

Review

Patient-reported outcomes (PROs) in chronic urticaria

Kristian Moestrup¹, BSc, Misbah N. Ghazanfar¹, MD, and Simon F. Thomsen^{1,2}, MD, PhD¹Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark, and²Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark**Correspondence**

Misbah N. Ghazanfar, MD
Department of Dermatology
Bispebjerg Hospital
Bispebjerg Bakke 23
DK-2400 Copenhagen NV
Denmark
E-mail: misbah.noshela.ghazanfar@regionh.dk

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Introduction

Urticaria is an itching skin disease characterized by wheals, angioedema, or both. Urticaria can be divided into acute (symptoms persist for <6 weeks) and chronic (symptoms persist for >6 weeks). Further, chronic urticaria can be subdivided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CINDU). CINDU usually appears due to physical stimuli such as heat, cold, or sunlight.^{1,2}

CSU is the most common of the nonacute types of urticaria. The estimated prevalence of CSU is 0.5–1% in the general population with females being affected almost twice as often as males. The highest incidence occurs between ages 20–40 years with an average duration of 3–5 years.³

CSU has great impact on the patient's daily life due to the fluctuating nature of symptoms and unpredictability of attacks, which complicate diagnosis, monitoring, and treatment of the disease. Factors such as reduced sleep quality and social isolation, contribute to reduced quality of life (QoL). CSU also carries great socioeconomic burden,^{3,4} both directly and indirectly. The direct socioeconomic burden stems from the costs of medication, laboratory tests, and regular or unanticipated healthcare visits, in particular angioedema patients seen in emergency departments. Further, CSU has an indirect socioeconomic burden caused by lowered productivity due to reduced sleep quality and following fatigue underlined by the fact that CSU is most prevalent between ages 20 and 40.

Abstract

Chronic urticaria is an itching skin disease which persists for more than 6 weeks. Chronic urticaria has great impact on the daily life of the patient, and the fluctuating nature of the symptoms complicates the monitoring and treatment of the disease. Currently, there are no reliable biomarkers to identify and measure disease activity in chronic spontaneous urticaria. Consequently, use of patient-reported outcomes (PROs) is crucial when evaluating and monitoring different aspects of chronic urticaria such as disease activity/severity, disease control, and quality of life. We present an overview of seven different PROs used in chronic urticaria and highlight their strengths, limitations, and use in clinical practice and research.

Currently, there are no reliable biomarkers to identify and measure disease activity in CSU. Consequently, use of patient reported outcomes (PROs) is crucial when evaluating and monitoring different aspects of chronic urticaria such as disease activity/severity, disease control, and QoL. This review gives an overview of the most commonly used PROs in chronic urticaria and highlight current unmet needs in clinical practice and research.

Overview of PROs used in chronic urticaria

Seven different PROs that measure various aspects of disease severity/activity and QoL are used routinely in research and clinical practice of chronic urticaria. Four of these PROs are urticaria-specific: Urticaria Activity Score (UAS); Urticaria Control Test (UCT); Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL); and Urticaria Severity Score (USS); two are angioedema-specific: Angioedema Activity Score (AAS) and Angioedema Quality of Life Questionnaire (AE-QoL); whereas one is a generic, skin-specific QoL questionnaire: Dermatology Life Quality Index (DLQI) (Table 1).

Urticaria-specific PROs

The UAS is a CSU-specific, prospective, and patient reported measure mainly used to assess CSU activity/severity and treatment response. It contains two components: intensity of itch (ranging from 0: none to 3: severe) and number of

Table 1 Overview of patient-reported outcomes in chronic urticaria

Patient-reported outcome	Type	Domains	Scoring system	Score range	MID	Comment
Urticaria Activity Score (UAS) ^{5,6}	Prospective diary	Itch and wheals	Each question is scored from 0 to 3	0–42 points	10 points	A score ≤6 indicates minimal disease activity. A total score of ≥28 indicates severe urticaria
Urticaria Control Test (UCT) ^{7,8}	Retrospective 4-item questionnaire based on the last 4 weeks	Disease control	Each question is scored from 0 to 4	0–16 points	3 points	A score ≥12 indicates well-controlled disease
Urticaria Severity Score (USS) ¹¹	12 questions	Quality of life impairment, duration of itch and swelling, medication	10 questions scored from 0 to 7. One question (corticosteroid) weighs double.	0–93 points	–	A higher score indicates more impact on quality of life
Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) ^{9,10}	23 questions	Pruritus, swelling, daily life activities, sleep, appearance, and limitations	Two questions 0 to 8 Each question is scored from 1 to 5	23–115 points	15 points	A higher score indicates stronger impairment of health-related quality of life
Angioedema Activity Score (AAS) ¹²	5 questions	Severity of physical discomfort, ability to perform daily activities, cosmetic impact, and global assessment of severity	Each question is scored from 0 to 3	0–15 points (daily AAS scoring)	–	A higher score disease activity
Angioedema Quality of Life Questionnaire (AE-QoL) ¹³	17 questions	Functioning, fatigue/mood, fears/shame, and food	Each question is scored from 0 to 5	0–85 points	–	A higher score indicates more impact on quality of life
The Dermatology Life Quality Index (DLQI) ^{14,15}	10 questions	Symptoms, social activities, work/school, personal relationships, and treatment associated problems	Each question is scored from 0 to 3	0–30 points	2.24–3.10 points	A higher score indicates more impact on quality of life

MID, minimal important difference.

wheals (ranging from 0: none to 3: more than 50 wheals). Patients are asked to document in 24-hour intervals, and the summed result gives a daily UAS score (0–6 points). This score can be summed over a number of days; notably 7 giving the UAS7 score (0–42 points). UAS7 cut-off values are not currently globally defined, but a UAS7 score of 0 corresponds to the total absence of wheals and itch, whereas a $UAS7 \leq 6$ corresponds to minimal disease activity. Cut-off values have been proposed as follows: a UAS7 score of 7–15 indicates mild disease activity, a UAS7 score of 16–27 indicates moderate disease activity, and a UAS7 score of 28–42 indicates severe disease activity.⁵ The minimal clinically important difference in UAS7 has been evaluated by Mathias *et al.*⁶ and was determined to be a reduction of 9.5–10.5 points (equivalent to 10 points). However, it is currently unclear if the MID reported by Mathias *et al.* is valid for all levels of disease activity.

The UCT is a retrospective (past 4 weeks) 4-question instrument designed to assess disease control in patients with CSU. The questions cover severity of physical symptoms, how much symptoms have affected QoL, how often treatment had been inadequate to control symptoms, and lastly how well symptoms had been under control. Each answer is scored ranging from 0 to 4 with a summed score ranging from 0: no control to 16: full control. A UCT score of ≤ 11 indicates poor disease control, whereas a score of ≥ 12 indicates well-controlled CSU.⁷ The minimal clinical change, which can be regarded as meaningful to patients, is determined to be 3 points.⁸

The CU-Q2oL is a CSU-specific health-related QoL questionnaire consisting of 23 questions. The questions cover different aspects of CSU's impact on patients' lives including: pruritus, swelling, daily life activities, sleep, appearance, and limitations.⁹ CU-Q2oL scores range from 23 to 115, with a higher score indicating stronger impairment of health-related QoL. In a Thai study by Kulthanan *et al.*,¹⁰ the authors concluded that the minimal clinically important difference in CU-Q2oL corresponds to a reduction of 15 points.

The USS is an instrument used to monitor severity of urticaria, QoL, and treatment efficacy.¹¹ It contains 12 questions covering several specific aspects of CSU including distinct QoL impairment, degree and duration of itching and/or swelling, and amount of medication required for symptom control. Ten of the questions are scored on a Likert scale ranging from 0: no symptoms/no QoL impairment/no medication use, to 7: severe symptoms/strong QoL impairment/high medication use, whereas two of the questions cover areas of the body experiencing symptoms with a score of 0–8; a higher score indicating a larger surface area affected by urticaria. One of the questions regarding oral corticosteroid use has its score multiplied by 2 based on the assumption that this correlates with greater disease severity. The summed USS score ranges from 0 to 93, with a higher score indicating bigger impact on QoL as well as greater disease severity.¹¹

PROs specific for angioedema

The AAS is a five-item tool used to assess disease activity in recurrent angioedema. The five items are number of affected 8-h periods, severity of physical discomfort, ability to perform daily activities, cosmetic impact, and global assessment of severity.¹² Each item is scored ranging from 0: none to 3: severe. Accordingly, the AAS scores range from 0 to 15 (daily AAS score), 0 to 105 (AAS7), and 0 to 420 (AAS28).

The AE-QoL is an angioedema-specific health-related QoL questionnaire containing 17 items. The 17 items cover: functioning, fatigue/mood, fears/shame, and food.¹³ AE-QoL scores range from 0 to 85, with a higher score indicating stronger impairment of health-related QoL.

Dermatology Life Quality Index

The DLQI is a generic skin-specific questionnaire used to evaluate health-related QoL for various dermatological diseases. The DLQI contains 10 questions covering: symptoms, social activities, work/school, personal relationships, and treatment associated problems. Each question is scored ranging from 0: not at all to 3: very much. This gives a summed DLQI score ranging from 0 to 30, where a 0–1 score indicates no negative effect on health-related QoL and scores of 11–20 and 21–30 indicate, respectively, great and very great negative effect on patients' health-related QoL.¹⁴ The minimal clinically important difference in DLQI among patients with chronic urticaria is in the range of 2.24–3.10.¹⁵

Disease activity and disease control in chronic urticaria

Due to the fluctuating nature of the symptoms of chronic urticaria, it is often difficult for physicians to determine the severity and activity of the disease in the clinical setting. However, there are some factors such as autoimmunity, which can help predict response to treatment and severity of disease in CSU patients. In particular, a prospective observational study investigated prognostic factors for CSU among 75 Korean patients from three different university hospitals.¹⁶ In total, 3% of the patients achieved complete remission, 36% achieved well-controlled disease, 44% remained partly controlled, while 17% were uncontrolled. It was observed that autologous serum skin test (ASST) positivity was a significant predictor of disease control and that both UAS7 and CU-QoL are helpful tools in monitoring therapeutic response.¹⁶ In another study from Israel,¹⁷ the authors investigated whether parameters such as angioedema, ASST, antithyroid antibodies, and total IgE can be used to predict disease duration and severity. A total of 139 patients were followed during a 5-year period for disease duration, severity, and the presence of angioedema. It was observed that symptoms persisted for more than 1 year in 70% of the cases and in 14% after 5 years. Angioedema was present or occurred during the course of the disease in 40% of the patients and was

associated with prolonged disease duration. Furthermore, disease duration was associated with the presence of ASST and antithyroid antibodies.¹⁷ However, in a systemic review by Rabelo-Filardi *et al.*,¹⁸ it was concluded that there was no evidence to support the association between ASST positivity and a longer disease duration and severity in patients with chronic urticaria. They also found that plasma levels of prothrombin fragment 1 + 2, D-dimer, and CRP might be predictors of CSU severity. Likewise, a review by Kolkhir *et al.*¹⁹ found a significant association between values of biomarkers and CSU activity for D-dimer, CRP, prothrombin fragment 1 + 2, MPV, and IL-6. Furthermore, it was seen that levels of D-dimer and IL-31 were elevated before treatment and decreased after treatment with omalizumab.

Previously, several different PRO tools have been used for assessing CSU activity. These include Visual Analogue Scales and Likert type scales. This heterogeneous symptom scoring made comparison of clinical trial results very difficult and also led to great variation in clinical practice between centers. This prompted guidelines to recommend the use of a well-established and validated symptom scores like the UAS. The UAS has been used in numerous randomized controlled trials (RCTs) of various medications for CSU.²⁰ Notably, patients with a UAS7 score ≥ 16 at baseline were included in the RCTs of omalizumab.^{21–23} Saini *et al.*²¹ reported a UAS7 score ≤ 6 in 52% of the patients at week 12 and a complete response (UAS7 = 0) in 36% of the patients. Likewise, in a study by Kaplan *et al.*,²² 336 CSU patients with a UAS7 score ≥ 16 were included. At week 12, 34% of the patients treated with omalizumab reported a UAS7 = 0 compared to 5% in the placebo group. Maurer *et al.*²³ also reported a UAS7 score ≤ 6 among 109 patients treated with omalizumab versus 15 patients in the placebo group. Another RCT²⁴ included 49 patients with CSU and IgE autoantibodies against TPO who had a UAS7 score > 10 despite treatment with antihistamines. At week 24, patients treated with omalizumab reported a reduction of 17.8 points in UAS7 score from baseline versus a reduction of 7.9 points in the placebo group. Similar results were seen in a study by Saini *et al.*²⁵ A total of 90 patients with refractory CSU with a UAS7 ≥ 12 were included. At week 4 after initiating treatment, a decrease of 13 points from the baseline UAS7 score was seen in the omalizumab group versus a reduction of 7.7 points in the placebo group (see Table 2).

UAS7 has become a widely used tool to assess disease activity in CSU in routine clinical practice and is therefore often referred to as the *golden standard* in CSU disease activity assessment.²⁶ Still, it has some limitations. Due to the fact that UAS7 is a prospective tool, it is inherently difficult to assess CSU activity with UAS7 during a first patient contact. This also makes the UAS7 scoring dependent on patients themselves remembering to do a proper completion on all days until the next consultation. Further, angioedema and CINDU subtypes of urticaria are not included in the scoring, even though these are

Table 2 Overview of clinical studies using Urticaria Activity Score (UAS)

Study	Number of patients	Results
Saini <i>et al.</i> ²¹	262	UAS7 score ≤ 6 in 52% of the patients Complete response: 36% of the patients
Kaplan <i>et al.</i> ²²	336	Complete response (UAS7 = 0) in 34% of the patients versus 5% of the patients in placebo group
Maurer <i>et al.</i> ²³	322	UAS7 score ≤ 6 in 109 patients versus 15 patients in placebo group
Maurer <i>et al.</i> ²⁴	42	Reduction of 17.8 points in UAS7 score from baseline versus a reduction of 7.9 points in the placebo group
Saini <i>et al.</i> ²⁵	90	A decrease of 13 points from the baseline UAS7 score was seen in the omalizumab group versus a reduction of 7.7 points in the placebo group

associated with CSU in many patients.⁷ To meet these terms, the UCT was developed with the intention of adding a tool to assess urticaria that would help covering UAS limitations. Among benefits of the UCT are its retrospective nature meaning it can be independent of any previous patient contacts, and the fact that it is simple and fast to complete for patients and physicians alike. Most notably it was designed to help assess disease control in patients with urticaria. UAS focuses on two key symptoms of CSU, wheals and itch, while UCT focuses on disease control in all forms of chronic urticaria. An ideal way to use these two questionnaires in chronic urticaria patients would be in combination with each other, as they focus on different aspects of chronic urticaria. A combined use of these two questionnaires in a clinical setting would give the physician a better overview of disease activity as well as disease control.

Quality of life in chronic urticaria

Patient QoL can be measured generically with organ-independent universal instruments, with organ-specific instruments, and with disease-specific instruments. Disease-specific QoL refers to a patient's experience of the functional impact of a disease and its treatment. It is a subjective quality that has become a fundamental factor in gauging especially chronic diseases including CSU as well as comparing treatments. In contrast to symptom scoring, QoL questionnaires can assess and monitor changes in various key aspects of a given disease including emotional reactions. Given CSU's low mortality and unpredictable nature of attacks, QoL becomes an even more important factor in the assessment of disease control.

The generic QoL questionnaires can be used to assess the impact of different diseases and thereby to some extent enable comparison of cross-population results. A commonly used questionnaire in this category is the Short Form 36 Health Survey

(SF-36). It consists of 36 questions grouped into two main areas, mental and physical, and spread across eight domains.²⁶ SF-36 and the smaller SF-12 have been used to compare CSU patients and patients with allergic respiratory disease. It indicated overall stronger health-related QoL impairment in CSU patients including areas such as sleep, productivity, and general functioning.²⁷ At present, SF-36 is not commonly used in research or in clinical practice to assess the impact of chronic urticaria.

Health-related QoL questionnaires for skin diseases include DLQI and Skindex-29. The DLQI has been used to compare CSU with other skin diseases, indicating a similar health-related QoL impairment in CSU to that of atopic dermatitis and worse impairment than that of psoriasis and acne.²⁸ DLQI has also been used in RCTs to evaluate QoL in CSU patients. Maurer *et al.* reported significant improvement of DLQI scores among patients treated with omalizumab compared to a placebo group.²⁴ Similarly, Saini *et al.*²¹ also reported a decrease in DLQI, mounting to 10.29 points from baseline in the omalizumab group compared to a reduction of 6.13 points from baseline in the placebo group. Likewise, Kaplan *et al.*²² also reported a mean reduction of 9.7 points in DLQI score in patients treated with 300 mg omalizumab (see Table 3).

The Skindex-29 questionnaire contains 29 items covering three domains: symptoms, activity, and emotions. Skindex-29 has been used in an online-survey with 321 adult CSU patients²⁹ showing a strong impairment in daily life activities such as sleep, occupation, and social life, with the major impact on sleep. It also indicated that CSU has major impact on emotions such as shame, anxiety, and depression.

The specific CSU health-related QoL questionnaire (CU-Q2oL) provides greater detail on CSU relevant factors and can therefore be a great tool to capture and compare QoL changes in CSU over time and/or with different treatments. One of its limitations is the calculation of its scores, which is more difficult and time consuming than DLQI. Additionally, it does not include impact of angioedema on QoL, which is common in CSU patients, and sometimes patients with angioedema are

excluded from participation in clinical trials. A better assessment of angioedema in CSU patients is needed, and the implementation of the AE-QoL in clinical practice will help fulfill this need.

An Indian study used CU-Q2oL to assess QoL among 48 patients with daily symptoms of chronic urticaria.³⁰ The study showed a significant interitem correlation with the highest score observed in the domain of symptoms, while sleep disturbance, effect on life activities, limits, and looks also were affected, but to a smaller extent. It was also observed that CU-Q2oL was able to reveal involvement of items such as bad mood, fatigue, etc., which were not recognized by the patients themselves beforehand. Overall, the results suggested that CU-Q2oL should be used routinely during the initial and follow-up visits to assess baseline QoL impairment and effect of the treatment. Further, in a study of 110 Greek adult patients with CSU,³¹ the correlation between disease activity and impairment of QoL was investigated by CU-Q2oL along with DLQI and UAS7. Disease activity assessed by UAS7 was found to be a significant predictor for overall CU-Q2oL score, while age, gender, and disease duration did not predict the total score, except in the domain of mental status, where female patients were significantly more affected than males. The correlation of UAS7 with DLQI was a bit lower than the correlation between UAS7 and CU-Q2oL. Interestingly, there was a group of patients with low UAS7 score but with remarkable impairment of QoL. This suggests that other factors apart from disease activity also influence CSU patients' QoL. Overall, the study highlighted the need for assessing chronic urticaria patients with several scoring systems, i.e. CU-Q2oL, DLQI, and UAS7 in clinical practice, to get a more comprehensive picture of disease status.³¹

A particular example was a German study³² which indicated that DLQI is not a suitable questionnaire for assessing QoL by itself in patients with chronic urticaria, as it does not focus on sleep, eating habits, and mental status, which are factors often affected. Chinese patients with chronic urticaria assessed by DLQI reported the greatest impact of their disease on *symptoms/feelings* and *work/school*, whereas a modest impact was seen on *personal relationships* and *daily activities*.³³ Importantly, and in line with the results among Greek patients,³¹ QoL among female patients with chronic urticaria was more impaired compared to male patients. A Japanese study of 42 children with chronic urticaria³⁴ also used UAS7 and children's DLQI concluding that UAS is a useful tool for assessing QoL in pediatric patients as UAS scores reflected changes in the patient's QoL. Also, in a study among 206 CSU patients aged 2–11 years from 30 different centers³⁵ (Germany, Romania, Hungary, and South Africa), the investigators used a modified UAS7 score to assess disease activity. The aim of the study was to investigate efficacy and safety of rupatadine in children also using children's DLQI. The study showed that rupatadine is significantly better at reducing UAS7 scores than placebo among children with chronic urticaria.

Table 3 Overview of clinical studies using Dermatology Life Quality Index (DLQI)

Study	Number of patients	Results
Saini <i>et al.</i> ²¹	262	Decrease of DLQI by 10.29 points in omalizumab group compared to 6.13 in placebo group
Kaplan <i>et al.</i> ²²	336	Reduction in DLQI score by 9.7 points from baseline
Maurer <i>et al.</i> ²⁴	42	Mean change in DLQI score between omalizumab and placebo group was reported to be 4.8

Discussion

PROs have become important instruments in the evaluation of the impact of chronic urticaria. However, although several validated PROs exist, there is still much work to be done in order to optimize the use of PROs in research and in the clinical management of chronic urticaria.

Current work with PROs in chronic urticaria attempts to assess more domains simultaneously so that disease activity, disease control, and QoL are better implemented into a single tool. Further, certain areas are poorly covered by current scoring systems. Particularly, although CINDU to some degree can be evaluated, the symptoms are very heterogeneous and different from those of CSU. This is due to the fact that many patients with CINDU exhibit avoidance behavior, i.e., actions that prevent exposure to certain stimuli associated with flaring of symptoms such as cold or heat. Further, the biomedical approach is dualistic and views emotional factors and physical manifestations of disease as separate entities. The standard approach to CSU treatment is no different even though literature suggests an important role of stress and emotional factors in CSU.^{36–39}

A pilot study⁴⁰ explored a whole person treatment including psychological factors with CSU treatment for dealing with symptoms triggered by stress. Three of four patients identified as nonresponders to standard treatment evaluated using UAS and USS improved, with almost no disease activity (<6 in UAS scoring and 0 in USS scoring) compared with pretreatment scores, supporting a connection between emotional factors and disease activity.

Knowledge regarding the prevalence and etiology and disease management and therapy response in CSU among children and adolescents is scarce.⁴¹ Gathering information regarding prevalence might best be done with school-based programs, as most CSU cases in childhood never reach specialists but are managed by general practitioners and from home. Specific targeted questionnaires for CSU in children and adolescents are also needed to begin investigations in clinical practice.

Despite international guidelines, urticaria is still treated and scored heterogeneously. There is a need to harmonize diagnostic and therapeutic approaches.⁴² GA²LEN recently began development of the pilot project Urticaria Center of Reference and Excellence Program to help combat this issue. The goal is to establish specific urticaria referral centers providing excellence in urticaria management, increase the knowledge of urticaria by research and education, and promote awareness of urticaria by advocacy activities.⁴² Furthermore, the international Cochrane Skin Group Core Outcome Set Initiative (CSG-COUSIN) is working on developing outcome measurement instruments in dermatology for use in every clinical study to ensure comparability of the results across the studies.⁴³ The results of this initiative could also be transferred to routine care.

References

- 1 Zuberbier T, Aberer W, Asero R, *et al*. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014; **69**: 868–887.
- 2 Gimenez-Arnau AM, Grattan C, Zuberbier T, *et al*. An individualized diagnostic approach based on guidelines for chronic urticaria (CU). *J Eur Acad Dermatol Venereol* 2015; **29** (Suppl 3): 3–11.
- 3 Maurer M, Weller K, Bindslev-Jensen C, *et al*. Unmet clinical needs in chronic spontaneous urticaria. A GA(2)LEN task force report. *Allergy* 2011; **66**: 317–330.
- 4 Delong LK, Culler SD, Saini SS, *et al*. Annual direct and indirect health care costs of chronic idiopathic urticaria: a cost analysis of 50 nonimmunosuppressed patients. *Arch Dermatol* 2008; **144**: 35–39.
- 5 Weller K, Zuberbier T, Maurer M. Clinically relevant outcome measures for assessing disease activity, disease control and quality of life impairment in patients with chronic spontaneous urticaria and recurrent angioedema. *Curr Opin Allergy Clin Immunol* 2015; **15**: 220–226.
- 6 Mathias SD, Crosby RD, Zazzali JL, *et al*. Evaluating the minimally important difference of the Urticaria Activity Score and other measures of disease activity in patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol* 2012; **108**: 20–24.
- 7 Weller K, Groffik A, Church MK, *et al*. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol* 2014; **133**: 1365–1372. e1–6.
- 8 Weller K, Siebenhaar F, Hawro T, *et al*. Clinical measures of chronic urticaria. *Immunol Allergy Clin North Am* 2017; **37**: 35–49.
- 9 Baiardini I, Pasquali M, Braidò F, *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.
- 10 Kulthanan K, Chularojanamontri L, Tuchinda P, *et al*. Minimal clinically important difference (MCID) of the Thai Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL). *Asian Pac J Allergy Immunol* 2016; **34**: 137–145.
- 11 Jariwala SP, Moday H, de Asis ML, *et al*. The Urticaria Severity Score: a sensitive questionnaire/index for monitoring response to therapy in patients with chronic urticaria. *Ann Allergy Asthma Immunol* 2009; **102**: 475–482.
- 12 Weller K, Groffik A, Magerl M, *et al*. Development, validation, and initial results of the Angioedema Activity Score. *Allergy* 2013; **68**: 1185–1192.
- 13 Weller K, Groffik A, Magerl M, *et al*. Development and construct validation of the angioedema quality of life questionnaire. *Allergy* 2012; **67**: 1289–1298.
- 14 Basra MKA, Fenech R, Gatt RM, *et al*. The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159**: 997–1035.
- 15 Shikier R, Harding G, Leahy M. Minimal important difference (MID) of the Dermatology Life Quality Index (DLQI): results from patients with chronic idiopathic urticaria. *Health Qual Life Outcomes* 2005; **20**: 36.
- 16 Young-Min Y, Park J-W, Kim S-H, *et al*. Prognostic factors for chronic spontaneous urticaria: a 6-month prospective

- observational study. *Allergy Asthma Immunol Res* 2016; **8**: 115–123.
- 17 Toubi E, Kessel A, Avshovich N, *et al.* Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. *Allergy* 2004; **59**: 869–873.
 - 18 Rabelo-Filardi R, Daltro-Oliveira R, Campos RA. Parameters associated with chronic spontaneous urticaria duration and severity: a systematic review. *Int Arch Allergy Immunol* 2013; **161**: 197–204.
 - 19 Kolkhir P, André F, Church MK, *et al.* Potential blood biomarkers in chronic spontaneous urticaria. *Clin Exp Allergy* 2017; **47**: 19–36.
 - 20 Urgert MC, van den Elzen MT, Knulst AC, *et al.* Omalizumab in patients with chronic spontaneous urticaria: a systematic review and GRADE assessment. *Br J Dermatol* 2015; **173**: 404–415.
 - 21 Saini S, Bindslev-Jensen C, Maurer M, *et al.* Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol* 2015; **135**: 67–75.
 - 22 Kaplan A, Ledford D, Ashby M, *et al.* Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol* 2013; **132**: 101–109.
 - 23 Maurer M, Rosén K, Hsieh H, *et al.* Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013; **368**: 924–935.
 - 24 Maurer M, Altrichter S, Bieber T, *et al.* Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol* 2011; **128**: 202–209.
 - 25 Saini S, Rosen KE, Hsieh HJ, *et al.* A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine – refractory chronic idiopathic urticaria. *J Allergy Clin Immunol* 2011; **128**: 567–573.
 - 26 Mlynek A, Zalewska-Janowska A, Martus P, *et al.* How to assess disease activity in patients with chronic urticaria? *Allergy* 2008; **63**: 777–780.
 - 27 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473–483.
 - 28 Baiardini I, Braidò F, Brandi S. Allergic diseases and their impact on quality of life. *Ann Allergy Asthma Immunol* 2006; **97**: 419–428; quiz 429–30, 476.
 - 29 Maurer M, Ortonne JP, Zuberbier T. Chronic urticaria: an internet survey of health behaviours, symptom patterns and treatment needs in European adult patients. *Br J Dermatol* 2009; **160**: 633–641.
 - 30 Pherwani AV, Bansode G, Gadhia S, *et al.* The impact of chronic urticaria on the quality of life in Indian patients. *Indian J Dermatol* 2012; **57**: 110–113.
 - 31 Koti I, Weller K, Makris M, *et al.* Disease activity only moderately correlates with quality of life impairment in patients with chronic spontaneous urticaria. *Dermatology* 2013; **226**: 371–379.
 - 32 Mlynek A, Magerl M, Hanna M, *et al.* The German version of the Chronic Urticaria Quality-of-Life Questionnaire: factor analysis, validation, and initial clinical findings. *Allergy* 2009; **64**: 927–936.
 - 33 Liu JB, Yao MZ, Si AL, *et al.* Life quality of Chinese patients with chronic urticaria as assessed by the dermatology life quality index. *J Eur Acad Dermatol Venereol* 2012; **26**: 1252–1257.
 - 34 Asaumi T, Iikura K, Yanagida N, *et al.* Assessment of QOL by Urticaria Activity Score in pediatric patients with chronic urticaria. *Arerugi* 2016; **65**: 41–47 [abstract].
 - 35 Potter P, Mitha E, Barkai L, *et al.* Rupatadine is effective in the treatment of chronic spontaneous urticaria in children aged 2–11 years. *Pediatr Allergy Immunol* 2016; **27**: 55–61.
 - 36 Staubach P, Dechene M, Metz M, *et al.* High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. *Acta Derm Venereol* 2011; **91**: 557–561.
 - 37 Staubach P, Eckhardt-Henn A, Dechene 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.
 - 38 Metz M, Krull C, Hawro T, *et al.* Substance P is upregulated in the serum of patients with chronic spontaneous urticaria. *J Invest Dermatol* 2014; **134**: 2833–2836.
 - 39 Broom BC. A reappraisal of the role of ‘mindbody’ factors in chronic urticaria. *Postgrad Med J* 2010; **86**: 365–370.
 - 40 Lindsay K, Goulding J, Solomon M. Treating chronic spontaneous urticaria using a brief ‘whole person’ treatment approach: a proof-of-concept study. *Clin Transl Allergy* 2015; **5**: 40.
 - 41 Church MK, Weller K, Stock P. Chronic spontaneous urticaria in children: itching for insight. *Pediatr Allergy Immunol* 2011; **22**(1 Pt 1): 1–8.
 - 42 Maurer M, Church MK, Marsland AM, *et al.* Questions and answers in chronic urticaria: where do we stand and where do we go? *J Eur Acad Dermatol Venereol* 2016; **30**(Suppl 5): 7–15.
 - 43 Schmitt J, Deckert S, Alam M, *et al.* Report from the kick-off meeting of the Cochrane Skin Group Core Outcome Set Initiative (CSG-COUSIN). *Br J Dermatol* 2016; **174**: 287–295.