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REVIEW

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Patient-Reported Outcomes in Assessing Disease Activity, Control, and Quality of Life in Chronic Spontaneous Urticaria

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ABSTRACT

Chronic spontaneous urticaria (CSU) is a heterogeneous disease that significantly affects patients' quality of life due to its unpredictable nature and discomforting symptoms. Due to the variable course of the disease, the current condition of the disease should be comprehensively evaluated at every visit by healthcare providers. However, objective and specific biomarkers are lacking. Information about disease activity, disease control and quality of life can only be obtained from patients' reports regarding their health status, symptoms, life quality, or improvements during treatment. To do that, using patient-reported outcomes (PROs) is crucial in assessing the effectiveness of treatments, making decisions about treatment changes, and evaluating the patient's general well-being. This article will provide information about current validated PROs recommended by guidelines for evaluating CSU.

Keywords: Patient-reported outcomes, chronic spontaneous urticaria, disease activity, disease control, quality of life

Abbreviations: **CSU:** Chronic Spontaneous Urticaria, **CIndU:** Chronic Inducible Urticaria, **CU:** Chronic Urticaria, **PROs:** Patient-Reported Outcomes, **HRQL:** Health-Related Quality of Life, **EAACI:** European Academy of Allergy and Clinical Immunology, **GA²LEN:** Global Allergy and Asthma European Network, **EuroGuiDerm:** European Guidelines on Dermatology, **APAAACI:** Asia Pacific Association of Allergy, Asthma, and Clinical Immunology, **UAS:** Urticaria Activity Score, **UAS7:** Urticaria Activity Score over Seven Days, **AAS:** Angioedema Activity Score, **AAS7:** Angioedema Activity Score over Seven Days, **UCT:** Urticaria Control Test, **UCT7:** Urticaria Control Test over Seven Days, **AECT:** Angioedema Control Test, **QoL:** Quality of Life, **CU-QoL:** Chronic Urticaria Quality of Life Questionnaire, **AE-QoL:** Angioedema Quality of Life Questionnaire, **DLQI:** Dermatology Life Quality Index, **CRUSE:** Chronic Urticaria Self Evaluation App, **UCARE:** Urticaria Centers of Reference and Excellence, **HAE:** Hereditary angioedema

INTRODUCTION

Chronic urticaria (CU) - a heterogeneous disease that manifests itself with urticaria, angioedema, or both - is triggered by the activation and degranulation of skin mast cells due to known or unknown reasons (1,2). The point prevalence of CU is approximately 0.5% to 1%, and the duration of the disease generally ranges from 1 to 5 years (3). The prevalence of the disease continues to increase over time and affects the female gender more (4). CU can be categorized into two primary types: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU) (1). In CSU, individuals experience sudden and unpredictable onset of wheals and/or angioedema without the presence of a distinct trigger. In CIndU, there are specific triggers such as heat, cold or pressure.

Chronic urticaria symptoms can appear daily or intermittently/recurrently and can recur after complete remission lasting months or years (1). The unpredictability of symptom recurrence, itching, and physical appearance can dramatically affect daily activities and life quality. CU

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can affect patients' daily lives, such as through sleep disturbance, anxiety and depression, sexual dysfunction, and loss of work capacity (5). The goal of treatment in CU is to achieve complete disease control [Urticaria Activity Score (UAS)=0, Urticaria Control Test (UCT) = 16], normalize the patient's quality of life and provide practical and regular treatment until the disease is entirely resolved (1).

For CSU, objective and specific biomarkers that demonstrate disease activity and severity have not yet been established. Therefore, this information can only be obtained from the patients. Information about disease activity and impact of disease symptoms can be obtained from the patients' assessments of their health status, without intervention or interpretation from a physician, using patient-reported outcomes (PROs) (6,7). PROs include all health-related reports coming from the patient, encompassing symptoms, health-related quality of life (HRQL), disease perception, and satisfaction (8). PROs are essential for managing treatment and patient monitoring in individuals with CSU. Additionally, PROs are considered critical in clinical research for comparing the benefits of different drugs. In this context, determining changes in patients' health status during follow-ups, measuring their quality of life, and guiding treatment decisions using PRO scores are essential (9). The guidelines provided by EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI recommend the use of validated PROs such as the UAS (and the weekly urticaria activity score derived from it, i.e., UAS7), the Angioedema Activity Score (AAS), the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), the Angioedema Quality of Life Questionnaire (AE-QoL), the UCT, and the Angioedema Control Test (AECT) for assessing disease activity, impact, and control in patients with CSU (Table I). This review will focus on PROs that were developed and validated to measure disease activity, disease control, and quality of life for CSU, as well as their use in patient follow-ups, the results, and other significant practical issues regarding their interpretation (Table II).

PATIENT-REPORTED OUTCOMES FOR CHRONIC SPONTANEOUS URTICARIA

Urticaria Activity Score

The Urticaria Activity Score, a crucial assessment tool, is used to determine the severity of the disease and monitor the progress of treatment (10). The GA^{2}LEN task force strongly advocates for the use of UAS in measuring symptoms (8). This scoring system is primarily based on the evaluation of daily itchiness and swelling experienced by patients (Table III). The severity of itching and the number of hives are recorded daily on a scale from 0 to 3, allowing the UAS to reach a maximum of 6 points daily (11).

Given the daily fluctuations of the disease, the Urticaria Activity Score-Seven (UAS7), a weekly assessment, is used to provide a more accurate reflection of the disease's activity. This includes the daily UAS scores obtained over a week, ranging between 0 and 42. High UAS7 scores indicate severe symptoms, prompting a reassessment of the treatment plan (12). A UAS7 score of 0 signifies the patient is symptom-free; a score of 6 or below indicates the disease is well-controlled; a score between 7 and 15 suggests a mild severity; a score between 16 and 27 indicates a moderate severity; and a score between 28 and 42 indicates a severe condition (10). The consistent use of the UAS is crucial for comprehensive monitoring of patient conditions and modifying the treatment strategy.

When completed prospectively and regularly by patients, the UAS7 yields valuable insights. Its concise format, availability in both paper and electronic versions, daily completion capability, and the option to finalize it before healthcare visits provide clear benefits. Except for the initial visit, it is recommended for assessment at all subsequent appointments. This tool is handy for informing changes in the treatment plan. However, since it necessitates a forward-looking evaluation, the outcomes will only

Table I: Patient reported outcomes that were recommended and validated in different languages to evaluate disease activity, disease control and quality of life for patients with urticaria and/or angioedema.

PROs	Suitable for patients with		
	Isolated urticaria	Urticaria and angioedema	Isolated angioedema
UAS	Yes	Yes	No
UCT	Yes	Yes	Yes
AAS	No	Yes	Yes
AECT	No	Yes	Yes
DLQI	Yes	Yes	Yes
CU-QoL	Yes	Yes	No
AE-QoL	No	Yes	Yes

PRO: Patient-Reported Outcome; **UAS:** Urticaria Activity Score; **UCT:** Urticaria Control Test; **AAS:** Angioedema Activity Score; **AECT:** Angioedema Control Test; **DLQI:** Dermatology Life Quality Index; **CU-QoL:** Chronic Urticaria Quality of Life Questionnaire; **AE-QoL:** Angioedema quality of life

Table II: Brief descriptions on patient-reported outcomes

PROs	Assessment categories	When to use	Items	Scoring method	MIDs	Interpreting results
UAS7	Prospective: daily questionnaire over 7 consecutive days	At every assessment except for the initial one When considering stepping up or down the treatment	2	Each question is scored from 0 to 3 (separate questions for itch and wheals) Score range: 0–42 points	11 points	0: no urticaria (complete control) 1–6: Well controlled 7–15: Mild disease 16–27: Moderate disease 28–42: Severe disease
UCT	Retrospective: condition over the previous 4 weeks	At initial assessment and every follow-up assessment	4	Each question is scored from 0 to 4 Score range: 0–16 points	3 points	≤11: Poorly controlled 1-15: Well controlled =16: Complete controlled
AAS7, AAS28	Prospective: daily questionnaire over 7 days or 4 weeks	At every assessment except for the initial one It can be used in histamine mediated and bradykinin-mediated angioedema	6	Each question has different scores Score range: 0–15 points (daily) 0–105 (7-day score) 0-420 (4-week score)	8 points (for AAS7)	For AAS7 =0: No angioedema 1–6: Mild activity 7–18: Moderate activity 19–105: Severe activity For AAS28 =0 days: No angioedema 1–3 days: Mild disease 4–7 days: Moderate disease 8–28 days: Severe disease
AECT	Retrospective: condition over the previous 4 weeks or 3 months	At initial assessment and every follow-up assessment	4	Each question is scored from 0 to 4 Score range: 0–16 points	3 points	≤10: Poorly controlled 10–15: Well-controlled =16: Complete controlled
DLQI	Retrospective: condition over the 7 days	Ideally at every assessment	10	Each question is scored from 0 to 3 Score range: 0–30 points	-	0–1: No impact 2–5: Small impact 6–10: Moderate impact 11–20: Large impact 21–30: Very large impact
CU-QoL	Retrospective: condition over the previous 2 weeks	Ideally at every assessment	23	Each question is scored from 0 to 4 Score range: 0–92 points	3–15 points	Higher scores indicate a greater impact on QoL
AE-QoL	Retrospective: condition over the previous 4 weeks	At every assessment in patients with recurrent angioedema	17	Each question is scored from 0 to 4 Score range: 0–68 points	6 points	0–23: No effect 24–38: Small effect ≥39: Moderate to large effect

PRO: Patient-Reported Outcome; **UAS7**: Weekly Urticaria Activity Score; **UCT:** Urticaria Control Test; **AAS7:** Weekly Angioedema Activity Score; **AAS28:** Monthly Angioedema Activity Score; **AECT:** Angioedema Control Test; **DLQI:** Dermatology Life Quality Index; **CU-QoL:** Chronic Urticaria Quality of Life Questionnaire; **AE-QoL:** Angioedema Quality of Life Questionnaire; **MID**: Minimal Important Difference; **QoL:** Quality of Life.

Table III: Urticaria Activity Score

Hives		Itch	
Number of Hives	**Score***	**Itch Severity**	**Score***
None	0	None	0
Mild (<20 hives/24 h)	1	Mild (present, but not annoying or troublesome)	1
Moderate (20–50 hives/24 h)	2	Moderate (troublesome, but does not interfere with normal daily activity or sleep)	2
Intense (50 hives/24 h or large confluent areas of hives)	3	Intense (severe itch, which is sufficiently troublesome to interfere with normal daily activity or sleep)	3

* It is advised to utilize the Urticaria Activity Score (UAS7) for a duration of 7 days to document disease activity. Each day is scored within the range of 0 to 6, resulting in a total UAS7 score ranging from 0 to 42.

be accessible at the next visit. A limitation of the UAS7 is its inattention to angioedema, rendering it unsuitable for cases of isolated angioedema. It is also not recommended for assessing disease activity in cases of CIndU. A potential issue with the scoring process is that it captures all types of itchiness, irrespective of their cause, which could lead to inaccurately elevated scores.

Urticaria Control Test

The Urticaria Control Test, developed and validated in 2014, plays a crucial role in assessing disease control in patients with CU and supporting treatment decisions (13). The UCT is not only designed for CSU but is also applicable to all types of CU and is used in patients experiencing recurrent angioedema. It consists of four questions, each with five response options (0-4 points), asking about the extent of impairment over the previous four weeks (Table IV). The first question asks about the frequency of urticaria and/or angioedema symptoms, and the second addresses the impact on overall quality of life. The third question seeks to understand how often the treatment fails to control symptoms, and the last question focuses on how effectively the disease is being controlled. Therefore, the total score, ranging from 0 to 16, reflects symptom control and quality of life. A high score suggests good control of symptoms and quality of life, while a low score indicates poor control of symptoms and the need to review the treatment plan. A UCT score of 11 or lower indicates insufficient disease control; a score of 12 or higher suggests that CSU is being effectively managed; and a score of 16 indicates complete control (1). Guidelines recommend increasing the dose of second-generation H1 antihistamines up to fourfold the average dose before adding omalizumab treatment for CU if there is no improvement within two weeks or less. The UCT covers a recall period of 4 weeks. However, this duration is considered too long and may delay treatment decisions. Researchers have thus developed the UCT7 tool by reducing the recall period in the UCT questions to 7 days to address this limitation (14).

The UCT, an easily completable tool by patients, offers a practical method to be filled out before doctor visits during routine examinations. Its simple structure and understandable scoring system support a patient-centered approach in managing CU, contributes improving treatment strategies. However, it is important to note that the UCT, based on patients' perceptions, is subjective and should be evaluated with other objective measurements. This comprehensive assessment helps optimize treatment plans more effectively, taking into account both the patient's experience and the medical professional's expertise.

Angioedema Activity Score

Angioedema Activity Score is a validated PRO tool designed and verified to measure disease activity, assess response to treatment, and optimize the treatment plan for patients with recurrent angioedema (15). AAS is applicable across all subtypes of recurrent angioedema, including bradykinin-mediated hereditary angioedema (HAE) and CSU, providing a comprehensive assessment. Like the UAS, this PRO is filled out prospectively and daily, evaluating five main factors related to angioedema: duration, physical discomfort caused, impact on daily activities, effect on appearance, and overall severity, each scored between 0 and 3 (Table V). Consequently, AAS scores can range daily from 0 to 15, over seven days (AAS7) from 0 to 105, and for four weeks (AAS28) from 0 to 420. Higher AAS scores may indicate frequent and severe attacks, sug-

Table IV: Urticaria Control Test

Question	Score				
	0	1	2	3	4
1. How much have you suffered from the physical symptoms of the urticaria (itching, hives, or swelling) in the last 4 weeks?	very much	much	somewhat	a little	not at all
2. How much has your quality of life been adversely affected by urticaria in the last 4 weeks?	very much	much	somewhat	a little	not at all
3. How often was the treatment for your urticaria insufficient to control symptoms in the last 4 weeks?	very often	often	sometimes	seldom	not at all
4. Overall, how well have you had your urticaria under control in the last 4 weeks?	not at all	a little	somewhat	well	very well
If score is <12: The disease is uncontrolled. 12 – 15: The disease is well controlled 16: The disease is completely controlled					

gesting a need to review the treatment plan. In contrast, lower AAS scores can indicate well-controlled symptoms and the effectiveness of the current treatment, underscoring the critical importance of regular AAS utilization for monitoring patient health and adjusting treatment as necessary.

However, it's important to note that AAS has its limitations. For instance, it might not objectively measure the impacts of angioedema attacks, thus considered a subjective assessment tool. Its prospective nature means results can only be obtained during follow-up visits, requiring high patient compliance due to the necessity of daily documentation. The time-consuming nature of scoring can also pose a barrier to its routine application in clinical care.

Angioedema Control Test

The Angioedema Control Test is a validated, retrospective tool for evaluating the management of angioedema in patients. It boasts validation across a spectrum of languages due to its concise nature and straightforward scoring mechanism (16,17). It finds utility in both clinical and therapeutic investigations (1,18).

Aiming for the gold standard in treating mast cell-mediated and bradykinin-mediated recurrent angioedema, the AECT underscores the importance of achieving complete disease remission, the absence of symptoms, and restoring a quality of life (1,19). AECT is available in two versions: one with a recall period of four weeks and another spanning three months. Both versions are designed for easy application, completion, and utilization within routine clinical practice. Apart from the difference in recall periods, the two versions share identical question-and-answer options (Table VI). The questions address the frequency of symptoms, quality of life (QoL) impairment, unpredictability of attacks, and the level of control achieved with current treatment (16). Responses are presented on a scale rang-

Table V: Angioedema Activity Score

Dimension	Answer options	Score*
Have you had a swelling episode in the last 24 h?	No, yes	
1. At what time(s) of day was this swelling episode(s) present? (Please select all applicable times)	Midnight–8 a.m., 8 a.m.–4 p.m., 4 p.m.–midnight	0–3
2. How severe is / was the physical discomfort caused by this swelling episode(s) (e.g., pain, burning, itching?)	No discomfort, slight discomfort, moderate discomfort, severe discomfort	0–3
3. Are / were you able to perform your daily activities during this swelling episode(s)?	No restriction, slight restriction, severe restriction, no activities possible	0–3
4. Do / did you feel your appearance is / was adversely affected by this swelling episode(s)?	No, slightly, moderately, severely	0–3
5. How would you rate the overall severity of this swelling episode?	Negligible, mild, moderate, severe	0–3

Note: For the AAS, scores are summed up to an AAS day sum score (0–15), 7 AAS day sum scores to an AAS week sum score (AAS7, 0–105), 4 ASS week sum scores may be summed up to an AAS 4-week sum score (AAS28, 0–420)

Table VI: Angioedema Control Test

Question (Completed AECT 4-week questions)	Score				
	0	1	2	3	4
1. In the last 4 weeks, how often have you had angioedema?	very often	often	sometimes	seldom	not at all
2. In the last 4 weeks, how much has your quality of life been affected by angioedema?	very much	much	somewhat	a little	not at all
3. In the last 4 weeks, how much has the unpredictability of your angioedema bothered you?	very much	much	somewhat	a little	not at all
4. In the last 4 weeks, how well has your angioedema been controlled by your therapy?	not at all	a little	somewhat	well	very well
If score is ≤10: The disease is poorly controlled. 10–15: The disease is well-controlled. =16: The disease is completely controlled					

ing from 0 to 4, with the total score varying between 0 and 16. A higher score represents better angioedema control (17). Cut-off points for determining well-controlled and poorly controlled patients are set at ≥10 and <10, respectively (17). A limitation of the AECT is the lack of in-depth insights into recurrent angioedema. However, its brevity and clear outcomes allow for straightforward application and interpretation in daily patient care.

The Dermatology Life Quality Index

Dermatological conditions can lead to psychological effects such as low self-esteem, social exclusion, and isolation due to visible lesions, adversely impacting quality of life. Quality of life measurement tools evaluate physical activity, emotional well-being, and occupational and social functioning, which illness can affect. The Dermatology Life Quality Index (DLQI) is among the most widely used instruments for assessing HRQL specific to dermatology (20). The survey was developed from responses to the open-ended question, "How does your skin disease affect you?" posed to patients.

The DLQI comprises a validated, dermatology-specific 10-item questionnaire covering six domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and the impact of treatment on daily living. Implementing and scoring the DLQI in routine clinical practice are quick and straightforward. The DLQI score ranges from 0 to 30, with a score between 0 and 1 indicating no impact on the patient's quality of life. Scores of 2-5, 6-10, and 11-20, respectively, indicate a small, moderate, and large impact of CSU symptoms on quality of life (20). Scores between 21 and 30 indicate a very large impact. DLQI scores have shown a positive and significant correlation with the UAS in patients with CSU (21,22). While the DLQI primarily focuses on functional impairments, it may fail to address the emotional and mental effects of the condition (23).

Chronic Urticaria Quality of Life Questionnaire

The intensity of itching in urticaria and/or angioedema, its physical appearance, and the potential for life-threatening situations significantly impact the QoL. Patients often visit doctors frequently, leading to unnecessary laboratory tests and burdening both the patient and the healthcare system. The CU-QoL questionnaire is a validated disease-specific survey that assesses the disease-related quality of life and contributes to documenting the benefits of treatments (1,8,24). The CU-QoL questionnaire consists of 23 questions that cover topics like symptom severity and frequency over the past two weeks, response to treatment, sleep quality, limitations in daily activities, and changes in social relationships. When evaluating CU-QoL, each question is scored from 0 to 4, resulting in a total score ranging from 0 to 92. The obtained score is then multiplied by 100 and divided by 92 to obtain a score out of 100. A higher score may indicate a worse quality of life, while a lower score may reflect a better quality of life.

The quality of life questionnaires play a crucial role in following up on patients' responses to treatment. However, the evaluation of QoL is often overlooked in clinical practice. As treatment effectiveness increases, there is typically a noticeable improvement in quality of life. Therefore, the CU-QoL questionnaire is used to compare treatment options, monitor treatment effectiveness, and assess progress in clinical research (25,26).

Angioedema Quality of Life Questionnaire

Recurrent angioedema, a condition characterized by its unpredictable, painful, disfiguring, and potentially life-threatening clinical manifestations, significantly disrupts the quality of life (27,28). The impact of angioedema attacks extends beyond physical discomfort, often leading to a halt in daily activities and social interactions. This can result in high rates of absenteeism in work and education, and in some cases, even render the patient unable to work (29,30).

Angioedema Quality of Life Questionnaire is the first symptom-specific patient-reported outcome measure developed to assess angioedema-specific quality of life impairment (31). The questionnaire consists of a total of 17 questions evaluating four different domains ("Function," "Fatigue/Mood," "Fear/Shame," and "Diet"). Each question assesses a recall period of 4 weeks and includes five response options scored from 0 to 4 (31). There is a wide range of possible values, from 0 to 68. The obtained score is then multiplied by 100 and divided by 68 to obtain a score out of 100. Values define no (0–23), small (24–38), or moderate to significant effect (≥39) on recurrent angioedema patients' QoL (31,32). A higher score indicates a more significant impairment in quality of life. AE-QoL has been successfully used in clinical studies in CU and HAE, providing valuable data on the effects of new treatments on quality of life in recurrent angioedema (33).

Chronic Urticaria Self Evaluation App

Chronic Urticaria Self Evaluation App (CRUSE® Control) is an innovative digital application explicitly designed for the needs of CSU patients. Developed by Urticaria Centers of Reference and Excellence (UCARE), CRUSE facilitates patients' access to treatment and contributes important data to medical research (34,35).

The app's priorities are based on the latest CU findings to enable patients to monitor their symptoms, medication usage, and photos to optimize their treatment processes. CRUSE® includes patient-specific and clinically tailored PROs, including UAS, AAS, UCT, and AECT. Additionally, the app provides real-time insights to doctors by securely providing data such as patients' age, gender, disease onset, triggers, medications, and CSU characteristics. Initial data from CRUSE® indicates potential progress towards effectively monitoring disease activity and control and personalized CSU management (36). This application will empower patients to control their health and collaborate more effectively with their doctors.

CONCLUSION

Standardized, validated, and reliable PROs are crucial when monitoring CSU. This article reviewed existing tools to assess disease activity, control, and impact on patient life. PROs can assist in clinical practice by aiding in patient monitoring, better documenting changes in disease status over time, and maintaining more standardized and reliable medical records. Their use in clinical research can provide important information from the patient perspective in standardization of the studies, comparability of study results, and evaluation of treatment effectiveness. However, all the tools necessary for effective implementation need to be integrated into clinical practice in patient management.

Patients should be encouraged to fill out retrospective PROs such as UCT, AECT, CU-QoL, and AE-QoL during or before doctor visits to facilitate treatment planning. Prospective PROs such as UAS7 and AAS should be provided to patients after informing them how to fill them out at home after the doctor's visit. These criteria should be more integrated into daily routines, including less commonly used specific PROs for angioedema (AAS, AECT, and AE-QoL). Additionally, digital health technologies, mobile applications, web-based platforms, and AI-powered virtual assistants can be used to optimize the collection of PROs, enabling patients to monitor their health status more effectively and actively participate in their treatment processes.

Conflict of Interest

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