom scores in terms of their correlation to patients' levels of QoL (Fig. 2). This was true for perfect datasets, i.e. diaries of compliant patients containing $>95\%$ of the data (Fig. 2A), as well as for incomplete datasets, i.e. diaries of non-compliant patients with $\geq 5\%$ missing data items (Fig. 2B); (ii) we found a clear preference of patients to document their daily numbers of wheals and the intensity of pruritus (i.e. the two components of the UAS) as compared to other CU symptoms (Table 1); (iii) symptom score correlations

with QoL levels improved during the first 4 days of documentation, after which they plateaued. Correlations of all symptoms scored with DLQI values, but especially that of the UAS for the non-compliant CU patients' dataset, were markedly better after 4–7 days of documentation as compared with those of single day recordings.

Discussion

Here, we provide the first formal evidence that the UAS, which is recommended by current guidelines as the 'gold standard' for measuring CU activity, is indeed a valid tool for measuring and monitoring the disease activity in CU patients. Moreover, the UAS has proven to be as good as other more complex symptom scores and patients are more likely to document the two symptom qualities that make the UAS (i.e. wheal numbers and intensity of pruritus) than other CU symptoms. These observations

recommend the use of the UAS for assessing CU activity of patients treated in clinical practice and in controlled trials and for monitoring their responses to treatment. Interestingly, UAS scores best match CU patients' QoL impairment when averaged from four or more consecutive days, which suggests that future revisions of current CU guidelines should recommend to assess CU activity by using the weekly total values of the UAS (UAS 7).

Acknowledgments

We thank the doctors and patients from the Berlin and Mainz urticaria clinics for their support in this study. We thank Jodie Urcioli for proof reading the manuscript. We thank ECARF (<http://www.ecarf.org>) for supporting the study. This work was supported in part by the EU Framework programme for research, contract n° FOOD-CT-2004-506378, the GA²LEN project, Global Allergy and Asthma European Network.

References

1. Zuberbier T, Maurer M. Urticaria: current opinions about etiology, diagnosis and therapy. *Acta Derm Venereol* 2007;**87**:196–205.
2. Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CE, Greaves MW, Henz BM et al. EAACI/GA2-LEN/EDF guideline: definition, classification and diagnosis of urticaria. *Allergy* 2006;**61**:316–321.
3. Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CE, Greaves MW, Henz BM et al. EAACI/GA2LEN/EDF guideline: management of urticaria. *Allergy* 2006;**61**:321–331.
4. Berrino AM, Voltolini S, Fiaschi D, Pellegrini S, Bignardi D, Minale P et al. Chronic urticaria: importance of a medical-psychological approach. *Allergy Immunol* 2006;**38**:149–152.
5. Buffet M. Management of psychological factors in chronic urticaria. When and how? *Ann Dermatol Venereol* 2003;**130**:145–159.
6. Baiardini I, Giardini A, Pasquali M, Dignetti P, Guerra L, Specchia C et al. Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. *Allergy* 2003;**58**:621–623.
7. Lennox RD, Leahy MJ. Validation of the Dermatology Life Quality Index as an outcome measure for urticaria-related quality of life. *Ann Allergy Asthma Immunol* 2004;**93**:142–146.
8. Weldon DR. Quality of life in patients with urticaria. *Allergy Asthma Proc* 2006;**27**:96–99.
9. Nettis E, Colanardi MC, Barra L, Ferrannini A, Vacca A, Tursi A. Levocetirizine in the treatment of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2006;**154**:533–538.
10. Lachapelle JM, Decroix J, Henrijean A, Roquet-Gravy PP, De Swertdt A, Boonen H et al. Desloratadine 5 mg once daily improves the quality of life of patients with chronic idiopathic urticaria. *J Eur Acad Dermatol Venereol* 2006;**20**:288–292.
11. Kapp A, Pichler WJ. Levocetirizine is an effective treatment in patients suffering from chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled, parallel, multicenter study. *Int J Dermatol* 2006;**45**:469–474.
12. Maurer M, Hanau A, Metz M, Magerl M, Staubach P. Relevance of food allergies and intolerance reactions as causes of urticaria. *Hautarzt* 2003;**54**:138–143.
13. Di Lorenzo G, Pacor ML, Mansueto P, Martinelli N, Esposito-Pellitteri M, Lo Bianco C et al. Food-additive-induced urticaria: a survey of 838 patients with recurrent chronic idiopathic urticaria. *Int Arch Allergy Immunol* 2005;**138**:235–242.
14. Werfel T. Skin manifestations in food allergy. *Allergy* 2001;**56**:98–101.
15. Asero R, Ballmer-Weber BK, Beyer K, Conti A, Dubakiene R, Fernandez-Rivas M et al. IgE-mediated food allergy diagnosis: current status and new perspectives. *Mol Nutr Food Res* 2007;**51**:135–147.