The benefit of complete response to treatment in patients with chronic spontaneous urticaria – CURE results

Short title: CURE results: complete control of urticaria

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Conflicts of interest

P. Kolkhir has been a speaker for Novartis and Roche. **P.A. Laires** is an employee of Novartis. **R. Asero** has been speaker and served on advisory boards for Novartis outside the submitted work. Furthermore, he has served on advisory boards or has been a speaker for Allergy Therapeutics, GSK, Hal Allergy, Lofarma, Malesci, Smart Practice, and Thermo Fisher. **M. Bizjak** has been a speaker and served on advisory boards for Novartis, outside the submitted work. **J. Dissemond** has been a speaker and advisor for Novartis outside of the submitted work.

M. B. A. van Doorn has received consulting fees or honorarium from Abbvie, Celgene, Janssen, Leo Pharma, Lilly, Novartis, Pfizer, and Sanofi, and has received grants and payment for lectures including services on speakers' bureaus from Janssen, Novartis, and Sanofi outside the submitted work. **A. Kasperska-Zajac** has been a speaker for Novartis outside the submitted work. **E. Kocatürk** has been a speaker and advisor for Novartis, Menarini and Sanofi outside the submitted work. **J. Peter** has received institutional funding from Novartis and Sanofi for clinical trials; honoraria for lectures from Sanofi, Novartis, Jansen and CSL Behring; and institutional funding for trials from Biocryst. **K. Kulthanan** is or recently was a speaker and/or advisor for Novartis, Menarini and Takeda outside the submitted work. **M. Khoshkhui** has received research grants from Abidi Pharma and has participated in educational activities for Cipla and Danone outside the submitted work. **A. Du-Thanh** is or recently was a speaker and/or advisor for Novartis, Sanofi, Biocryst and Takeda outside the submitted work. **A. Bauer** is or recently was a speaker and/or advisor for, and/or has received research funding from Abbvie, Almirall, Amgen, AstraZeneca, Biofrontera, Celldex, Lilly, L'Oreal, Genentec, Leo Pharma, Novartis, Pharvaris, Regeneron, Sanofi, Shire, and Takeda. **C. Grattan** declares the following conflict of interests Argenx, Blueprint Medicines, Celltrion, Inc., Novartis, and Sanofi. **P. Staubach** is or recently was a speaker and/or advisor for, and/or has received research funding from Abbvie, Almirall, Amgen, AstraZeneca, Biofrontera, Celldex, Genentec, Leo Pharma, Lilly, Novartis, Pharvaris, Regeneron, Sanofi, Shire, and Takeda. **L. Bouillet** reports grants and personal fees from Takeda, Biocryst, Novartis, and GSK. **A. M. Giménez-Arnau** has been a Medical Advisor for Almirall, Amgen, Celldex, FAES, Genentech, GSK, Leo Pharma, Novartis, Sanofi–Regeneron, Thermo Fisher Scientific, and Uriach Pharma. She has had research grants supported by Instituto Carlos III-FEDER, Novartis and Uriach Pharma, and has performed educational activities for Almirall, Avene, Genentech, GSK, Leo Pharma, Menarini, MSD, Novartis, Sanofi-Regeneron, and Uriach -Neucor Pharma. **M. Maurer** is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Amgen, Aralez, ArgenX, AstraZeneca, Celldex, Centogene, CSL Behring, FAES, Genentech, GI Innovation, Innate Pharma, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Roche, Sanofi/Regeneron, Third Harmonic Bio, UCB, and Uriach. **K. Weller** is or recently was a speaker and/or advisor for, and/or has received research funding from MOXIE, Novartis, Pharvaris, Shire, Takeda and Uriach. **M. Košnik , P. Salameh, T. Hawro, Magdalena Zając, C.A.S. Parisi, C.A. Ritchie, P. Tuchinda, D. Fomina, E. Kovalkova, S. Kouzegaran, N. Papapostolou, A. Kamegashira, R. Meshkova,** and **A. Vitchuk** declare no conflict of interest in relation to this work**.**

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Abbreviations:

CC, complete control; CIndU, chronic inducible urticaria; CR, Complete response; CSU, Chronic spontaneous urticaria; CU, chronic urticarial CU-Q_2oL, Chronic Urticaria Quality of Life Questionnaire; CURE, Chronic Urticaria Registry; DLQI, Dermatology Life Quality Index; FU, follow-up; GA, global assessment; HRQoL, health-related quality of life; IQR, interquartile range; ORa, adjusted odds ratio;

PhyGA, physician global assessment; PRO, Patient-reported outcome; sgAH, second-generation antihistamine; SPSS, Statistical Package for the Social Sciences; UAS7, weekly Urticaria Activity Score; UCT, urticaria control test

Abstract

Background and Objective

Chronic spontaneous urticaria (CSU) is a distressing disease. We report real-world data from the global Chronic Urticaria Registry (CURE) about associations between various CSU states and sleep impairment, plus important health-related quality of life (HRQoL) outcomes and compared different methods to assess CSU states.

Methods

CURE data were collected at baseline and 6-monthly follow-ups (FU). Assessments included CSU states using the urticaria control test (UCT), weekly Urticaria Activity Score (UAS7) and physician global assessment (PhyGA) of treatment response. Complete response to treatment (CR, UAS7=0), complete control of disease (CC, UCT=16) and PhyGA=CR was assessed, plus the Dermatology Life Quality Index and the Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL) sleep domain.

Results

Overall, 2078 patients were included. At baseline, 9.8%, 17.9% and 42.3% of patients had UCT=16, UAS7=0, or PhyGA=CR, respectively, which increased at FU1 and FU2. Patients with higher UCT scores had better sleep and HRQoL. Presence of angioedema without wheals, episodic disease, omalizumab treatment, and male sex were associated with CC (p<0.05). Among 469 patients who achieved CC or CR, 16.4% (n=77) showed CC or CR with all three instruments. Agreement between UCT=16 and UAS7=0 measurements was moderate (κ=0.581), but poor between UCT=16 and PhyGA=CR (κ=0.208).

Conclusions

Few patients had CR/CC of their CSU at baseline entry. Disease control strongly related to good sleep and better HRQoL; therefore, it is important to aim for CR in CSU treatment. Patient-reported UCT and UAS7 assessments demonstrated a more accurate measurement of CSU state versus physician assessments.

Highlights

What is already known about this topic?

The negative impacts of Chronic Spontaneous Urticaria (CSU) reach far beyond the skin, affecting many aspects of patients' health-related quality of life (HRQoL). Consequently, urticaria guidelines recommend to "treat the disease until it is gone".

What does this article add to our knowledge?

Disease control correlates with sleep, HRQoL, and patient clinical benefits. Angioedema, episodic disease, male sex, and omalizumab treatment predict CSU complete control. Patient-reported outcomes (PROs) are more accurate than physician assessments for evaluating CSU.

How does this study impact current management guidelines?

The predictors of disease complete control and the correlation between CSU level and sleep and HRQoL should be considered by clinicians' aiming for complete disease resolution, and PROs are recommended to evaluate patient disease control.

1. INTRODUCTION

Chronic spontaneous urticaria (CSU) is a distressing skin condition of long duration and an estimated point prevalence of 2.6% globally.[1,2] CSU has no definitive triggers,[3] and owing to this unpredictable, sudden and recurrent nature, some patients feel that they are not in control of their life.[4] Thus, the negative impacts of CSU affect many aspects of patients' health-related quality of life (HRQoL), including mental health, emotional wellbeing and sleep.[5-9] Sleep interference includes difficulties falling asleep, lack of concentration and awakenings during the night.[10] CSU can also impact daily activities and work productivity.[8,11,12]

The EAACI/GA²LEN/EuroGuiDerm/APAAACI urticaria guideline[3] states that first-line treatment for CU should be a non-sedating, standard-dosed, second-generation antihistamine (sgAH). However, a systematic review reported that the majority of CSU symptoms are not resolved with standard doses of sgAH, and even with up-dosing (i.e. second-line treatment), over a third of patients remain symptomatic.[13] It is therefore important to aim for a complete response to treatment (CR, defined as a weekly Urticaria Activity Score [UAS7] of 0), as recommended in the current urticaria guideline ('treat the disease until it is gone').[3]

Currently, limited real-world information exists on how different levels of disease activity and disease control impact HRQoL and sleep impairment in patients with CSU. Data suggest that patients who no longer develop wheals or itch, (UAS7=0), achieve lower rates of sleep interference and better HRQoL.[14] It is unclear whether no impact versus minimal impact and complete control versus well-controlled disease correlate with a clinically relevant difference from the patients' perspective. Moreover, the real-world predictors of achieving CSU complete control and normal HRQoL have not been well-defined.

Therefore, we utilised real-world data from the Chronic Urticaria Registry (CURE), the first global disease registry for patients with chronic urticaria (CU).[15] CURE was set up to enhance medical knowledge and understanding of CU, particularly its symptom patterns, triggers and risk factors, co-morbidities, burden on patients' HRQoL, response to treatments, and healthcare costs in patients in the healthcare system.

In the current analysis, data from CURE were used to evaluate baseline patient characteristics and the association between CSU states, sleep impairment and HRQoL outcomes.

2. METHODS

2.1 Study design and patients

CURE is a prospective, international, multicentre, observational registry, with no prespecified closure date or sample size. Data are collected by physician-reported and/or patient-reported questionnaires at baseline and then at 6-month interval follow-up (FU) visits on an ongoing basis.

Inclusion criteria have been described previously.[15] Briefly, patients must have physician-diagnosed CU, be under the care of a physician who has provided written informed consent to participate in the CURE. For the current analysis, patients diagnosed with CSU as their predominant form of urticaria, who were ≥12 years old on the day of inclusion and had been assessed with the urticaria control test (UCT) were selected.

Data were collected from 40 European countries, Asia, the Middle East, Africa, Oceania, and Latin America, most of them being GA^{2}LEN Urticaria Centers of Reference and Excellence (UCAREs;[16] see **Table E1**).[17]

2.2 Data collection and analysis

Physician and patient questionnaires differ only in the wording, aimed at the respective user. CURE is open to every physician experienced in treating CU.[18]

The baseline questionnaire focuses on patient demographics, disease history, symptoms, triggers, risk factors, co-morbidities, therapies and healthcare utilisation. FU questionnaires focus on symptoms, treatments and healthcare utilisation since the last consultation. Both the baseline and FU patient questionnaires include the UCT and items to assess disease activity via the UAS7,[3,19,20] and impact on HRQoL via the Dermatology Life Quality Index (DLQI)[21,22] and the Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL).[19,23,24] Data are entered into the registry by the treating physician or medical staff, via a secure webpage.

2.3 Outcome measures

In this analysis, baseline and FU visits were examined; data were retrieved in March 2021. CSU disease state was recorded using three different measurements. Once-daily reported UAS7[25] results of any week from the last 4 weeks were recorded in the CURE electronic case report form. The scores were grouped into CSU activity bands: UAS7=0, complete response (no urticaria activity); UAS7=1–6, minimal disease activity; UAS7=7–15, mild activity; UAS7=16–27, moderate activity; UAS7=28–42, severe activity.[26]

The UCT is a validated instrument for assessing urticaria control during the past 4 weeks, with 4 questions, each using a 5-point Likert scale.[19,27] Outcomes are banded as follows: UCT<12, poorly controlled CSU; UCT≥12, well-controlled CSU. For this analysis, we further banded the UCT≥12 range into UCT=12–13, well-controlled CSU (lower end); UCT=14–15, well-controlled CSU (upper end); UCT=16, completely controlled CSU. The rationale for this was that a 3-point difference in the UCT score provides a clinically meaningful change for the patient.[28]

The physician global assessment (PhyGA) of treatment response was documented in CURE with the categories 'complete response' ≥90% (symptom reduction), 'partial response' (<90% symptom reduction) and 'no response' (no symptom reduction).

Sleep disturbance was documented with a yes or no question (global assessment [GA] sleep) and with the sleep domain of the CU-Q_2oL.[24]

The following definitions were applied in this analysis: complete response (CR) was UAS7=0 and complete control (CC) was UCT=16 or PhyGA=CR.

2.4 Statistical analysis

Statistical analyses and visualisation were performed using Statistical Package for the Social Sciences (SPSS version 25.0; IBM Corp, New York, USA; all tables), R (R Foundation for Statistical Computing) and Python (version 3.7; Python Software Foundation). Normality was assessed using the Kolmogorov-Smirnov test. Non-parametric data are reported as median with the interquartile range (IQR). Categorical data are reported as a percentage and n/N (n=number of patients with outcome, N=total number of patients in group). Missing data were handled using complete case analysis assuming data were missing completely at random based on Little's test. The outcomes were analysed using the Spearman correlation, a binomial regression (ENTER method) and the Friedman's two-way analysis of variance by ranks. Cohen's κ was used to test the level of agreement between UCT=16, UAS7=0 and PhyGA=CR. We performed a post hoc analysis replacing missing values using expectation-maximisation approach, which showed a similar level of agreement between the three tools compared to complete case analysis. Categorical variables were compared using the chi-square test of homogeneity or Fisher's exact test (post hoc analyses involved pairwise comparisons using the z-test of two proportions or multiple Fisher's exact tests with a Bonferroni correction). Continuous variables with >2 groups were compared using the Kruskal-Wallis test with pairwise comparisons and Bonferroni correction. P values <0.05 were considered significant.

2.5 Ethics

The CURE was approved in 2014 by the Ethics Committee of the Charité – Universitätsmedizin Berlin, Germany (reference EA1/146/14); all contributing sites obtained ethic committee approvals prior to joining the CURE registry. Patient data may be entered into the registry only if patients have provided written informed consent to participate, or if <18 years, their guardian provides consent.

3. RESULTS

3.1 Few patients with CSU have complete control of their disease upon baseline entry into CURE

In total, 2078 patients met the inclusion criteria for this analysis (**Fig. E1**), 27.6% (573/2078) were male, and the median age was [IQR]: 43.0 [32.0–56.0] years. Baseline UCT scores of ≥12 (well-controlled CSU) were reported by 30.1% (625/2078) of patients and 9.8% (203/2078) had UCT=16 (CC; **Table 1**).

At baseline, 32.4% (389/1201) of patients reported a UAS7≤6 (indicating minimal disease activity) and 17.9% (215/1201) had UAS7=0. A PhyGA CR was reported in 42.3% (775/1833), a partial response in 47.0% (862/1833) and no response in 10.7% (196/1833) of patients.

At baseline, patients with UCT=16 had the longest disease duration (median 28.5 months), the highest proportion of male patients (36.9%; 75/203), patients with angioedema without wheals (10.8%; 22/203) and the lowest rate of concomitant chronic inducible urticaria (CIndU, 19.5%; 38/195) compared with patients in other UCT categories. Across the different UCT groups, patients with UCT=16 had the lowest use of standard or up-dosed sgAH treatment and the highest use of omalizumab treatment versus the other UCT bands (33.3% vs 7.3%–15.4%; **Table 1**).

3.2 Complete control of CSU at baseline entry is associated with better quality of life and sleep

Patients with higher UCT scores at baseline had better HRQoL (measured by DLQI and CU-Q_2oL) and sleep (measured by CU-Q_2oL-sleep domain and GA sleep). (**Table 2, Fig. 1A** and **B**); patients in the poorly controlled group (UCT<12) were affected the most (**Table 2**). Further, sleep impairment (GA sleep) generally was more common if patients had a lower UCT: 59.5% (800/1,345; UCT<12), 22.4% (59/263; UCT=12–13), 16.9% (22/130; UCT=14–15), and 19.1% (33/173; UCT=16; **Table 2**).

Similarly, when analysed by UAS7 bands, patients with CR of CSU (UAS7=0) had lower impairment of HRQoL and sleep according to DLQI, CU-Q_2oL and CU-Q_2oL-sleep domain compared with those with UAS7=28–42 (**Table 2, Fig. 1A** and **B**). Higher baseline UAS7 correlated with higher scores for DLQI, CU-Q_2oL and CU-Q_2oL-sleep domain (**Fig. E2**).

Patients with UCT=16 or UAS7=0 had better sleep and better HRQoL compared with patients in the UCT<12 and UAS7=28–42 bands (**Fig. 1A** and **B**, **Table 2**). Apart from the CU-Q_2oL sleep domain, other HRQoL outcomes (CU-Q_2oL total score and DLQI) were significantly improved in the UCT=16 patient group versus other bands. A statistically significant difference in the frequency of sleep impairment was seen between the UCT=16 versus UCT<12 groups, and UAS7=0 versus UAS7=16–27 and UAS7=28–42 groups (p<0.05 for all).

Similarly, when analysed by PhyGA, patients with CR had lower impairment in HRQoL and sleep according to the DLQI, CU-Q_2oL and CU-Q_2oL-sleep domain compared with a partial response and non-response (**Fig. E3**).

3.3 Presence of angioedema without wheals, episodic disease, male sex and treatment with omalizumab are associated with complete control of CSU

At baseline, patients with UCT=16 had a stronger association with angioedema without wheals (adjusted odds ratio [ORa]=5.84; p=0.003), male sex (ORa=1.71; p=0.006), and treatment with omalizumab (ORa=3.41; p<0.001). The use of sgAHs, especially at high doses, was less frequent among patients with higher control of CSU (ORa=0.14; p<0.001); this is also true for elevated leukocytes (ORa=0.38; p=0.044, **Fig. 2A**).

In patients with UAS7=0, episodic disease (ORa=2.10; p<0.001) and omalizumab use (ORa=2.50; p=0.017) were associated with CR (UAS7=0). Contrarily, anxiety (ORa=0.31; p=0.005), sgAH at high doses (2- to 4-fold, ORa=0.14–0.44; p<0.05) and systemic steroids (ORa=0.19; p=0.014) were less frequently found among this patient group **(Fig. 2B).**

3.4 Frequency of disease control increases over time but may not be sustained

Overall, 26.8% (557/2078) of patients had FU1 data, and 12.4% (257/2078) also had FU2 data. In general, the proportion of patients with UCT=16 at baseline increased at FU1 and FU2 (9.8% [203/2078; baseline] versus 18.9% [105/557; FU1] and 21.4% [55/257; FU2]) (**Fig. 3** and **Table E2**). At both FU visits, patients who had poorly controlled disease at baseline experienced an increase in disease control rates over time (**Fig. 3**).

Of the 203 patients who had UCT=16 at baseline, disease control was assessed in 47 patients at FU1 and 17 at FU2. At FU1, 51.1% (24/47) and 27.7% (13/47) of patients who had UCT=16 at baseline still had completely controlled and well-controlled disease, respectively. In 21.3% (10/47) of patients who had UCT=16 at baseline, CSU became poorly controlled. At FU2, 47.1% (8/17) and 50.0% (18/36) of patients who had UCT=16 at baseline and FU1, respectively, still had CC.

In total, 43 of the 215 patients who had, UAS7=0 at baseline were assessed for disease activity at FU1 and 24 at FU2. At FU1, 62.8% (27/43) of patients who had UAS7=0 at baseline still were symptom-free. At FU2, 54.2% (13/24) and 58.1% (25/43) of patients who had UAS7=0 at baseline and FU1, respectively, were still symptom-free.

3.5 Level of urticaria control is best assessed with patient-reported outcome measures

Of the total population analysed, 52.4% (1089/2078) of patients were assessed with all three tools used in this analysis (UCT, UAS7 and PhyGA). Overall, 43.1% (469/1089) of patients achieved CR based on one or more of the tools used in this analysis. Only 16.4% (77/469) of patients had simultaneous UCT=16, UAS7=0 and PhyGA=CR assessments, indicating that less than one-fifth of

patients were fully aligned between patient-reported outcomes and the physician's assessment (**Fig. 4**). Less than 0.5% (2/469) of patients had UCT=16, 4.9% (23/469) had UAS7=0 and 58.0% (272/469) had PhyGA=CR confirmed only by the respective method but not by the other methods.

Of the patients with UCT=16, UAS7=0 and PhyGA=CR, 77.8% (77/99), 40.7% (77/189) and 17.7% (77/434), respectively, also had CR or CC as assessed by two other methods. There was moderate agreement between UCT=16 and UAS7=0 (κ=0.581, $p<0.0005$) and poor agreement between UCT=16 and PhyGA=CR (κ=0.208, $p<0.0005$).

4. DISCUSSION

The real-world CU registry CURE offers important information about patients treated in daily healthcare practice. In the current analysis, we specifically report the burden on patients' HRQoL, the level of disease control and factors associated with achieving CC in patients with CSU.

The characteristics of the population at baseline in CURE were consistent with those reported for patients with CSU in randomised controlled trials in terms of the average age (43 years) and the percentage of female patients included (72%).[29,30] Our analysis showed high levels of poorly controlled disease, with only around one in ten patients having CC of their disease at baseline when self-assessed using the UCT. The level of patients who had CR or CC varied, however, depending on the method of assessment used (range, 9.8%–42.3% [when assessed by a physician]), with the patients assigning themselves worse scores.

Group comparisons (logistic regression analyses) showed that patients whose CSU was completely controlled (UCT=16) at baseline entry were more often males and had lower usage of sgAHs (licensed doses [32.8%] and up-dosed [14.4%]) compared with the poorly controlled group. This indicates that many poorly controlled patients could have refractory disease and are unresponsive to the current EAACI/GA²LEN/EuroGuiDerm/APAAACI-recommended first-line treatment.[3] Many patients with CSU are refractory to sgAHs treatment, with a systematic review reporting that around 39% of patients are unresponsive to standard doses.[13] Another real-world questionnaire-based study reported that 36.5% of patients experienced insufficient symptom control with their medication.[7] Together, these data indicate an unmet need in patients with poorly controlled CSU.

Those patients who had CC of their CSU had better sleep and significantly better HRQoL. Patients with symptomatic CSU have disturbed sleep,[31,32] partly because pruritus intensity is exacerbated at night.[33] Sleep and HRQoL are strongly connected,[34] and this was also observed in the present study; patients who had better sleep and less sleep impairment also had a better quality of life, as shown by their DLQI. The UCT and UAS7 bands correlated with sleep quality and HRQoL. This

stresses the importance of treating patients with CSU until their symptoms are resolved as not achieving CR or CC could have a direct impact on many aspects of the patients' lives.

Sleep disturbance is drastically underappreciated by physicians in patients with CSU as a burdensome and clinically relevant consequence of the disease. Studies have shown that sleep quality improves when CSU symptoms are treated pharmacologically,[31,35] and when medication is discontinued, CSU symptoms have been shown to return alongside sleep problems.[32] A significant difference in the frequency of sleep impairment was observed in our study in UCT=16 versus UCT<12, UAS7=0 versus UAS7=16–27, and UAS7=0 versus UAS7=28–42 groups, which is likely to correspond to a clinically relevant improvement for the patient. A statistically significant improvement was seen in overall HRQoL measured in patients with CC versus the other bands (excluding sleep). A change in the DLQI total score between 2.2 and 3.1 points is clinically relevant from a patients' perspective[36]; changes in DLQI of at least 2.2 were observed between UAS7=0 and the other UAS7 bands (from 0 [UAS7=0] to 13 [UAS7=28–42]).

The frequency of patients with UCT=16 or UAS7=0 at baseline generally increased over time, but the reasons behind this remain unclear; this should be investigated in further studies. One possibility is that CSU improves because patients are under the care of physicians in CURE centres and therefore have access to appropriate treatments. An alternative explanation is that CSU has the potential for changes in activity and natural remission, with a recent review showing that up to 47% of patients achieve remission within the first year.[37]

Limited literature exists for factors associated with the CC or clinical remission of CSU;[38] this is one of the first studies to analyse predictors of CC or CR. The results of the regression analyses showed that angioedema without wheals, episodic disease, male sex, and treatment with omalizumab were all factors that were linked to achieving a fully controlled disease state. However, patients with episodic disease have sign- and symptom-free intervals, which could influence disease status indices depending on when they were collected. The use of sgAHs, especially at higher doses, and systemic steroids was more frequently found among patients with lower control of CSU symptoms,[3] while anxiety was associated with higher disease activity according to UAS7. These results corroborate the overall low response rates to sgAHs in CSU symptom control.[13] It is important that treating physicians consider this information before starting patients with CSU on any new therapies.

CSU disease status can be assessed using different methods that are patient- or physician-based. Results from CURE show that UCT and UAS7 correlate with each other; however, there is a clear misalignment between patient self-assessments and physician-reported assessments. Only 18% of participants who were recorded to have a PhyGA=CR also had UCT=16 or UAS7=0, whereas 77.8% of patients with UCT=16 also had CR or CC, as assessed by two other methods. These differences could

be due to a variety of reasons, such as physicians being more optimistic about their patients' CSU status or the fluctuating nature of the disease, which requires continuous assessment using patient-reported outcome measures. We recommend that patient assessments or a combination of tools should be favoured over physician-only assessments. Using only the latter may lead to an inaccurate underestimation of the true disease status and the humanistic burden CSU has on daily life and might also lead to undertreatment of individual cases.

Along with the obvious limitations of an observational registry, CURE has some specific limitations. Most participating physicians were specialised in the field of urticaria, so the registry is likely to contain data from patients with more severe and more antihistamine-refractory disease than the average urticaria patient seen in general practice. Medications were not randomly assigned to patients, and their association with control of CSU is only suggestive of real-life situations, with no implication of causality.

A 'complete response' describes the response to treatment, and within CURE, it is noted that 7.5% of patients were not receiving any treatment at baseline entry. Some patients with UCT=16 or UAS7=0 had a high DLQI score (low quality of life); possible reasons include an association with other concomitant diseases, side effects of treatment, feeling burdened with CSU, the burden of having to take daily medication or anticipation anxiety of symptom recurrence, which should be investigated further. UAS7 is not a suitable tool for assessing angioedema without wheals; specific questionnaires should be used to assess this, such as the Angioedema Activity Score[39] or Angioedema Control Test[39,40]; therefore, results including angioedema should be interpreted with caution. CURE has an unavoidable selection bias because participating physicians are not obliged to register all their patients consecutively. Recall bias and, importantly, attrition bias are likely as patients who are lost from the registry are most likely to be patients whose symptoms improved the most.

A large amount of data were missing for FU1 and FU2. Also, data entry into the registry occurs after the original data collection, the accuracy and completeness of which has not yet been audited. Indeed, several patients' data were not entered at FU visits, and this is not a mandatory requirement. Moreover, despite CURE being a worldwide registry, specific geographical regions are better represented than others, with a notable portion of patients thus far coming from Europe and Central Asia. These results may therefore not be generalisable to patients in other regions of the world. Finally, we do not have full data to track the medication use of patients enrolled in the CURE and therefore do not know if patients continued to take the same treatment. Caution therefore needs to be exercised when interpreting the results. Nevertheless, observational registries offer invaluable evidence on real-world effectiveness and safety outside of the confined setting of a randomised controlled trial.

5. CONCLUSIONS

In conclusion, the data presented here suggest that, in agreement with previous research,[41,42] low percentages of patients have CC of their CSU, with <10% reaching this goal in CURE at baseline. However, patients who are refractory to antihistamines would be more likely to attend specialised urticaria centres participating in CURE. There is a vastly unmet need in patients with CSU. The level of disease control strongly correlated with improvements in sleep and HRQoL and clinically relevant benefits to patients. Only by achieving complete or nearly CC of their CSU could patients fully eliminate negative impacts on their sleep and HRQoL, which supports the EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline-recommended treatment aim of achieving complete resolution of the disease.[3] The presence of angioedema without wheals, episodic disease, male sex and omalizumab treatment were associated with CC of CSU. Further, patient-reported outcomes demonstrate a more accurate measurement of the CSU disease status and of the true impact of CSU on the patients' lives compared with physician assessments; therefore, these should be used wherever possible.

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AUTHOR CONTRIBUTIONS

All authors have contributed to the acquisition, analysis, or interpretation of data; have revised each draft for critical input; and have approved the final manuscript to be published.

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Table 1: Clinical and demographic characteristics of patients with CSU at baseline entry to CURE by disease control band

Parameter		UCT=16 Group 1	UCT=14–15 Group 2	UCT=12–13 Group 3	UCT<12 Group 4	*p* value[a]	Pairwise comparisons between the groups[a]	Total
% (n/total)		9.8 (203/2078)	7.0 (145/2078)	13.3 (277/2078)	69.9 (1,453/2078)	–	–	2078
Age in years, median [IQR] N=2044		46.0 [34.0–58.8]	45.0 [32.0–59.0]	46.0 [33.5–59.0]	42.0 [32.0–55.0]	0.001	1 vs 4	43.0 [32.0–56.0]
CSU disease duration in months, median [IQR]		28.5 [16.0–79.5]	26.0 [11.0–80.0]	27.0 [12.0–90.2]	21.0 [7.0–64.0]	–	–	24.0 [8.0-70.0]
Gender, % (n/total) Male		36.9 (75/203)	24.8 (36/145)	31.4 (87/277)	25.8 (375/1453)	0.003	1 vs 4	27.6 (573/2078)
Disease duration in months, median [IQR] N=2044		28.5 [16.0–79.0]	26.0 [11.0–79.5]	27.0 [12.0–89.5]	21.0 [7.0–64.0]	<0.0005	1 vs 4	24.0 [8.0–70.0]
Disease pattern, % (n)	Wheals only	31.5 (64/203)	48.3 (70/145)	41.6 (114/274)	35.0 (501/1433)	<0.0005	1 vs 2	36.4 (749/2055)
	Angioedema without wheals	10.8 (22/203)	5.5 (8/145)	2.9 (8/274)	2.2 (31/1433)		1 vs 3,4	3.4 (69/2055)
	Both	57.6 (117/203)	46.2 (67/145)	55.5 (152/274)	62.9 (901/1433)		ns	60.2 (1237/2055)
Concomitant CIndU, % (n/total)		19.5 (38/195)	27.8 (40/144)	21.8 (57/262)	25.8 (359/1393)	0.130	ns	24.8 (494/1994)
Current treatment,[b] % (n)	sgAHs licensed dose	32.8 (66/201)	46.2 (66/143)	44.4 (122/275)	35.4 (503/1420)	<0.005	ns	37.1 (757/2039)
	sgAHs up-dosed	14.4 (29/201)	23.8 (34/143)	23.6 (65/275)	35.6 (506/1420)	<0.0005	1 vs 4	31.1 (634/2039)
	Omalizumab	33.3 (67/201)	15.4 (22/143)	13.1 (36/275)	7.3 (104/1420)	<0.0005	1 vs 2,3,4	11.2 (229/2039)
	Ciclosporin	1.0 (2/201)	0.7 (1/143)	0.0 (0/275)	0.6 (8/1420)	–	–	0.5 (11/2039)
	Other treatment	7.5 (15/201)	5.6 (8/143)	10.5 (29/275)	14.4 (204/1420)	–	–	12.6 (256/2039)

Baseline data are shown in this table. [a]Categorical variables were compared using the chi-square test of homogeneity or Fisher's exact test (post hoc analyses involved pairwise comparisons using the z-test of two proportions or multiple Fisher's exact tests with a Bonferroni correction). Continuous variables were compared using the Kruskal-Wallis test with pairwise comparisons and Bonferroni correction. The 'p-value' column shows a p-value for difference in proportions between groups. In the 'pairwise' column, statistically significant differences between the UCT=16 group and other groups are included (p-values and comparisons of groups other than the UCT=16 are not shown). [b]7.5% of patients (152/2039) were not receiving any treatment at baseline.

CIndU, chronic inducible urticaria; IQR, interquartile range; n, number of patients; ns, non-significant; sgAH, second-generation antihistamine; UCT, urticaria control test.

606 **Table 2**: **Comparison of HRQoL and sleep scores between CSU patients with different levels of disease control (UCT) and disease activity (UAS7)**

	UCT				UAS7				
Parameter	**16**	**14–15**	**12–13**	**<12**	**0**	**1–6**	**7–15**	**16–27**	**28–42**
DLQI, median [IQR]	0.0 [0.0–0.0]	1.0 [0.0–2.0]	2.0 [1.0–5.0]	9.0 [5.0–14.0]	0.0 [0.0–1.0]	3.0 [1.0–6.0]	4.0 [2.0–8.0]	8.0 [5.0–14.0]	13.0 [11.0–17.0]
CU-Q_2oL, median [IQR]	0.0 [0.0–8.7]	9.8 [2.2–14.1]	15.2 [6.5–23.9]	39.1 [27.2–52.2]	8.7 [0.0–22.3]	20.7 [6.8–31.5]	26.1 [14.1–38.0]	37.0 [27.2–48.9]	48.9 [38.6–60.9]
Sleep domain of CU-Q_2oL, median [IQR]	0.0 [0–23.4]	6.2 [0.0–25.0]	18.8 [0.0–37.5]	50.0 [25.0–68.8]	6.3 [0.0–37.5]	12.5 [0.0–37.5]	31.3 [3.1–56.3]	43.8 [25.0–62.5]	56.3 [43.8–75.0]
GA sleep, % with sleep impairment (n/total)[a]	19.1 (33/173)	16.9 (22/130)	22.4 (59/263)	59.5 (800/ 1,345)	22.9 (47/ 205)	25.1 (42/167)	32.5 (76/234)	58.3 (133/228)	83.8 (269/321)

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608 [a]Statistically significant difference in frequency of sleep impairment (GA sleep) was seen only in UCT=16 versus UCT<12, UAS7=0 versus UAS7=16–27 and UAS7=0 versus UAS7=28-42 groups

609 (p<0.05 for these comparisons).

610 CU-Q_2oL, Chronic Urticaria Quality of Life questionnaire; DLQI, Dermatology Life Quality Index; GA, global assessment; IQR, interquartile range; n, number of patients; UAS7, weekly Urticaria

611 Activity Score; UCT, urticaria control test.

Figures

Figure 1: Patients with completely controlled CSU or absence of wheals and itch have better sleep and clinically relevant better HRQoL

A, Boxplots show the comparisons between the UCT=16 group of CSU patients (blue colour) and other groups. B, Boxplots show the comparisons between the UAS7=0 group of CSU patients (green colour) and other groups. Boxplots are displayed as median and interquartile ranges. Outliers are shown by circles. Data were analysed by using the Kruskal-Wallis test with pairwise comparisons and Bonferroni correction.

****p<0.0001, ***p<0.001, **p<0.01, *p<0.05.

DLQI, Dermatology Life Quality Index; CU-Q_2oL, Chronic Urticaria Quality of Life questionnaire; UAS7, weekly Urticaria Activity Score; UCT, urticaria control test; Sleep, Sleep domain of Chronic Urticaria Quality of Life questionnaire.

Figure 2: Binomial regression analyses (A: UCT=16, B: UAS7=0)

Readings to the right of 1.0 are associated with CC (A) or CR (B).

AE, angioedema; BMI, body mass index; CI, confidence interval; CC, complete control; CR, complete response; CRP, C-reactive protein; CSU, chronic spontaneous urticaria; ESR, erythrocyte sedimentation rate; ORa, adjusted odds ratio; sgAH, second-generation antihistamines; SD, standard dose.

Figure 3: Frequency of complete response and non-complete response over time measured using UCT and UAS7

The line plot depicts UCT (n=228) and UAS7 (n=181) scores at BL, FU1 (median duration in months [IQR]: 5 [4-6]) and FU2 (12 [11-15]) assessed in the same patients over time. Lines are mean values and filled areas are standard deviations. Total scores for UCT are 0–16 and for UAS7 are 0–42. Within the groups differences were evaluated with related-samples Friedman's two-way analysis of variance by ranks. *P*-value for A and B is <0.0001. (A) UCT, mean ranks, BL vs FU1 vs FU2: 1.60 vs 2.10 vs 2.30. (B) UAS7, mean ranks, BL vs FU1 vs FU2: 2.38 vs 1.95 vs 1.68. (C) Represents the percentage of CSU patients who had UAS=0 and UCT=16 at BL, FU1 and FU2. (D) Represents the percentage of CSU patients who had incomplete UAS7 and UCT responses (UAS7>0 and UCT<16) at BL, FU1 and FU2.

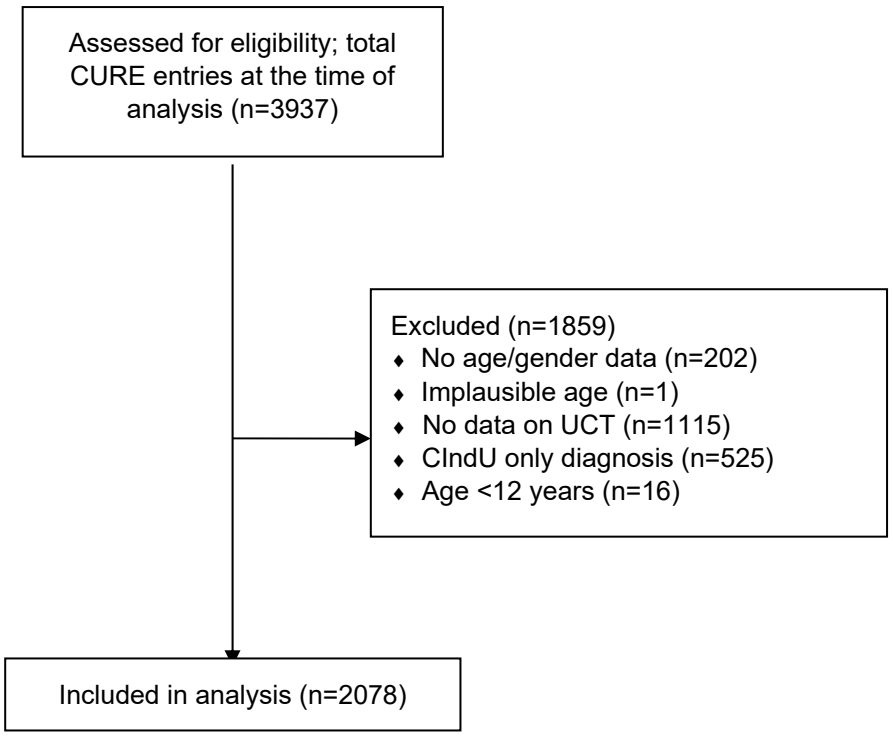
BL, baseline; FU1, follow-up 1; FU2, follow-up 2; IQR, interquartile range; UAS7, weekly Urticaria Activity Score; UCT, urticaria control test.

Figure 4: Venn diagram of overlap of UAS7=0 and UCT=16 and PhyGA=complete response

The diagram shows the numbers of 469 patients who had a complete response based on UCT=16 only (n=2, 0.4%), UAS7=0 only (n=23, 4.9%), PhyGA=CR only (n=272, 58.0%), all three tools (n=77, 16.4%), UCT=16 and UAS7=0 (n=10, 2.1%), UCT=16 and PhyGA=CR (n=10, 2.1%), and UAS7=0 and PhyGA=CR (n=75, 16.0%).

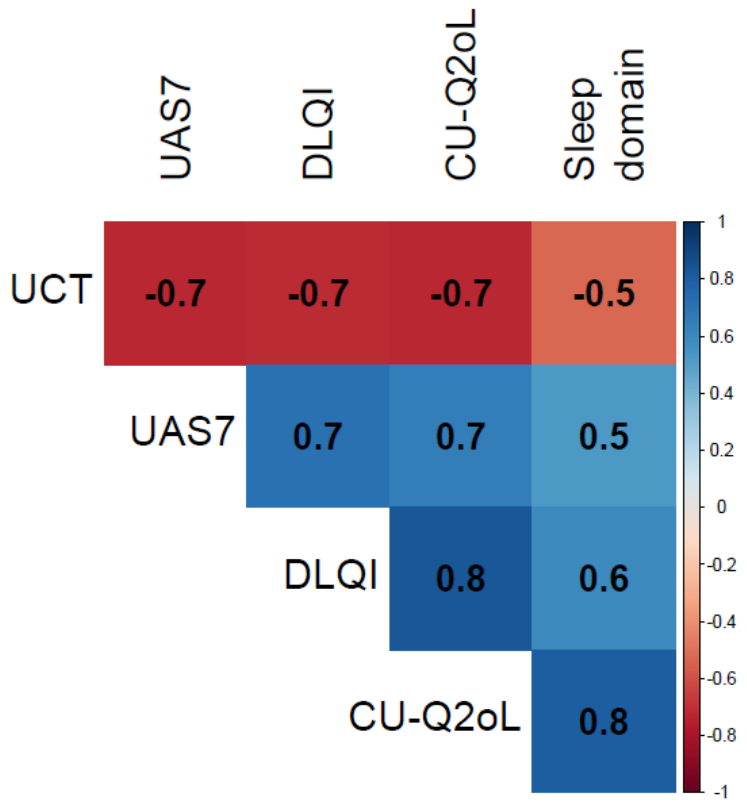
PhyGA=CR, physician global assessment=complete control; UAS7, weekly Urticaria Activity Score; UCT, urticaria control test.

Figure E1: Patient disposition



The figure shows the patients who were assessed for eligibility from CURE, and those who were excluded because they did not meet the eligibility criteria.

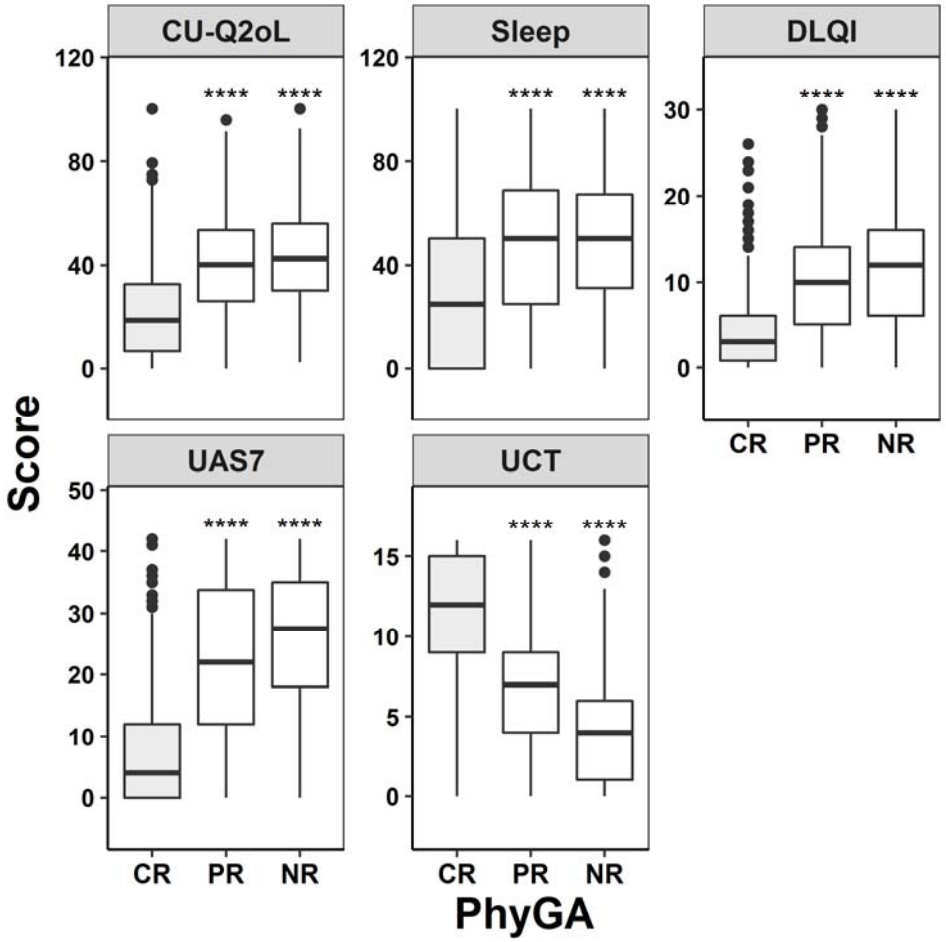
Figure E2: Correlogram of CSU patients' disease control, activity, quality of life and sleep scores



Correlations between continuous variables are measured by Spearman rho. The significance level was set to less than 0.05. Only statistically significant correlations are shown. The shading in the correlation plot represents the degree of association. Positive correlations are displayed in blue and negative correlations in red.

DLQI, Dermatology Life Quality Index; CU-Q_2oL, Chronic Urticaria Quality of Life questionnaire; UAS7, weekly Urticaria Activity Score; UCT, urticaria control test.

Figure E3. Patients with completely controlled CSU, measured using PhyGA, have better sleep and clinically relevant better HRQoL



Boxplots show the comparisons between the PhyGA=CR group of CSU patients (grey) and other groups.

****p <0.0001, ****p*<0.001, ***p*<0.01, **p*<0.05.

CR, complete response; DLQI, Dermatology Life Quality Index; CU-Q_2oL, Chronic Urticaria Quality of Life questionnaire; NR, no response; PhyGA, physician's global assessment; PR, partial response; UAS7, weekly Urticaria Activity Score; UCT, urticaria control test.

Table E1: Participating countries in CURE

Country	CURE centre	Included in analysis/total (as of May 2021)
United Arab Emirates	Abu Dhabi	70/99
Argentina	Bahía Blanca	2/6
	Buenos Aires	26/100
Brazil	Salvador-BA	22/27
	São Paulo	4 /31
China	Guangzhou	12/16
	Suzhou	24 /33
Columbia	Medellín	32/43
Germany	Allergie-Centrum-Charite	155/605
	Elbe Kliniken Buxtehude	5/10
	Uniklinikum Essen	64/66
	UMC-Mainz	68/82
	Uniklinikum Dresden	65/90
	Uniklinikum Jena	19/22
Spain	Barcelona	76/280
France	CHU Grenoble	21/93
	Metz	3/17
	Montpellier	78/115
	Paris (aphp)	11/16
Greece	Athens	38/52
India	Navi Mumbai	3/33
Iran	Mashhad	114/135
	Teheran	19/23
Japan	Hiroshima	25/52
	Kobe	2/6
	Yokohama	30/47
Macedonia	Skopje	2/2
	Hospital Espanol	3/3
The Netherlands	Rotterdam	45/74
Poland	Lublin	1/24
	Poznan	5/7
	Zabrze	272/490
Portugal	Porto	14/19
Russia	Kazan	8/20
	Moscow	1/46
	Moscow | CSH 52	374/483
	Smolensk	62/104
Slovenia	Golnik	83/159
Thailand	Bangkok	127/145
Turkey	Istanbul	8/12
	Koç University Hospital	27/45
South Africa	Cape Town	58/87
Total n of entries included in the analysis		**2078**

Table E2: Frequency of CC/CR over time

	BL, % (n)	FU1		FU2		
		% (n)	% (n) of BL	% (n)	% (n) of BL	% (n) of FU1
UCT=16	9.8 (203/2078)	18.9 (105/557)	51.1 (24/47*)	21.4 (55/257)	47.1 (8/17*)	50.0 (18/36¥)
UCT<16	90.2 (1875/2078)	81.1 (452/557)	84.1 (429/510≠)	78.6 (202/257)	80.4 (193/24≠)	84.3 (161/191∞)
UAS=0	17.9 (215/1201)	26.9 (116/431)	62.8 (27/43*)	30.6 (68/222)	54.2 (13/24*)	58.1 (25/43¥)
UAS>0	82.1 (986/1201)	73.1 (315/431)	78.8 (256/325≠)	69.4 (154/222)	74.1 (137/185≠)	78.6 (114/145∞)

*Patients who had UCT=16 or UAS7=0 at BL; ≠Patients who had UCT<16 or UAS7>0 at BL; ¥Patients who had UCT=16 or UAS7=0 at FU1; ∞Patients who had UCT<16 or UAS7>0 at FU1. Data shown as percentage of patients who had CR at baseline or FU1.

BL, baseline; CC, complete control; CR, complete response; FU1, follow-up 1; FU2, follow-up 2; PhyGA=CR, physician global assessment=complete control; UAS7, weekly Urticaria Activity Score; UCT, urticaria control test.