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Evaluating the minimally important difference of the urticaria activity score and other measures of disease activity in patients with chronic idiopathic urticaria

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ABSTRACT

Background: The Urticaria Activity Score (UAS) is a widely used patient-reported outcome measure for patients with chronic idiopathic urticaria (CIU) that includes 2 items: intensity of pruritus and number of hives. Items are scored individually, and the UAS7 is calculated as the sum of pruritus and number of hives over 1 week. Recently, its instructions were enhanced.

Objective: To assess the measurement properties of the enhanced UAS.

Methods: Seventy-three subjects with CIU completed the UAS with enhanced instructions, other measures of disease activity including the size of the largest hive, and collateral measures during a multicenter, randomized, double-blind, placebo-controlled study of omalizumab for the treatment of CIU. The minimal important difference (MID) was estimated through distribution- and anchor-based approaches. Test-retest reliability was assessed with the intraclass correlation coefficient (ICC); internal consistency reliability was evaluated with Cronbach's alpha; 3 responsiveness coefficients were calculated; known groups validity was assessed based on physician in-clinic UAS scores; and construct validity was assessed through Spearman correlation coefficients with collateral measures.

Results: The MID ranged from 9.5 to 10.5 for the UAS7, 5.0 to 5.5 for number of hives (weekly average), and 4.5 to 5.0 for pruritus and size of largest hive (weekly average). Internal consistency was supported by alpha coefficients greater than 0.80. The ICC values for test-retest reliability ranged from 0.602 to 0.884. For subjects on active treatment, responsiveness coefficients were greater than 0.80. Known-groups validity was supported for most UAS scores; and construct validity was demonstrated by relationships with collateral measures.

Conclusions: The enhanced UAS has adequate measurement properties to support its use in clinical research.

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Introduction

Chronic Idiopathic Urticaria (CIU), also known as chronic spontaneous urticaria, is a skin disorder characterized by the recurrent appearance of wheals or angioedema for at least 6 weeks. Chronic idiopathic urticaria is very common, with up to 1% of the population affected.¹ Approximately 50% of CIU patients are affected for

longer than 1 year, with the average duration being 3 to 5 years.² Chronic idiopathic urticaria is caused by the activation of skin mast cells and basophils and the subsequent release of histamine and other proinflammatory mediators, responsible for the induction of symptoms.

Chronic idiopathic urticaria has been shown to have a substantial negative impact on the health-related quality of life (HRQOL) of patients.^{3–6} In a qualitative study of CIU patients, patients reported being affected by physical symptoms and interference with usual activities, social and emotional functioning, sleep and work, as well as reduced overall health-related quality of life.³

The Urticaria Activity Score (UAS) is a widely used patient-reported CIU measure with a simple scoring system, which captures intensity of pruritus, and number of hives.^{7–9} Daily intensity of pruritus (range: 0 = none to 3 = severe) and number of hives ratings (range: 0 = none to 3 = more than 12 hives) are summed to create a daily UAS score (range: 0–6 points/day); daily UAS scores

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are summed over a week to create the UAS7 (range: 0–42). Another measure of disease activity, size of the largest hive, is recorded on a scale ranging from 0 = none to 3 = greater than 2.5 cm, and is scored independently from the other 2 items.

Although the UAS is commonly used, its measurement properties are not well documented, with only 3 published studies. Two supported its construct validity, particularly for the UAS7, by documenting its correlation with the Dermatology Life Quality Index (DLQI)⁹ and the Chronic Urticaria Quality of Life Questionnaire (CU-QoL), the only disease-specific quality of life measure available.⁴ The last, more recent, study supported its content validity, with some enhancements to the instructions.³ These instructions contain clarification on how to count the number of hives and how to measure hive size. To fully support the use of the UAS in clinical research, one must examine its reliability, construct validity, known-groups validity, responsiveness, and the minimum important difference (MID). The objective of this study was to assess the measurement properties of the UAS with enhanced instructions.

Methods

Measurement properties were analyzed using data from a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of subcutaneously administered omalizumab as add-on therapy for the treatment of CIU.

The study consisted of a screening (day 14 to day 7; eligibility determined), run-in (day 7 to day 0), treatment (day 0 through week 4), and follow-up (week 4 through 16) phase. At day 0, eligible patients were randomly allocated (in 1:1:1:1 ratio) to receive placebo or monthly omalizumab doses of 75 mg, 300 mg, or 600 mg.

The study was approved by the ethics committee of each participating study center. Written informed consent was obtained from all patients before their participation in the study.

Study population

Patients from the United States and Germany with a diagnosis of moderate to severe CIU at screening (defined by pruritus and hives for greater than 3 days in a 7-day period for more than 6 consecutive weeks despite treatment with an H₁ antihistamine) were eligible. Additional study details, including inclusion criteria, are provided elsewhere.¹⁰

Study instruments

The UAS with enhanced instructions and the item on hive size were completed twice daily throughout the study. Morning and evening scores for itch (severity), hive (number), and hive (size) were averaged daily, and a weekly UAS7 score (ranging from 0 to 42) was computed. Weekly scores for hive (size) ranged from 0 to 21. The Physician's In-Clinic UAS, a rating of the patient's overall condition of pruritus and hives (measured on a 0–6 scale), the DLQI, the MOS Sleep Scale (MOS), a patient in-clinic global assessment measured on a 0 to 3 scale (Patient Rating), and a physician in-clinic global assessment measured on a 0 to 3 scale (Physician Rating) were completed at screening, baseline, and multiple times throughout the study.

Statistical methods

Patient characteristics

Analyses were conducted using data from US subjects with a minimum baseline UAS7 score of 16 ($n = 73$). Data from subjects in Germany ($n = 13$) were excluded because of potential variations by country.

Overview of analyses

Response characteristics, including the percentage of scores at minimum (floor) and maximum (ceiling), were calculated at baseline and week 4/early termination (week 4) for the UAS7, weekly average pruritus score (pruritus score), weekly average score for

the number of hives (number of hives score), and weekly average score for the largest hive (largest hive score).

Test-retest reliability, measured by the intraclass correlation coefficient (ICC), was calculated using UAS scores from days -14 (screening) and -7 (start of run-in). Internal consistency reliability, as measured by Cronbach's alpha coefficients, was calculated using UAS7 scores before baseline. For both the ICC and Cronbach's alpha, a coefficient of 0.70 or higher is generally considered acceptable.

Three measures of responsiveness (ability of a measure to detect clinically important changes) between baseline and week 4 were calculated for the UAS7, pruritus, and number of hives. These included the standardized effect size (SES)¹¹, standardized response mean,¹² and responsiveness statistic.¹³

Known-groups validity was assessed by comparing UAS7 scores with Physician In-Clinic UAS ratings using ranked analysis of variance. Construct validity was assessed using Spearman correlation coefficients between UAS scores and the DLQI, MOS, the Patient and Physician Ratings, and the Physician In-Clinic UAS rating, and also between changes in UAS scores from baseline to week 4 and changes in collateral measures.

The minimal important difference (MID), the smallest difference in scores considered clinically meaningful, was calculated using the Patient and Physician Ratings and the DLQI as anchors, using 5 approaches: (1) Changes from baseline to week 4 for the UAS, Patient and Physician Ratings, and DLQI (categorized as no effect (0–1), small effect (2–5), moderate effect (6–10), very large effect (11–20), and extremely large effect (21–30) were calculated¹⁴; (2) Ordinary least squares regression analyses were used to regress changes in UAS scores on changes in Patient Ratings from baseline to week 4 and the interaction between baseline patient ratings and changes in patient ratings from baseline to week 4. This model was repeated for Physician Ratings. Next, a distribution-based analysis of UAS Scores was conducted using: (3), the standard error of measurement (SEM¹⁵); (4) the SES¹¹; and (5) the responsiveness statistic.¹³ Threshold values of 1 SEM,¹⁶ 0.50 SES,¹¹ and a responsiveness statistic of 0.50¹⁷ have been suggested for defining clinically meaningful differences.

The minimal detectable change (MDC), the smallest change that can be reliably distinguished from random fluctuation, represents the lower bound for establishing the MID and was determined by comparing distribution-based estimates. Although the SEM was the primary distribution-based estimate (because it considers the measure's reliability and estimates the instrument's precision),¹⁸ other measures were also considered. Anchor-based MID estimates were then compared. A final MID range was established that exceeds the MDC and integrates estimates from the various anchors.

Results

Seventy-three subjects were included in the analyses, including 51 females (70%). Mean age was 39.7 ± 15.0 years (range, 13–70 years), and most ($n = 58$, 80%) were white.

Response characteristics are presented in Table 1. The full range of response options were used, with 18% and 21% of subjects at the ceiling on the number of hives and largest hive at baseline, respectively. At week 4, the percent at the floor ranged from 18% (UAS7, pruritus) to 19% (number of hives, largest hive).

Test-retest reliability and internal consistency reliability

The ICCs were above the generally accepted standard of 0.70 for number of hives (0.764) and size of largest hive (0.884), and slightly below the standard for the UAS7 (0.659) and pruritus (0.602) scores. Cronbach's alpha coefficients ranged from 0.819 (pruritus) to 0.930 (largest hive), all above 0.70.

Responsiveness

Mean baseline and week 4 scores are shown in Figure 1. Mean scores decreased at week 4 for all groups, with the active treatment

Table 1
Response characteristics for the UAS7 and disease activity items

Modified UAS score	Visit	N	Mean	STD	Min	Max	Median	N (%) at floor	N (%) at ceiling
UAS7	Baseline	73	28.7	6.7	16.0	42.0	28.3	0 (0%)	5 (7%)
	Week 4/ET	72	15.2	12.6	0.0	42.0	12.8	13 (18%)	1 (1%)
Weekly average pruritus score	Baseline	73	13.3	3.4	6.0	21.0	13.0	0 (0%)	6 (8%)
	Week 4/ET	72	7.1	5.7	0.0	21.0	7.0	13 (18%)	2 (3%)
Weekly average number of hives score	Baseline	73	15.4	4.6	5.0	21.0	16.0	0 (0%)	13 (18%)
	Week 4/ET	72	8.1	7.5	0.0	21.0	6.5	14 (19%)	8 (11%)
Weekly average largest hive size score	Baseline	73	14.9	5.0	5.5	21.0	15.1	0 (0%)	15 (21%)
	Week 4/ET	72	8.0	7.2	0.0	21.0	6.8	14 (19%)	4 (6%)

Abbreviations: STD, standard deviation; ET, early termination.

Possible range of scores for the UAS7 is 0–42, weekly average pruritus score is 0–21, and weekly average score for number of hives is 0–21.

groups reporting a larger improvement than placebo. Responsiveness coefficients increased from placebo to 300 mg and consistently dropped for the 600-mg group, suggesting that the maximum gain was obtained with the 300-mg dose. No further improvement was obtained by increasing the dose to 600 mg. The SES ranged from 0.78 to 1.12 (placebo), 1.28 to 1.91 (75 mg), 2.02 to 2.88 (300 mg), and 1.56 to 2.32 (600 mg). Coefficients for the standardized response mean and responsiveness statistic (not shown) showed similar patterns.

Known groups validity

Table 2 presents mean baseline UAS scores by baseline physician in-clinic UAS ratings. Significant differences were found for the UAS7, number of hives, and largest hive, but not pruritus. Subjects rated as more severe (higher baseline scores) by physicians had higher mean UAS scores.

Construct validity

Spearman correlation coefficients were significant between baseline UAS scores and baseline DLQI ($r = 0.283$ – 0.459), physi-

cian in-clinic UAS (0.237–0.444), MOS Sleep Quantity (-0.231 to -0.319 ; excluding largest hive score), and MOS Sleep Problems (0.262–0.449; excluding number of hives and largest hive scores). None of the baseline correlations were significant with patient rating, and the physician rating was only significantly correlated with pruritus. Changes in scores for the UAS were significantly and strongly related to changes in DLQI, patient ratings, physician ratings, and physician in-clinic UAS rating ($r = 0.392$ – 0.626).

MID—Change in patient and physician ratings from baseline to week 4

When patient ratings did not change, the average reduction for severe to moderate scores ranged from -1.5 to -8.8 for the UAS7, -1.5 to -3.7 for pruritus, 0 to -5.1 for number of hives, and -0.3 to -5.1 (severe to mild) for largest hive. When patient ratings improved by 1 category (eg, severe to moderate), the average reduction ranged from 1.5 to -24.7 for the UAS7, 0.5 to -10.5 for pruritus, 1.0 to -14.2 for number of hives, and 2.2 to -13.6 for largest

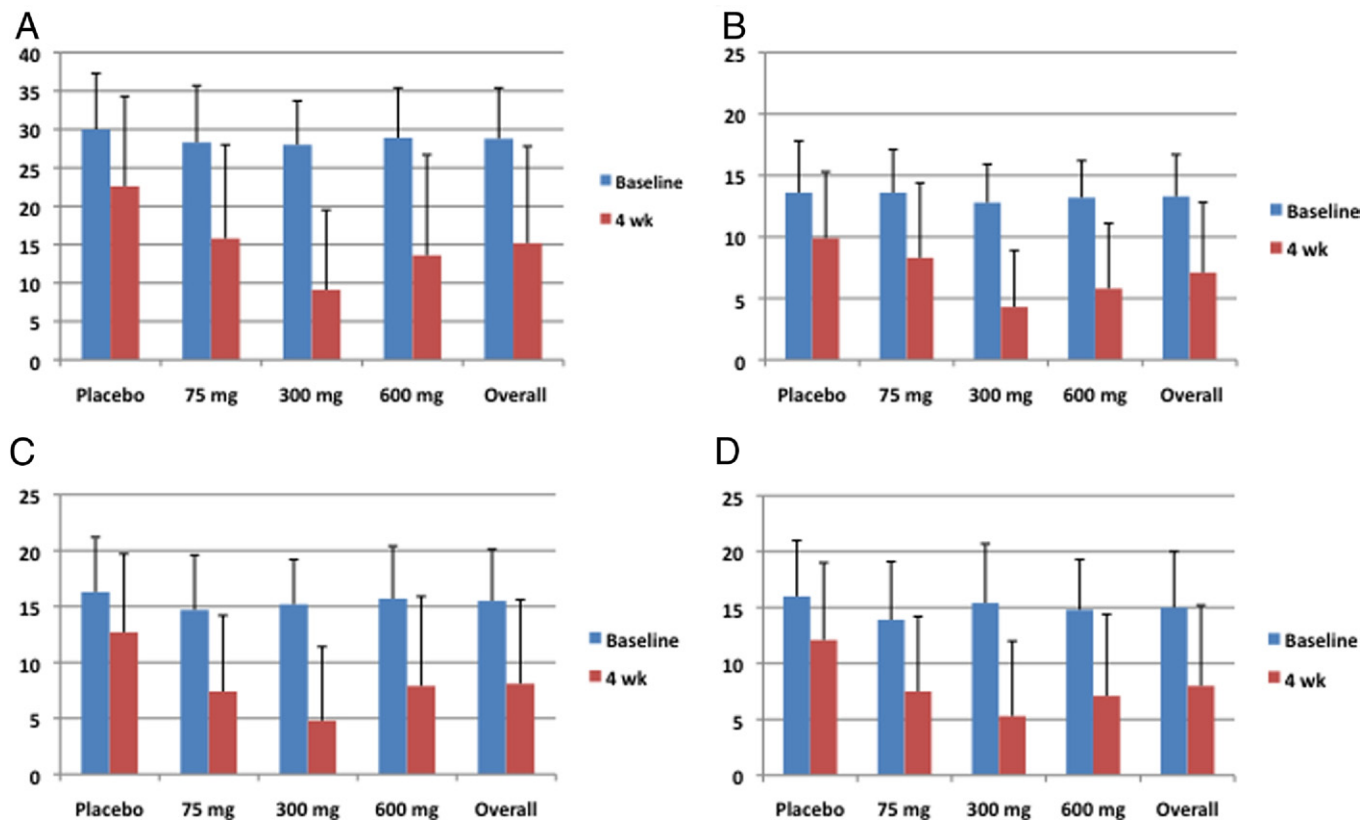


Fig. 1. Mean baseline and week 4 scores by treatment group: (A) UAS7, (B) Weekly average pruritus score, (C) Weekly average score by number of hives, and (D) Weekly average score for the largest hive. Error bars represent standard deviations.

Table 2

Known-groups validity of the UAS7 and disease activity items at baseline (by baseline in-clinic physician UAS)

Modified UAS score	Baseline in-clinic physician UAS ^a				P - value ^b	Partial eta-squared ^b
	< 4	4	5	6		
UAS7	25.4 ± 5.0 (n = 11)	25.9 ± 6.0 (n = 21)	30.1 ± 4.7 (n = 25)	32.3 ± 8.7 (n = 16)	.005	0.168
Weekly average pruritus score	11.8 ± 2.4 (n = 11)	13.2 ± 2.9 (n = 21)	13.1 ± 2.5 (n = 25)	14.8 ± 5.1 (n = 16)	.237	0.059
Weekly average number of hives score	13.6 ± 3.7 (n = 11)	12.7 ± 4.6 (n = 21)	17.1 ± 3.8 (n = 25)	17.5 ± 4.5 (n = 16)	<.001	0.235
Weekly average largest hive score	11.6 ± 4.3 (n = 11)	13.6 ± 5.5 (n = 21)	16.4 ± 4.4 (n = 25)	16.6 ± 4.6 (n = 16)	.013	0.143

^aCell entries represent mean, SD, n.^bBased on ranked data.

hive. Few patients reported worsening of symptoms, precluding the estimation for the MID of worsening conditions. The same general pattern of results is evident for the Physician Rating and DLQI, although somewhat less pronounced with the DLQI (data not shown). Different amounts of change can be expected based on baseline patient ratings.

Regression of changes in UAS scores with enhanced instructions on changes in patient ratings, baseline patient ratings, and the interaction of those terms

The regression coefficient (*b*) for the changes in patient ratings represents the change in score for the UAS for every 1-category change in patient rating. In Table 3, values range from 4.405 to 4.903 for pruritus, number of hives, and largest hive ratings (all scored on a 0–3 range) and is 8.816 for UAS7 total score. The intercept for these models represents the change in score for the UAS expected for the group rating themselves as “Moderate” (ie, reference group coded as “0”) at baseline when no change in patient ratings occurs from baseline to week 4. Intercepts range from a decrease of 2.071 to 3.780 points for pruritus, number of hives, and largest hive ratings and a decrease of 5.852 points for UAS7 total score. The *b* for the baseline Patient Rating (8.786 for UAS7) represents the difference in intercepts for the groups rating themselves “severe” or “mild” at baseline. For example, the intercept for the UAS7 score is –5.852, the expected change for the “moderate” group when their global rating does not change. Therefore, the expected change for the “severe” and “mild” groups when their global ratings do not change is 2.934 (–5.852 + 8.786) and 14.638 (–5.852 – 8.786), respectively. Regression coefficients are significant for all scores from the UAS, indicating that inter-

cepts differ by baseline ratings. Finally, regression coefficients for the interaction terms represent the differences in slope by baseline patient rating. None of these coefficients are significant, indicating that the slopes are not significantly different by baseline patient rating.

Regression of changes in scores for the UAS with enhanced instructions on physician ratings and DLQI

The results for regression of changes in scores for the UAS on physician ratings and DLQI parallel closely those for the patient ratings (data not shown). Specifically, changes in UAS scores for each 1-category change for the physician rating and DLQI were 8.788 and 2.138 for the UAS7, respectively, and ranged from 4.050 to 5.164 (physician rating) and 1.050 to 1.446 (DLQI) for pruritus, number of hives, and largest hive rating. Intercepts in the regression models ranged from a decrease of 2.042 to 3.084 points (physician rating) and a decrease of 4.600 to 6.376 points (DLQI) for pruritus, number of hives, and largest hive ratings, and a decrease of 5.127 points and 10.976 for UAS7 total score for physician rating and DLQI, respectively. All models, except largest hive, produced a significant main effect for baseline DLQI and physician rating, indicating that intercepts differ significantly by baseline ratings. Other than largest hive (*P* = .001), none of the tests for the interaction of changes in physician rating-by-baseline physician rating or DLQI-by-baseline DLQI were significant, indicating that slopes do not differ by baseline ratings.

Distribution-based estimates for the UAS with enhanced instructions

The SEM and 0.50 effect size suggest that the MDC for the UAS7 score ranges from 3.5–4.0 for the UAS7 score and from 1.5–2.5 for pruritus, number of hives, and largest hive scores.

Table 3Regression of changes in UAS7 and disease activity scores from baseline to week 4/early termination on baseline patient global rating^a and changes in patient global rating from baseline to week 4/early termination

Dependent measure	Predictor	<i>b</i>	SE	β	Sig.
UAS7 (n = 71)	Changes in PatGR	8.816	1.018	.914	<.001
	Baseline PatGR	8.786	2.058	.518	<.001
	Changes in PatGR-by-Baseline PatGR	–1.088	1.141	–.115	.344
	Intercept	–5.852	1.373	–	<.001
Weekly average pruritus score (n = 71)	Changes in PatGR	4.405	.496	.920	<.001
	Baseline PatGR	3.502	1.004	.416	.001
	Changes in PatGR-by-baseline PatGR	–.315	.557	–.067	.573
	Intercept	–2.071	.670	–	.003
Weekly average number of hives score (n = 71)	Changes in PatGR	4.411	.628	.810	<.001
	Baseline PatGR	5.284	1.270	.552	<.001
	Changes in PatGR-by-baseline PatGR	–.773	.704	–.145	.276
	Intercept	–3.780	.847	–	<.001
Weekly average largest hive score (n = 71)	Changes in PatGR	4.903	.659	.842	<.001
	Baseline PatGR	5.396	1.334	.528	<.001
	Changes in PatGR-by baseline PatGR	–.744	.739	–.131	.318
	Intercept	–2.837	.889	–	.002

b, regression coefficient; SE, standard error; β , standardized regression coefficient; Sig, significance level; PatGR, Patient Global Rating.^aBaseline Patient Global Rating coded as Mild = –1, Moderate = 0, Severe = 1.

Table 4
Minimal important difference (MID) of the UAS7 and disease activity items

Measure	MID range
UAS7	9.5–10.5
Weekly average pruritus score	4.5–5.0
Weekly average number of hives score	5.0–5.5
Weekly average largest hive score	4.5–5.0

MID based on integration of anchor- and distribution-based results

Regression models for patient and physician ratings both identified a slope of 8.8, providing an estimate of the expected change in the UAS7 given a meaningful change in global ratings (≤ 9 -point change when ratings do not change). Therefore, the MID for the UAS7 score should range from 9.5 to 10.5 points. A value of 4.3 provides an estimate of the expected change in pruritus given a meaningful change (≤ 4 point change when ratings do not change). The MID for pruritus ranges from 4.5 to 5.0 points. A value of 4.5 provides an estimate of the expected change in number of hives given a meaningful change. The MID for number of hives should range from 5.0 to 5.5 points. A value of 5.0 provides an estimate of the expected change in the largest hive given a meaningful change. The MID for largest hive ranges from 4.5 to 5.0 points (see Table 4).

Discussion

These results provide support for the measurement properties of the UAS with enhanced instructions in CIU patients who remain symptomatic on therapeutic doses of an H_1 antihistamine. The internal consistency reliability was supported by alpha coefficients above 0.80 for each of the 3 items and for the UAS7. Test–retest reliability was generally supported, although the ICC was slightly below the accepted standard of 0.70 for the UAS7 and the weekly average pruritus score. Most likely, the slightly low test–retest reliability for those 2 scores was attributable to the natural variability in symptoms over time. Responsiveness was demonstrated by large changes for subjects who received active treatment. Known-groups validity was established by demonstrating significant differences in the hypothesized direction based on physician baseline in-clinic UAS ratings for the UAS7, number of hives, and size of largest hive, but not for pruritus. Construct validity was established by demonstrating that changes in UAS scores were related to observed changes in collateral measures. Finally, the results provide evidence for estimating the MID, with a range of 9.5 to 10.5 for the UAS7, 5.0 to 5.5 for number of hives, and 4.5 to 5.0 for pruritus, and size of largest hive. These results represent the first comprehensive assessment of measurement properties of the UAS with enhanced instructions. Before the enhancement of instructions, the only measurement property found in the published literature for the UAS was convergent validity, based on the correlation between the UAS and the DLQI and CU-Q2oL. This study confirms that the convergent validity of the UAS and DLQI remains significant after enhancement of the instructions and suggests that the enhancement may have strengthened the correlation between the 2 measures.

One of the strengths of this study is the use of multiple methods to assess measurement properties when possible. For example, convergent validity was not only established with the DLQI, but also with several other measures. Responsiveness was evaluated using 3 different coefficients, and MID was estimated through multiple anchor-based and distribution-based approaches. The convergence of results from these multiple methods allows for greater confidence in the interpretation of the results, especially given the lack of prior research available for comparison.

Several limitations of this study should be mentioned. First, the sample size is relatively small ($n = 73$) and restricted to US participants, potentially limiting its generalizability. To address this concern, supplemental analyses were performed, to include the 13 German participants. The results were generally comparable. For instance, all responsiveness coefficients for the US and combined US/German sample exceeded 1.0, indicating high responsiveness to change. However, some responsiveness coefficients were lower in the German sample, probably because of the small sample size. Estimates of the MID were unchanged. Generalizability of the results could also be limited in the current study by the inclusion criteria. Possibly subjects with a wider range of CIU symptoms or severity would have produced different results. Finally, few patients in the current study experienced a worsening of symptoms, precluding the estimation of the MID for worsening symptoms. This may be related to the relatively short treatment period and the requirement that patients enter the study with a flare (UAS7 scores > 16).

In conclusion, this study provides an estimate of the MID for scores obtained with the UAS with enhanced instructions and provides evidence of its reliability, responsiveness, and validity. These results demonstrate that the enhanced UAS has adequate measurement properties to support its use in clinical research.

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