

Original Article

The Benefit of Complete Response to Treatment in Patients With Chronic Spontaneous Urticaria—CURE Results

Pavel Kolkhir, MD^{a,b}, Pedro A. Laires, PhD^{c,d,e}, Pascale Salameh, MPH, PhD^{a,f,g,h}, Riccardo Asero, MDⁱ, Mojca Bizjak, MD, PhD^j, Mitja Košnik, MD, PhD^{j,k}, Joachim Dissemond, MD^l, Martijn van Doorn, MD, PhD^{m,n}, Tomasz Hawro, MD^o, Alicja Kasperska-Zajac, MD, PhD^{p,q}, Magdalena Zajac, MD^{p,q}, Emek Kocatürk, MD^{a,b,r}, Jonny Peter, MD, PhD^{s,t}, Claudio A.S. Parisi, MD^u, Carla A. Ritchie, MD^u, Kanokvalai Kulthanan, MD^v, Papapit Tuchinda, MD^v, Daria Fomina, MD^{w,x}, Elena Kovalkova, MD^w, Maryam Khoshkhui, MD^y, Samaneh Kouzegaran, MD^z, Niki Papapostolou, MD^{aa}, Aurélie Du-Thanh, MD, PhD^{ab}, Akiko Kamegashira, MD^{ac}, Raisa Meshkova, MD, DSc^{ad}, Alexander Vitshuk, MD^{ad}, Andrea Bauer, MD^{ae}, Clive Grattan, MD^{af}, Petra Staubach, MD^{ag}, Laurence Bouillet, MD, PhD^{ah}, Ana M. Giménez-Arnau, MD, PhD^{ai}, Marcus Maurer, MD^{a,b}, and Karsten Weller, MD^{a,b}
 Berlin, Essen, Lübeck, Dresden, and Mainz, Germany; Basel, Switzerland; Lisbon, Portugal; Nicosia, Cyprus; Paderno Dugnano, Italy; Golnik and Ljubljana, Slovenia; Rotterdam and Leiden, the Netherlands; Zabrze, Poland; Istanbul, Turkey; Cape Town, South Africa; Buenos Aires, Argentina; Bangkok, Thailand; Moscow and Smolensk, Russian Federation; Mashhad, Iran; Athens, Greece; Montpellier and La Tronche, France; Hiroshima, Japan; London, United Kingdom; Barcelona, Spain

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 without wheals, 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.

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

^aInstitute of Allergology, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

^bFraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany

^cNovartis Pharma AG, Basel, Switzerland

^dNOVA National School of Public Health, Public Health Research Center, NOVA University Lisbon, Lisbon, Portugal

^eComprehensive Health Research Center, NOVA University Lisbon, Lisbon, Portugal

^fDepartment of Primary Care and Population Health, University of Nicosia Medical School, Nicosia, Cyprus

^gSchool of Medicine, Lebanese American University, Lebanon

^hInstitut National de Santé Publique, Epidémiologie Clinique et Toxicologie (INSPECT-LB), Lebanon

ⁱAmbulatorio di Allergologia, Clinica san Carlo, Paderno Dugnano, Italy

^jDivision of Allergy, University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia

^kMedical Faculty, University of Ljubljana, Ljubljana, Slovenia

^lDepartment of Dermatology, Venerology and Allergology, University of Essen, Essen, Germany

^mDepartment of Dermatology, Erasmus MC, Rotterdam, the Netherlands

ⁿCentre for Human Drug Research, Leiden, the Netherlands

^oDepartment of Dermatology, Allergology and Venereology, Institute and Comprehensive Center for Inflammation Medicine, University Medical Center Schleswig-Holstein, Lübeck, Germany

^pEuropean Center for Diagnosis and Treatment of Urticaria/Angioedema (GA2LEN UCARE Network), Zabrze, Poland

^qDepartment of Clinical Allergology, Urticaria Center of Medical University of Silesia, Zabrze, Poland

^rDepartment of Dermatology, Koç University School of Medicine, Istanbul, Turkey

^sDivision of Allergy and Clinical Immunology, Department of Medicine, University of Cape Town, Cape Town, South Africa

^tAllergy and Immunology Unit, University of Cape Town Lung Institute, Cape Town, South Africa

^uAllergy Section, Italian Hospital of Buenos Aires, Buenos Aires, Argentina

Abbreviations used

CC- Complete control
CR- Complete response
CSU- Chronic spontaneous urticaria
CU- Chronic urticaria
CU-Q2oL- 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
UAS7- Weekly Urticaria Activity Score
UCT- Urticaria Control Test

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 were assessed, plus the

Dermatology Life Quality Index and the Chronic Urticaria Quality-of-Life Questionnaire (CU-Q2oL) 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. The presence of angioedema without wheals, episodic disease, omalizumab treatment, and male sex were associated with CC ($P < .05$). Among 469 patients who achieved CC or CR, 16.4% ($n = 77$) showed CC or CR with all 3 instruments. Agreement between UCT = 16 and UAS7 = 0 measurements was moderate ($\kappa = 0.581$), but poor between UCT = 16 and PhyGA = CR ($\kappa = 0.208$).
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. © 2022 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;■:■-■)

Key words: Chronic spontaneous urticaria; Complete control/complete response to treatment; CURE registry; Patient-reported outcomes; Quality of life

^vDepartment of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

^wCenter of Allergy and Immunology, Clinical State Hospital 52, Moscow Healthcare Ministry, Moscow, Russian Federation

^xDepartment of Clinical Immunology and Allergology, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation

^yAllergy Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

^zDepartment of Allergy and Clinical Immunology, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran

^{aa}Allergy Unit "D. Kalogeromitros", 2nd Dpt. Dermatology and Venereology, National and Kapodistrian University of Athens, "Attikon" University Hospital, Athens, Greece

^{ab}Dermatology Department, University of Montpellier, Montpellier, France

^{ac}Department of Dermatology, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

^{ad}Department of Clinical Immunology and Allergology, Smolensk State Medical University, Smolensk, Russian Federation

^{ae}Department of Dermatology, University Allergy Center, University Hospital Carl Gustav Carus, Technical University, Dresden, Germany

^{af}St John's Institute of Dermatology, Guy's Hospital, London, United Kingdom

^{ag}Department of Dermatology, University Medical Center Mainz, Mainz, Germany

^{ah}CREAK, Internal Medicine, Centre Hospitalier Universitaire Grenoble Alpes, La Tronche, France

^{ai}Department of Dermatology, Hospital Del Mar, IMIM, Universitat Pompeu Fabra, Barcelona, Spain

Chronic Urticaria Registry (CURE) has been funded by the Urticaria Network e.V. (a German nonprofit organization), the European Academy of Dermatology and Venereology (proposal number 2014-013), Novartis, and Uriach. Sponsors have not been involved in the design or implementation of CURE.

Conflicts of interest: P. Kolkhir has been a speaker for Novartis and Roche. P. A. Laire 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. Dissemmond has been a speaker and advisor for Novartis, outside of the submitted work. M. 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 conflicts of interest: 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. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication September 27, 2022; revised XXX, XXXX; accepted for publication November 6, 2022.

Available online ■■

Corresponding author: Karsten Weller, MD, Institute of Allergology, Charité—Universitätsmedizin Berlin, Hindenburgdamm 30, 12203 Berlin, Germany. E-mail: karsten.weller@charite.de.

2213-2198

© 2022 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2022.11.016>

Chronic spontaneous urticaria (CSU) is a distressing skin condition of long duration and an estimated point prevalence of up to 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 well-being, 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 guideline³ states that first-line treatment for chronic urticaria (CU) should be a nonsedating, 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, 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 (CC) versus well-controlled disease correlate with a clinically relevant difference from the patients' perspective. Moreover, the real-world predictors of achieving CSU CC and normal HRQoL have not been well defined.

Therefore, we used real-world data from the CU Registry (CURE), the first global disease registry for patients with CU.¹⁵ CURE was set up to enhance medical knowledge and understanding of CU, particularly its symptom patterns, triggers and risk factors, comorbidities, burden on patients' HRQoL, response to treatments, and health care costs in patients in the health care 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.

METHODS

Study design and patients

CURE is a prospective, international, multicenter, 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 and 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 GA²LEN Urticaria Centers of Reference and Excellence¹⁶ (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).¹⁷

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, comorbidities, therapies, and health care utilization. FU questionnaires focus on symptoms, treatments, and health care utilization 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 CU Quality-of-Life Questionnaire (CU-Q2oL).^{19,23,24} Data are entered into the registry by the treating physician or medical staff via a secure webpage.

Outcome measures

In this analysis, baseline and FU visits were examined; data were retrieved in March 2021. CSU disease state was recorded using 3 different measurements. Once-daily reported UAS7²⁵ 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, CR (no urticaria activity); UAS7 = 1-6, minimal disease activity; UAS7 = 7-15, mild activity; UAS7 = 16-27, moderate activity; and 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); and 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 "CR" ($\geq 90\%$ 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-Q2oL.²⁴

The following definitions were applied in this analysis: CR was UAS7 = 0, PhyGA = CR and CC was UCT = 16.

Statistical analysis

Statistical analyses and visualization were performed using Statistical Package for the Social Sciences (SPSS version 25.0; IBM Corp, New York, NY; all tables), R (R Foundation for Statistical Computing), and Python (version 3.7; Python Software Foundation). Normality was assessed using the Kolmogorov-Smirnov test. Nonparametric 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 that data were missing completely at random based on Little's test. The outcomes were analyzed using the Spearman correlation, a binomial regression (ENTER method), and the Friedman 2-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

TABLE I. 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*	Pairwise comparisons between the groups*	Total
% (n/total)	9.8 (203/2078)	7.0 (145/2078)	13.3 (277/2078)	69.9 (1453/2078)	—	—	2078
Age (y), 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]	.001	1 vs 4	43.0 [32.0-56.0]
CSU disease duration (mo), 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]
Sex, % (n/total) male	36.9 (75/203)	24.8 (36/145)	31.4 (87/277)	25.8 (375/1453)	.003	1 vs 4	27.6 (573/2078)
Disease duration (mo), 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]	<.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)	<.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)	.130	ns	24.8 (494/1994)
Current treatment,† % (n)							
sgAHs licensed dose	32.8 (66/201)	46.2 (66/143)	44.4 (122/275)	35.4 (503/1420)	<.005	ns	37.1 (757/2039)
sgAHs updosed	14.4 (29/201)	23.8 (34/143)	23.6 (65/275)	35.6 (506/1420)	<.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)	<.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.

CIndU, Chronic inducible urticaria; CSU, chronic spontaneous urticaria; CURE, Chronic Urticaria Registry; IQR, interquartile range; ns, nonsignificant; sgAH, second-generation antihistamine; UCT, Urticaria Control Test.

*Categorical variables were compared using the χ^2 test of homogeneity or Fisher's exact test (*post hoc* analyses involved pairwise comparisons using the z-test of 2 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 the difference in proportions between the 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).

†7.5% of patients (152 of 2039) were not receiving any treatment at baseline.

TABLE II. Comparison of HRQoL and sleep scores between patients with CSU with different levels of disease control (UCT) and disease activity (UAS7)

Parameter	UCT					UAS7				
	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-Q2oL, 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-Q2oL, median [IQR]	0.0 [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)*	19.1 (33/173)	16.9 (22/130)	22.4 (59/263)	59.5 (800/1345)	22.9 (47/205)	25.1 (42/167)	32.5 (76/234)	58.3 (133/228)	83.8 (269/321)	

CSU, Chronic spontaneous urticaria; CU-Q2oL, Chronic Urticaria Quality-of-Life Questionnaire; DLQI, Dermatology Life Quality Index; GA, global assessment; HRQoL, health-related quality of life; IQR, interquartile range; UAS7, weekly Urticaria Activity Score; UCT, Urticaria Control Test.

*Statistically significant difference in frequency of sleep impairment (GA sleep) was seen only in the UCT = 16 vs UCT <12, UAS7 = 0 vs UAS7 = 16-27, and UAS7 = 0 vs UAS7 = 28-42 groups ($P < .05$ for these comparisons).

replacing missing values using the expectation-maximization approach, which showed a similar level of agreement between the 3 tools compared with complete case analysis. Categorical variables were compared using the χ^2 test of homogeneity or Fisher's exact test (*post hoc* analyses involved pairwise comparisons using the z-test of 2 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 <.05 were considered significant.

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 before 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 parent or legal guardians provide consent.

RESULTS

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 (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org), 27.6% (573 of 2078) were male, and the median [IQR] age was 43.0 [32.0-56.0] years. Baseline UCT scores of ≥ 12 (well-controlled CSU) were reported by 30.1% (625 of 2078) of patients, and 9.8% (203 of 2078) had UCT = 16 (CC; Table I).

At baseline, 32.4% (389 of 1201) of patients reported a UAS7 ≤ 6 (indicating minimal disease activity) and 17.9% (215 of 1201) had UAS7 = 0. A PhyGA CR was reported in 42.3% (775 of 1833), a partial response in 47.0% (862 of 1833), and no response in 10.7% (196 of 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 of 203), patients with angioedema without wheals (10.8%; 22 of 203), and the lowest rate of concomitant chronic inducible urticaria (19.5%; 38 of 195) compared with patients in other UCT categories. Across the different UCT groups, patients with UCT = 16 had the lowest use of standard or upodused sgAH treatment and the highest use of omalizumab treatment versus the other UCT bands (33.3% vs 7.3%-15.4%; Table I).

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-Q2oL) and sleep (measured by CU-Q2oL sleep domain and GA sleep) (Table II, Figure 1); patients in the poorly controlled group (UCT <12) were affected the most (Table II). Further, sleep impairment (GA sleep) generally was more common if patients had a lower UCT: 59.5% (800 of 1345; UCT <12), 22.4% (59 of 263; UCT = 12-13), 16.9% (22 of 130; UCT = 14-15), and 19.1% (33 of 173; UCT = 16; Table II).

Similarly, when analyzed by UAS7 bands, patients with CR of CSU (UAS7 = 0) had lower impairment of HRQoL according to DLQI and CU-Q2oL, and sleep (CU-Q2oL sleep domain) compared with those with UAS7 = 28-42 (Table II,

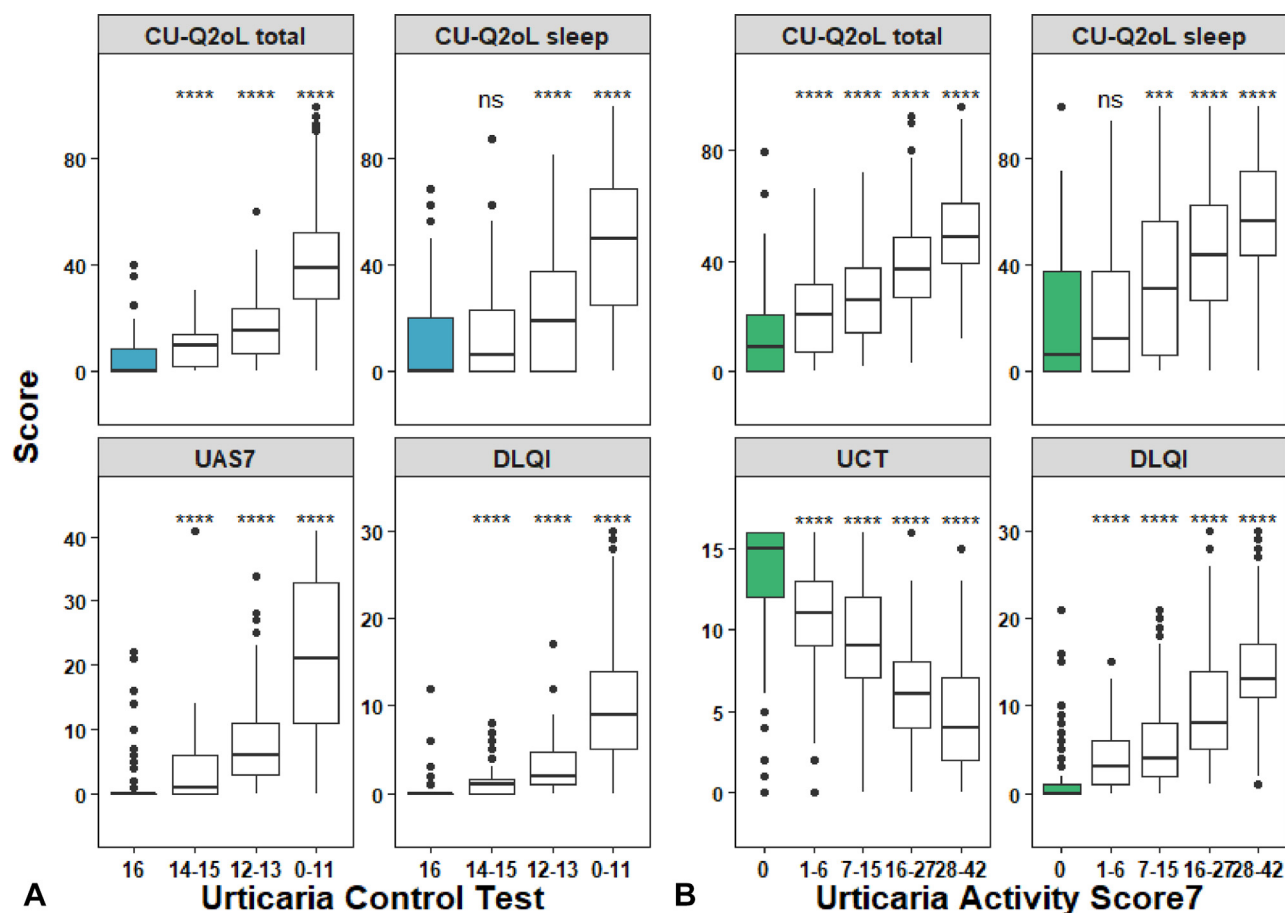


FIGURE 1. Patients with completely controlled chronic spontaneous urticaria (CSU) or the absence of wheals and itch have better sleep and clinically relevant better health-related quality of life. **(A)** Boxplots show the comparisons between the UCT = 16 group of patients with CSU (blue color) and other groups. **(B)** Boxplots show the comparisons between the UAS7 = 0 group of patients with CSU (green color) and other groups. Boxplots are displayed as median and interquartile ranges. Outliers are shown by circles. Data were analyzed by using the Kruskal-Wallis test with pairwise comparisons and Bonferroni correction. **** $P < .0001$, *** $P < .001$. *CU-Q2oL*, Chronic Urticaria Quality of Life Questionnaire; *DLQI*, Dermatology Life Quality Index; *ns*, nonsignificant; *Sleep*, sleep domain of Chronic Urticaria Quality of Life Questionnaire; *UAS7*, weekly Urticaria Activity Score; *UCT*, Urticaria Control Test.

Figure 1). Higher baseline UAS7 correlated with higher scores for DLQI, CU-Q₂oL, and CU-Q₂oL sleep domain (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org).

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 (Figure 1, Table II). Apart from the CU-Q₂oL sleep domain, other HRQoL outcomes (CU-Q₂oL 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 ($P < .05$ for all).

Similarly, when analyzed by PhyGA, patients with CR had lower impairment in HRQoL and sleep according to the DLQI, CU-Q₂oL, and CU-Q₂oL sleep domain compared with a partial response and nonresponse (Figure E3, available in this article's Online Repository at www.jaci-inpractice.org).

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; $P = .003$), male sex (ORa = 1.71; $P = .006$), and treatment with omalizumab (ORa = 3.41; $P < .001$). The use of sgAHs, especially at high doses, was less frequent among patients with higher control of CSU (ORa = 0.14; $P < .001$); this is also true for elevated leukocytes (ORa = 0.38; $P = .044$, Figure 2, A).

In patients with UAS7 = 0, episodic disease (ORa = 2.10; $P < .001$) and omalizumab use (ORa = 2.50; $P = .017$) were associated with CR (UAS7 = 0). Contrarily, anxiety (ORa = 0.31; $P = .005$), sgAH at high doses (2- to 4-fold, ORa = 0.14-0.44; $P < .05$), and systemic steroids (ORa = 0.19; $P = .014$) were less frequently found among this patient group (Figure 2, B).

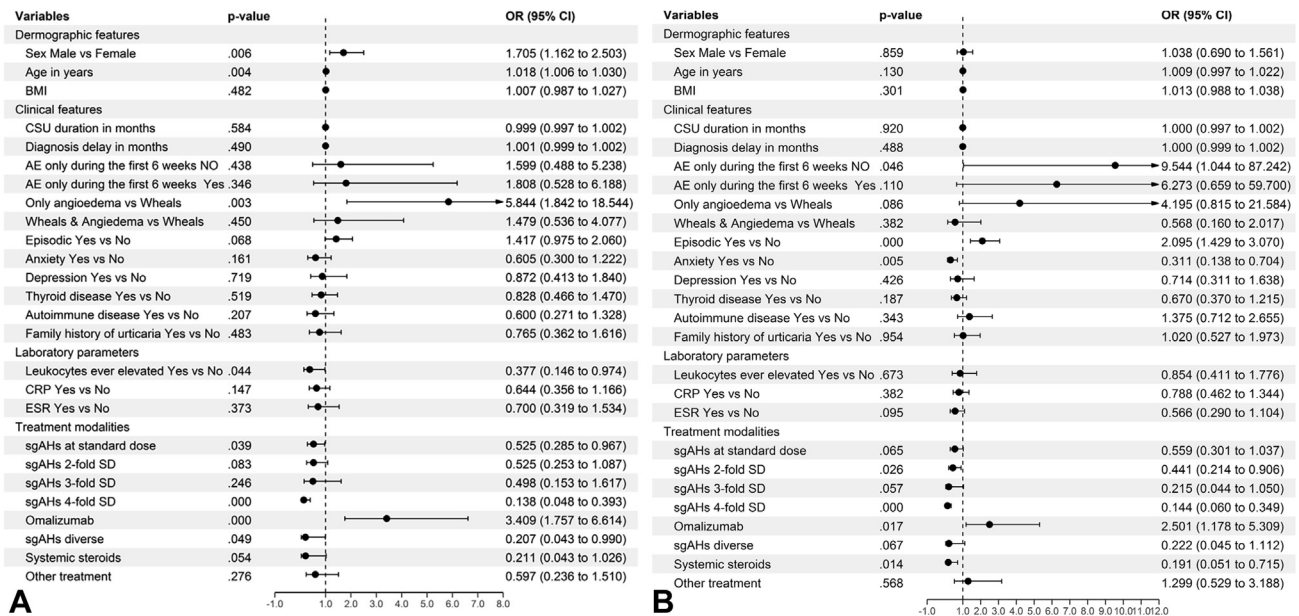


FIGURE 2. Binomial regression analyses (A: UCT = 16, B: UAS7 = 0). Readings to the right of 1.0 are associated with (A) CC or (B) CR. AE, Angioedema; BMI, body mass index; CC, complete control; CI, confidence interval; CR, complete response; CRP, C-reactive protein; CSU, chronic spontaneous urticaria; ESR, erythrocyte sedimentation rate; ORa, adjusted odds ratio; sgAH, second-generation antihistamines; SD, standard dose; UAS7, weekly Urticaria Activity Score; UCT, Urticaria Control Test.

Proportion of complete disease control increases over time but may not be sustained

Overall, 26.8% (557 of 2078) of patients had FU1 data, and 12.4% (257 of 2078) also had FU2 data. In general, the proportion of patients with UCT = 16 at baseline increased at FU1 and FU2 (9.8% [203 of 2078; baseline] vs 18.9% [105 of 557; FU1] and 21.4% [55 of 257; FU2]) (Figure 3 and Table E2, available in this article's Online Repository at www.jaci-inpractice.org). At both FU visits, patients who had poorly controlled disease at baseline experienced an increase in disease control rates over time (Figure 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 of 47) and 27.7% (13 of 47) of patients who had UCT = 16 at baseline still had completely controlled and well-controlled disease, respectively. In 21.3% (10 of 47) of patients who had UCT = 16 at baseline, CSU became poorly controlled. At FU2, 47.1% (8 of 17) and 50.0% (18 of 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 of 43) of patients who had UAS7 = 0 at baseline still were symptom-free. At FU2, 54.2% (13 of 24) and 58.1% (25 of 43) of patients who had UAS7 = 0 at baseline and FU1, respectively, were still symptom-free.

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

Of the total population analyzed, 52.4% (1089 of 2078) of patients were assessed with all 3 tools used in this analysis (UCT, UAS7, and PhyGA). Overall, 43.1% (469 of 1089) of patients achieved CR based on 1 or more of the tools used in this analysis.

Only 16.4% (77 of 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 PROs and the physician's assessment (Figure 4). Less than 0.5% (2 of 469) of patients had UCT = 16, 4.9% (23 of 469) had UAS7 = 0, and 58.0% (272 of 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 of 99), 40.7% (77 of 189), and 17.7% (77 of 434), respectively, also had CR or CC as assessed by 2 other methods. There was a moderate agreement between UCT = 16 and UAS7 = 0 ($\kappa = 0.581$, $P < .0005$) and a poor agreement between UCT = 16 and PhyGA = CR ($\kappa = 0.208$, $P < .0005$).

DISCUSSION

The real-world CU registry CURE offers important information about patients treated in daily health care 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 randomized 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 1 in 10 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 showed that patients whose CSU was completely controlled (UCT = 16) at baseline entry were more

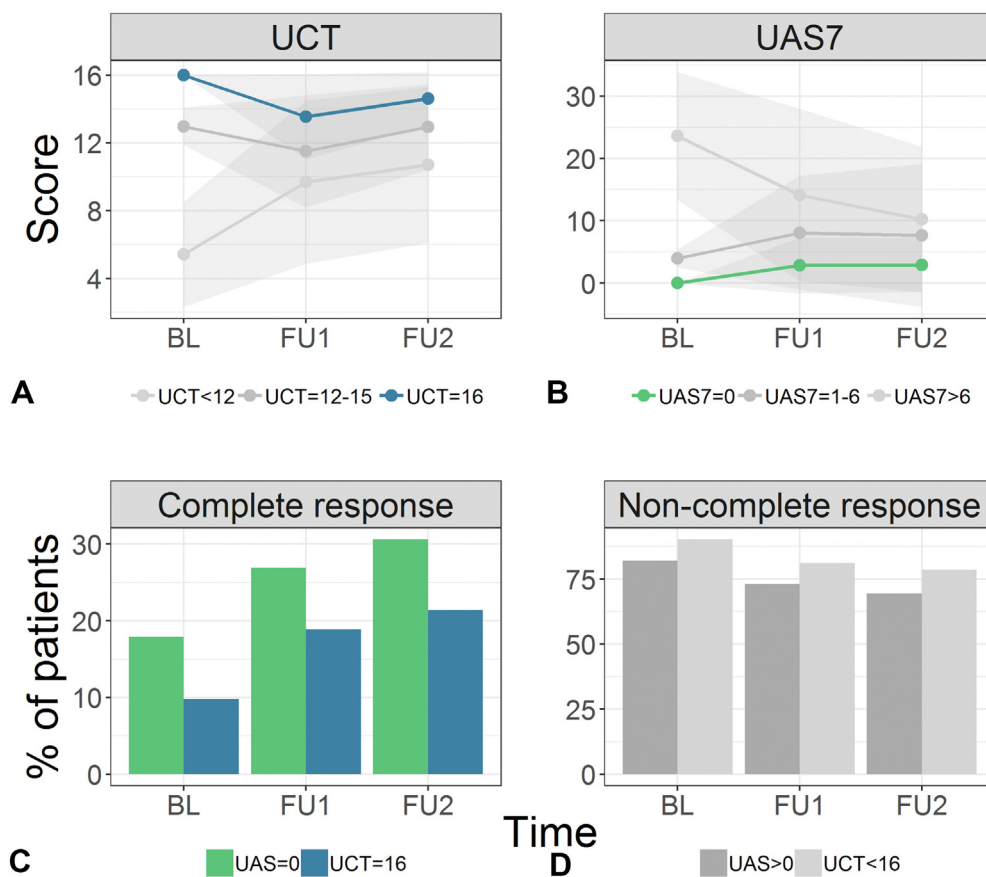


FIGURE 3. Frequency of complete response and noncomplete response over time measured using Urticaria Control Test (UCT) and weekly Urticaria Activity Score (UAS7). The line plot depicts UCT ($n = 228$) and UAS7 ($n = 181$) scores at baseline (BL), follow-up 1 (FU1) (median duration in months [IQR]: 5 [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 2-way analysis of variance by ranks. The P value for A and B is $<.0001$. (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) Percentage of patients with CSU who had UAS = 0 and UCT = 16 at BL, FU1, and FU2. (D) Percentage of patients with CSU who had incomplete UAS7 and UCT responses (UAS7 > 0 and UCT < 16) at BL, FU1, and FU2. *IQR*, Interquartile range.

often males and had lower usage of sgAHs (licensed doses [32.8%] and updosed antihistamines [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 the 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 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]).

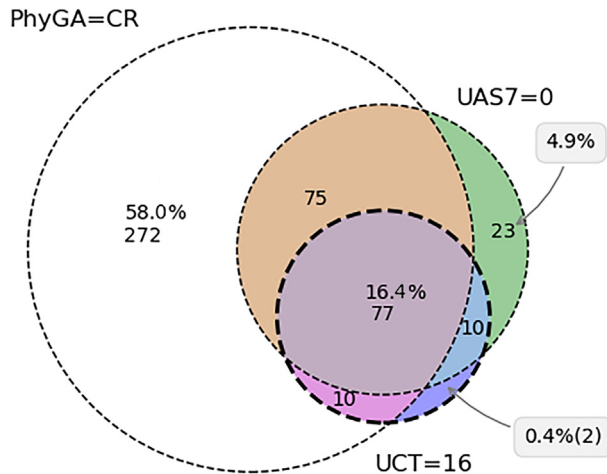


FIGURE 4. Venn diagram of overlap of UAS7 = 0 and UCT = 16 and PhyGA = complete response. The diagram shows the numbers of 469 patients who had a complete response based on UCT = 16 only (n = 2, 0.4%), UAS7 = 0 only (n = 23, 4.9%), PhyGA = CR only (n = 272, 58.0%), all 3 tools (n = 77, 16.4%), UCT = 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.

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 centers 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 analyze the 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 whereas 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 any new therapies on patients with CSU.

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 2 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 PRO measures. We recommend that patient assessments or a combination of tools should be favored 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 under-treatment of individual cases.

Along with the obvious limitations of an observational registry, CURE has some specific limitations. Most participating physicians were specialized 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 "CR" 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 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 generalizable 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 randomized controlled trial.

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 specialized urticaria centers 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, PROs 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.

Acknowledgments

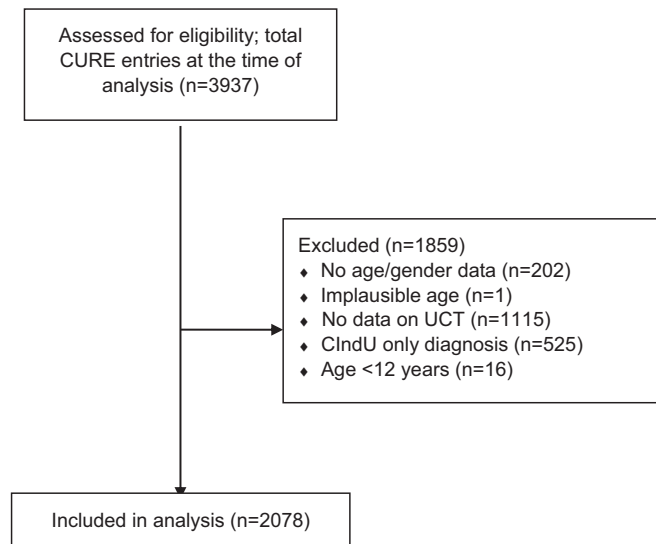
The authors thank all the participants and physicians involved in the CURE registry, and Gillian Brodie, MSc, and Linda Hassanali, PhD, of Novartis Ireland Ltd for editorial and medical writing support, which was funded by Novartis Pharma AG, Basel, Switzerland, in accordance with the Good Publication Practice (GPP3) guidelines (<http://www.ismpp.org/gpp3>).

REFERENCES

- Fricke J, Ávila G, Keller T, Weller K, Lau S, Maurer M, et al. Prevalence of chronic urticaria in children and adults across the globe: systematic review with meta-analysis. *Allergy* 2020;75:423-32.
- Zhang X, Song X, Zhang M, Li C, Huang Z, Liu B, et al. Prevalence and risk factors of chronic urticaria in China: a nationwide cross-sectional study. *Allergy* 2022;77:2233-6.
- Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy* 2022;77:734-66.
- O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997;136:197-201.
- Staubach P, Dechene M, Metz M, Magerl M, Siebenhaar F, Weller K, et al. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. *Acta Derm Venereol* 2011;91:557-61.
- Weller K, Maurer M, Grattan C, Nakonechna A, Abuzakouk M, Bérard F, et al. ASSURE-CSU: a real-world study of burden of disease in patients with symptomatic chronic spontaneous urticaria. *Clin Transl Allergy* 2015;5:29.
- Maurer M, Staubach P, Raap U, Richter-Huhn G, Baier-Ebert M, Chapman-Rothe N. ATTENTUS, a German online survey of patients with chronic urticaria highlighting the burden of disease, unmet needs and real-life clinical practice. *Br J Dermatol* 2016;174:892-4.
- Maurer M, Abuzakouk M, Bérard F, Canonica W, Oude Elberink H, Giménez-Arnau A, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. *Allergy* 2017;72:2005-16.
- Gonçalo M, Giménez-Arnau A, Al-Ahmad M, Ben-Shoshan M, Bernstein JA, Ensina LF, et al. The global burden of chronic urticaria for the patient and society. *Br J Dermatol* 2021;184:226-36.
- Yosipovitch G, Ansari N, Goon A, Chan YH, Goh CL. Clinical characteristics of pruritus in chronic idiopathic urticaria. *Br J Dermatol* 2002;147:32-6.
- Itakura A, Tani Y, Kaneko N, Hide M. Impact of chronic urticaria on quality of life and work in Japan: results of a real-world study. *J Dermatol* 2018;45:963-70.
- Weldon DR. Quality of life in patients with urticaria. *Allergy Asthma Proc* 2006;27:96-9.
- Guillén-Aguinaga S, Jáuregui Presa I, Aguinaga-Ontoso E, Guillén-Grima F, Ferrer M. Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. *Br J Dermatol* 2016;175:1153-65.
- Giménez-Arnau A, Bernstein JA, Maurer M, Staubach P, Barbier N, Hua E, et al. Complete symptom control in patients with chronic spontaneous urticaria is associated with an improvement in health-related quality of life: data from the phase 2b ligelizumab study. Paper presented at European Academy of Dermatology and Venereology (EADV 2021); September 2021; Vienna, Austria.
- Weller K, Giménez-Arnau A, Grattan C, Asero R, Mathelier-Fusade P, Bizjak M, et al. The Chronic Urticaria Registry: rationale, methods and initial implementation. *J Eur Acad Dermatol Venereol* 2021;35:721-9.
- UCARE GA2LEN, UCARE Urticaria Centers of Reference and Excellence; 2022. Accessed May 23, 2022. <https://www.ga2len-ucare.com/centers/centers>
- Maurer M, Metz M, Bindslev-Jensen C, Bousquet J, Canonica GW, Church MK, et al. Definition, aims, and implementation of GA(2) LEN Urticaria Centers of Reference and Excellence. *Allergy* 2016;71:1210-8.
- CURE. CURE Chronic Urticaria Registry; 2021. Accessed May 23, 2022. urticaria-registry.com
- Weller K, Siebenhaar F, Hawro T, Altrichter S, Schoepke N, Maurer M. Clinical measures of chronic urticaria. *Immunol Allergy Clin North Am* 2017;37:35-49.
- Mlynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? *Allergy* 2008;63:777-80.
- Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;19:210-6.
- Lewis V, Finlay AY. 10 years experience of the Dermatology Life Quality Index (DLQI). *J Invest Dermatol Symp Proc* 2004;9:169-80.
- Mlynek A, Magerl M, Hanna M, Lhachimi S, Baiardini I, Canonica GW, et al. The German version of the Chronic Urticaria Quality-of-Life Questionnaire: factor analysis, validation, and initial clinical findings. *Allergy* 2009;64:927-36.
- Baiardini I, Pasquali M, Braido F, Fumagalli F, Guerra L, Compalati E, 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;60:1073-8.
- Hawro T, Ohanyan T, Schoepke N, Metz M, Peveling-Oberhag A, Staubach P, et al. Comparison and interpretability of the available urticaria activity scores. *Allergy* 2018;73:251-5.
- Hollis K, Proctor C, McBride D, Balp MM, McLeod L, Hunter S, et al. Comparison of Urticaria Activity Score over 7 days (UAS7) values obtained from once-daily and twice-daily versions: results from the ASSURE-CSU study. *Am J Clin Dermatol* 2018;19:267-74.
- Weller K, Groffik A, Church MK, Hawro T, Krause K, Metz M, et al. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol* 2014;133:1365-72. 1372.e1-1372.
- Ohanyan T, Schoepke N, Bolukbasi B, Metz M, Hawro T, Zuberbier T, et al. Responsiveness and minimal important difference of the urticaria control test. *J Allergy Clin Immunol* 2017;140:1710-1713.e1.
- Maurer M, Giménez-Arnau AM, Sussman G, Metz M, Baker DR, Bauer A, et al. Ligelizumab for chronic spontaneous urticaria. *N Engl J Med* 2019;381:1321-32.
- Saini SS, Bindslev-Jensen C, Maurer M, Grob J, Bühl B, Basken E, Bradley MS, 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.
- Giménez-Arnau A, Maurer M, Bernstein J, Staubach P, Barbier N, Hua E, et al. Ligelizumab improves sleep interference and disease burden in patients with chronic spontaneous urticaria. *Clin Transl Allergy* 2022;12:e12121.
- Giménez-Arnau AM, Spector S, Antonova E, Trzaskoma B, Rosén K, Omachi TA, et al. Improvement of sleep in patients with chronic idiopathic/spontaneous urticaria treated with omalizumab: results of three randomized, double-blind, placebo-controlled studies. *Clin Transl Allergy* 2016;6:32.
- Spindler M, Przybyłowicz K, Hawro M, Weller K, Reidel U, Metz M, et al. Sleep disturbance in adult dermatologic patients: a cross-sectional study on prevalence, burden, and associated factors. *J Am Acad Dermatol* 2021;85:910-22.
- Lee S, Kim JH, Chung JH. The association between sleep quality and quality of life: a population-based study. *Sleep Med* 2021;84:121-6.
- Stull D, McBride D, Tian H, Gimenez Arnau A, Maurer M, Marsland A, et al. Analysis of disease activity categories in chronic spontaneous/idiopathic urticaria. *Br J Dermatol* 2017;177:1093-101.
- Shikar R, Harding G, Leahy M, Lennox RD. Minimal important difference (MID) of the Dermatology Life Quality Index (DLQI): results from patients with chronic idiopathic urticaria. *Health Qual Life Outcomes* 2005;3:36.
- Balp MM, Halliday AC, Severin T, Leonard A, Partha G, Kalra M, et al. Clinical remission of chronic spontaneous urticaria (CSU): a targeted literature review. *Dermatol Ther (Heidelb)* 2022;12:15-27.
- Stepaniuk P, Kan M, Kanani A. Natural history, prognostic factors and patient perceived response to treatment in chronic spontaneous urticaria. *Allergy Asthma Clin Immunol* 2020;16:63.
- Weller K, Donoso T, Magerl M, Aygören-Pürsün E, Staubach P, Martinez-Saguer I, et al. Development of the Angioedema Control Test-A patient-reported

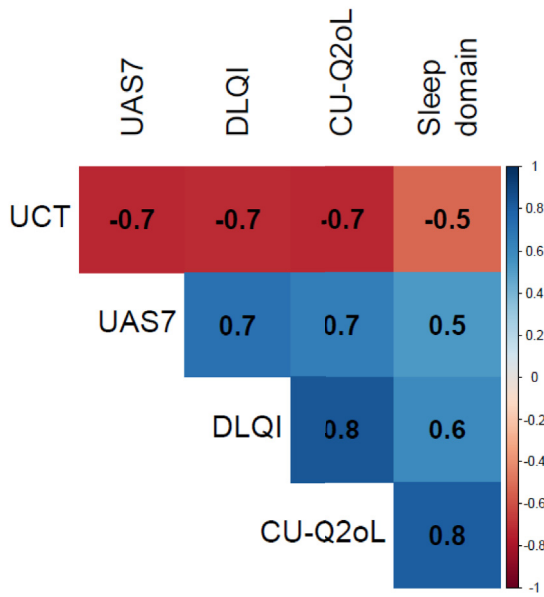
- outcome measure that assesses disease control in patients with recurrent angioedema. *Allergy* 2020;75:1165-77.
40. Weller K, Donoso T, Magerl M, Aygören-Pürsün E, Staubach P, Martinez-Saguer I, et al. Validation of the Angioedema Control Test (AECT)—a patient-reported outcome instrument for assessing angioedema control. *J Allergy Clin Immunol Pract* 2020;8:2050-2057.e4.
41. Maurer M, Weller K, Bindslev-Jensen C, Giménez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA(2)LEN task force report. *Allergy* 2011;66:317-30.
42. 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;160:633-41.

ONLINE REPOSITORY



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.

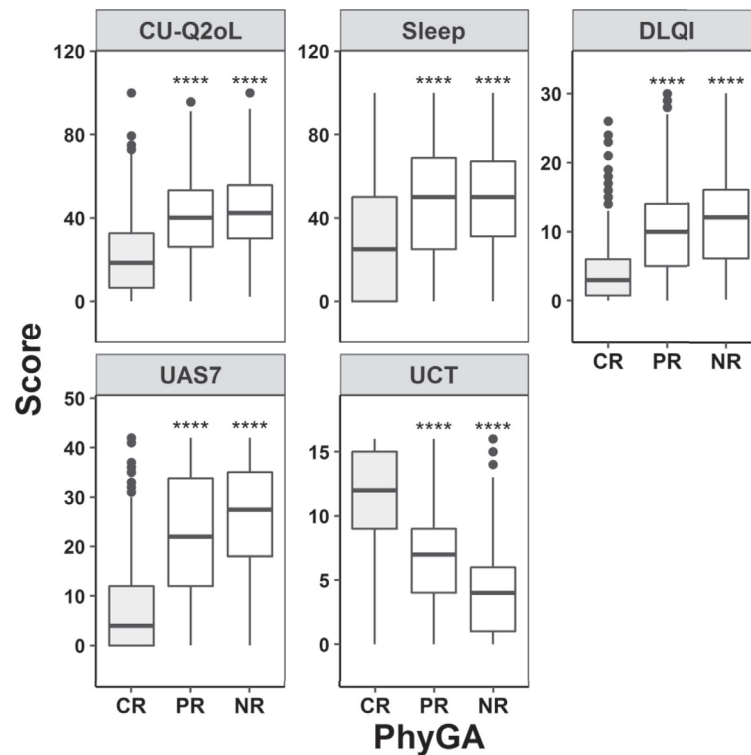
FIGURE E1. Patient disposition. The figure shows the patients who were assessed for eligibility from CURE, and those who were excluded because they did not meet the eligibility criteria. *CIndU*, Chronic inducible urticaria; *CURE*, Chronic Urticaria Registry; *UCT*, Urticaria Control Test.



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-Q2oL, Chronic Urticaria Quality of Life questionnaire; UAS7, weekly Urticaria Activity Score; UCT, urticaria control test.

FIGURE E2. Correlogram of chronic spontaneous urticaria 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 .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-Q2oL*, Chronic Urticaria Quality-of-Life Questionnaire; *UAS7*, weekly Urticaria Activity Score; *UCT*, Urticaria Control Test.



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-Q2oL, 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.

FIGURE E3. Patients with completely controlled chronic spontaneous urticaria (CSU), measured using Physician Global Assessment (PhyGA), have better sleep and clinically relevant better health-related quality of life. Boxplots show the comparisons between the PhyGA = CR group of patients with CSU (gray) and other groups. **** $P < .0001$. CR, Complete response; DLQI, Dermatology Life Quality Index; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; NR, no response; PR, partial response; UAS7, weekly Urticaria Activity Score; UCT, Urticaria Control Test.

TABLE E1. Participating countries in CURE

Country	CURE center	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 number 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§)

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; UAS, Urticaria Activity Score; UCT, Urticaria Control Test.

*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.