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Comparison and Interpretability of the available Urticaria Activity Scores

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Conflict of interest

None

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Author contributions

Tomasz Hawro performed statistical analyses, and drafted the manuscript. Tatevik Ohanyan, Martin Metz, Adriane Peveling-Oberhag, Petra Staubach-Renz collected the data, contributed to interpretation of the data, and revised the manuscript. Marcus Maurer designed the study, contributed to interpretation of the data, and drafted the manuscript. Karsten Weller designed the study, collected the data, performed statistical analyses, and drafted the manuscript. All authors provided critical review of the manuscript and final approval of the manuscript before submission.

Keywords

Disease activity, Patient Reported Outcomes, Pruritus, Urticaria, Urticaria Activity Score

Abbreviations

UAS, Urticaria Activity Score; CSU, chronic spontaneous urticaria; PRO, patient reported outcome; SD, standard deviation; IQR, interquartile range; PatGA, Patients' Global Assessment

Abstract

The urticaria activity score (UAS) is the gold standard for assessing disease activity in patients with chronic spontaneous urticaria (CSU). Two different versions, the UAS7 and UAS7_{TD}, are currently used in clinical trials and routine care. To compare both versions and to obtain data on their interpretability, 130 CSU patients applied both versions and globally rated their disease activity as none, mild, moderate, or severe. UAS7 and UAS7_{TD} values correlated strongly ($r=0.90$, $P<0.001$). Interquartile ranges for UAS7 and UAS7_{TD} values for mild, moderate and severe CSU were 11-20 and 10-24, 16-30 and 16-32, and 27-37 and 28-40. UAS7 values were slightly, but significantly lower as compared to UAS7_{TD} values (mean difference: 1.6 ± 4.6 , $P<0.001$). This difference was driven by lower wheal subscores (2.1 ± 3.5 , $P<0.001$) and was most pronounced in patients with severe CSU (2.5 ± 5.6 , $P<0.01$). The

UAS7/UAS7_{TD} ratio was 0.96 ± 0.21 and did not differ significantly between mild, moderate and severe CSU.

Introduction

The urticaria activity score (UAS) is the gold standard for measuring chronic spontaneous urticaria (CSU) activity. (1) Currently, two different versions of this patient reported outcome measure, the UAS7 and the UAS7_{TD}, are being used, both in clinical studies as well as in everyday medical practice. (2-7)

Both UAS versions entail the documentation of wheal numbers and itch intensity, which result in daily wheal and pruritus subscore values from 0 (no wheals, no itch) to 3 (many wheals, severe itch). Accordingly, the daily maximum value of both versions is 6, with an overall weekly range of 0-42. However, there are two important differences: First, the UAS7, which is recommended by the guidelines (8), captures the symptoms once daily, whereas the UAS7_{TD} requires twice daily recording of symptoms, i.e. during the past 12 hours in the morning and in the evening, and calculation of the mean, (2, 3) second, the UAS7 and the UAS7_{TD} use different wheal score categories. The UAS7 assigns 0, 1, 2, and 3 points to “no wheals”, “<20 wheals”, “20-50 wheals”, and “>50 wheals” per day, respectively. The corresponding wheal categories for the UAS7_{TD} are “no wheals”, “1-6 wheals”, “7-12” wheals, and “>12 wheals”.

As of now, it is unclear if the UAS7 and the UAS7_{TD} yield different results, if their results are comparable, and which of the two is preferable. In addition, the interpretability of both versions is currently hampered by the fact that it is not clear which scores relate to mild, moderate, and severe urticaria activity.

Materials and methods

Patient population and study design

We included 130 adult patients, referred to the urticaria specialty clinics of the Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin and of the Department of Dermatology in Mainz with difficult to treat CSU, i.e. CSU that did not respond sufficiently to second-generation antihistamines. Some of the patients

also had chronic inducible urticaria, but CSU was predominant in all of them. The median age of patients was 45 years (mean: 44.6, standard deviation: 16.2), and the majority (73%) was female. The study was approved by the responsible ethics committees.

Outcome tools

Patients were asked to continue their previous treatment with antihistamines over two weeks, before a planned change of their therapy to omalizumab, and to document prospectively their disease activity once daily using the UAS7 and twice daily using the UAS7_{TD}. For the analyses presented in this manuscript, only UAS7 and UAS7_{TD} from the second week were used. At the end of the second week, patients rated their disease activity, using a Patient's Global Assessment (PatGA) of their disease activity, which consisted of a four-item Likert scale ("none", "mild", "moderate", "severe"). PatGA was used to categorize patients according to their urticaria activity.

Statistical analysis

Relationships between UAS7 and UAS7_{TD} (total scores as well as subscores for wheal number and pruritus severity) were analyzed using Pearson's correlations. Differences between two independent groups of parametric variables were tested using Student's t-test. UAS7/UAS7_{TD} ratios between patients with mild, moderate and severe CSU were compared using ANOVA. $P \leq 0.05$ was considered statistically significant.

Results

Both urticaria activity scores, the UAS7 and the UAS7_{TD}, are comparable in their range of scores for mild, moderate and severe disease activity

Half of all patients with self-reported mild, moderate, and severe CSU had UAS7 values between 11 and 20, 16 and 30, and 27 and 37, respectively. The corresponding ranges of UAS7_{TD} values were 10 to 24, 16 to 32, and 28 to 40 (interquartile ranges, **Table 1** and **Fig. 1A**). 12 and 20 patients had UAS7 and UAS7_{TD} scores above 37, respectively.

The UAS7 and UAS7_{TD} strongly correlate

The results of the UAS7 and the UAS7_{TD} showed a strong correlation ($r=0.904$, $P<0.001$). The same was true for the UAS7 and UAS7_{TD} wheal ($r=0.842$, $P<0.001$) and pruritus subscore values ($r=0.938$, $P<0.001$).

UAS7 values are lower than those of the UAS7_{TD}

UAS7 values are slightly, but significantly lower as compared to UAS7_{TD} values (mean difference: 1.6 ± 4.6 , $P<0.001$) (**Table 1, Fig. 1A**). This difference is driven by lower wheal scores in the UAS7 than in the UAS7_{TD} (**Table 1, Fig. 1B**).

In the subgroup analyses, UAS7 values were slightly lower than UAS7_{TD} values in patients with mild, moderate and severe urticaria, but this difference was statistically significant only in patients with severe urticaria. The ratios of UAS7 to UAS7_{TD} as well as its wheal and pruritus subdomains did not differ significantly between patients with different disease activities as assessed by PatGA. The lowest ratio of UAS7 to UAS7_{TD} values was observed in patients with severe CSU (**Table 1**).

Total UAS7_{TD} morning values are slightly, but significantly lower as compared to evening values (mean difference: 1.1 ± 5.9 , $P<0.05$). This was particularly driven by differences in pruritus score values, which were slightly, but significantly higher in the evening as compared to the morning (mean difference: 0.7 ± 3.0 , $P<0.01$). In contrast, morning and evening wheal scores did not differ significantly (mean difference: 0.4 ± 3.7 , $P=0.25$), (**Fig. 1C**).

Discussion

This study shows that the UAS7 and the UAS7_{TD} yield largely similar results with only minor differences. Our findings make it possible to compare results of studies that use the UAS7 with those that use the UAS7_{TD}. In addition, our results make it possible to better interpret the scores values of both UAS versions with regard to mild, moderate, and severe disease activity.

CSU patients with mild, moderate and severe disease activity show different ranges of UAS scores. These score ranges are similar for both UAS instruments in mild urticaria. With increasing disease activities, the same categories are represented by slightly lower score values of the UAS7 than of the UAS7_{TD}. The UAS7 may,

therefore, better differentiate patients with severe urticaria activity because of the possible ceiling effect of the UAS7_{TD}.

Our data show that score values obtained using both UAS instruments correlate strongly, indicating that both instruments are comparable. However, the UAS7_{TD} overall score values are slightly higher as compared to those of the UAS7 which is driven by the wheal subscore values. This observation was to be expected, as the ranges for the UAS7 wheal score categories are more than twice as high as those of the UAS7_{TD}. The differences between the score values obtained with the UAS7 and the UAS7_{TD} are most prominent in patients with high disease activity. For this group, a factor of 0.93 may be recommended to translate UAS7 to UAS_{TD} score values. However, the ratios of UAS7 to UAS7_{TD} do not differ significantly between the subgroups of mild, moderate and severe urticaria patients. Therefore, for practical reasons a factor 0.96 may be used (**Table 1**), independent of urticaria activity, to translate scores of UAS7_{TD} to UAS7 ($0.96 \times \text{UAS7}_{\text{TD}} = \text{UAS7}$).

The overall UAS7 score values were lower because of lower wheal score values, and because the slightly, but significantly higher UAS7 pruritus score values did not completely compensate for this. This difference in pruritus scoring was probably caused by the fact that itch, in many patients, is stronger in the evening. In CSU, pruritus is more frequent in the evening and at night. (8) Patients with symptomatic dermographism also have increased pruritus in the evening. (9) Higher itch intensity and more frequent itch episodes in the evening and at night as compared to the morning were also reported for atopic dermatitis. (10, 11) Similarly, in lichen planus and small fiber neuropathies, itch occurs most frequently in the evening. (12, 13) The underlying pathomechanisms for this remain unknown. In any case, the pruritus score values obtained by UAS_{TD} were significantly higher in the evening than in the morning. Moreover, the evening pruritus score values for the UAS7_{TD} were similar to the UAS7 pruritus score values. The UAS7 calls for once daily documentation of the past 24 hours, and this is usually done in the evening. It appears that higher itch intensity in the evening results in higher itch ratings for the entire assessment period of 24 hours, when documented once daily by use of the UAS7.

Our data allow for two conclusions: First, in CSU, stronger itch in the evening cannot be explained by higher wheal numbers, which did not differ between both

assessment periods of the UAS7_{TD}. Second, the documentation of disease activity with the UAS7 (and UAS7_{TD}) may benefit from guidance for patients on how to document itch intensity. Some patients may document “the worst itch” experienced during the assessment period, while others may try to average their itch experience and document the “typical itch severity”. We recommend that patients document maximum itch intensity during the assessment.

A limitation of our study is that the recruited patients may not be representative for the whole population of CSU patients. All patients were recruited at tertiary referral centres, and they were refractory to H₁-antihistamines.

Our data provide evidence that both available versions of the UAS deliver largely comparable results. This supports the preferred use of the UAS7, as this tool is less burdensome for patients in its administration, less burdensome for physicians in its scoring, and may better differentiate patients with severe urticaria activity.

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Table 1 Comparison of UAS7 and UAS7_{TD} values in patients with different self-rated disease activity (PatGA disease activity)

Score	PatGA disease activity	Mean $\pm$ SD (median)	Mean difference $\pm$ SD (median) , significance level	IQR	UAS7/UAS7 _{TD} $\pm$ SD
UAS7	Mild (n = 18)	15.4 $\pm$ 7.1 (16)	1.2 $\pm$ 3.8 (0.3) <i>P</i> = 0.21 ⁺	11.25 – 20.25	0.969 $\pm$ 0.235
UAS7_{TD}		16.6 $\pm$ 8.1 (16)		9.875 – 24.00	
UAS7 wheal score		8.0 $\pm$ 4.7 (7)	2.0 $\pm$ 3.0 (1.5) <i>P</i> < 0.05 ⁺		0.852 $\pm$ 0.318
UAS7 _{TD} wheal score		10.0 $\pm$ 6.0 (9.75)			
UAS7 pruritus score		7.4 $\pm$ 3.3 (7)	-0.8 $\pm$ 1.7 (0.8) <i>P</i> = 0.06 ⁺		1.132 $\pm$ 0.218
UAS7 _{TD} pruritus score		6.6 $\pm$ 3.0 (6)			
UAS7	Moderate (n = 61)	22.5 $\pm$ 9.1 (24)	1.0 $\pm$ 4.4 (1) <i>P</i> = 0.06 ⁺	16.00 – 30.00	0.995 $\pm$ 0.214
UAS7_{TD}		23.6 $\pm$ 9.8 (25.5)		16.00 – 31.75	
UAS7 wheal score		10.7 $\pm$ 5.8 (11)	1.7 $\pm$ 3.4 (1.5) <i>P</i> < 0.001 ⁺		0.930 $\pm$ 0.340
UAS7 _{TD} wheal score		12.5 $\pm$ 6.4 (13)			
UAS7 pruritus score		11.8 $\pm$ 4.6 (13)	-0.7 $\pm$ 1.8 (-0.5) <i>P</i> < 0.01 ⁺		1.117 $\pm$ 0.257
UAS7 _{TD} pruritus score		11.1 $\pm$ 4.8 (12)			
UAS7	Severe (n = 42)	31.2 $\pm$ 8.5 (32)	2.5 $\pm$ 5.6 (1.8) <i>P</i> < 0.01 ⁺	26.75 – 37.25	0.927 $\pm$ 0.211
UAS7_{TD}		33.7 $\pm$ 6.6 (34.5)		28.00 – 39.5	
UAS7 wheal score		14.5 $\pm$ 5.5 (14)	2.8 $\pm$ 4.1 (1.8) <i>P</i> < 0.001 ⁺		0.836 $\pm$ 0.251
UAS7 _{TD} wheal score		17.3 $\pm$ 4.3 (19.75)			
UAS7 pruritus score		16.7 $\pm$ 4.0 (17)	-0.3 $\pm$ 2.3 (0) <i>P</i> = 0.41 ⁺		1.030 $\pm$ 0.200
UAS7 _{TD} pruritus score		16.4 $\pm$ 3.7 (16.75)			

UAS7	Overall (n=130)	24.1 ± 10.3 (26)	1.6 ± 4.6 (1.25) <i>P</i> < 0.001 ⁺		0.960 ± 0.210
UAS7_{TD}		25.7 ± 10.7 (28)			
UAS7 wheal score		11.4 ± 6.0 (12)	2.1 ± 3.5 (1.5) <i>P</i> < 0.001 ⁺		0.841 ± 0.301
UAS7 _{TD} wheal score		13.6 ± 6.4 (14)			
UAS7 pruritus score		12.7 ± 5.4 (13)	-0.5 ± 1.9 (-0.5) <i>P</i> < 0.01 ⁺		1.202 ± 0.231
UAS7 _{TD} pruritus score		12.1 ± 5.5 (12.5)			

⁺ paired Student's *t* - test

130 patients participated in the study. 121 patients were analyzed in the three disease activity subgroups, which were created according to their self-rated CSU activity using the Patients' Global Assessment (PatGA) score. Two patients recorded their disease activity as "none" on the Patients' Global Assessment (PatGA) score, and seven patients did not complete the PatGA, thus their data were not included in the subgroup analyses.

Differences of the values of ratios UAS7/UAS7_{TD} between groups of patients with mild, moderate and severe urticaria were not significant for the overall urticaria activity (ANOVA, $F = 1.239$; $P = 0.293$), the wheal score (ANOVA, $F = 1.257$; $P = 0.288$), or the pruritus score (ANOVA, $F = 2.085$; $P = 0.129$).

IQR – interquartile range

Figure legend

Figure 1. Comparison of UAS scores

- A) UAS7 and UAS7_{TD} values in patients with different self-rated global assessment of their disease activity (PatGA disease activity), (total n = 130, 7 patients did not provide a PatGA disease activity).
- B) UAS7 and UAS7_{TD} subscores for wheals and pruritus
- C) UAS7_{TD} morning and evening wheal and pruritus subscores

** $P < 0.01$, *** $P < 0.001$, paired Student's *t* test

Horizontal lines indicate means, whiskers indicate standard deviations

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