

Received Date : 27-Apr-2016

Revised Date : 05-Oct-2016

Accepted Date : 12-Jan-2017

Article type : Original Article-Epidemiology of Allergic Disease

H1-antihistamine-refractory chronic spontaneous urticaria: It's worse than we thought – first results of the multicenter real-life AWARE study

Marcus Maurer^{1*}, Petra Staubach^{2*}, Ulrike Raap^{3*}, Grit Richter-Huhn^{4*}, Andrea Bauer⁵, Franziska Ruëff⁶, Thilo Jakob^{7,8}, Amir S. Yazdi⁹, Vera Mahler¹⁰, Nicola Wagner¹¹, Undine Lippert¹², Uwe Hillen¹³, Andreas Schwinn¹⁴, Mario Pawlak¹⁵, Norbert Behnke¹⁶, Kamel Chaouche¹⁷ and Nadine Chapman-Rothe¹⁸

¹Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Berlin, Germany;

²Department of Dermatology, University Hospital Mainz, Mainz, Germany; ³Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany; ⁴Hautarztpraxis, Dresden, Germany; ⁵Department of Dermatology, University Allergy Center, University Hospital Carl Gustav Carus, Technical University Dresden, Germany; ⁶Department of Dermatology and Allergology, Ludwig-Maximilian University, Munich, Germany; ⁷Department of Dermatology and Allergology, Justus Liebig University, University Medical Center Gießen and Marburg, Gießen, Germany;

⁸Department of Dermatology, Medical Center - University of Freiburg, Freiburg, Germany;

⁹Department of Dermatology, University of Tübingen, Tübingen, Germany; ¹⁰Department of Dermatology, University Hospital Erlangen, Erlangen, Germany; ¹¹Department of Dermatology, Clinical Centre Darmstadt, Darmstadt, Germany; ¹²Department of Dermatology, Venereology and Allergology, University Medical Center, Georg-August-University, Göttingen, Germany;

¹³Department of Dermatology, University Hospital of Essen, University of Duisburg-Essen, Essen, Germany; ¹⁴Praxis für Dermatologie, Memmingen, Germany; ¹⁵Hautarztpraxis, Heilbad Heiligenstadt, Germany; ¹⁶Hautarztpraxis, Panketal, Germany; ¹⁷Novartis Pharma AG, Basel, Switzerland; ¹⁸Novartis Pharma GmbH, Nürnberg, Germany

*These authors have contributed equally to the manuscript

Condensed title: CSU characteristics – results of the AWARE study

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cea.12900

This article is protected by copyright. All rights reserved.

Corresponding author:

Professor Marcus Maurer,

Dpt. of Dermatology and Allergy,
Allergie-Centrum-Charité,
Charité - Universitätsmedizin Berlin,
Charitéplatz 1, D-10117 Berlin,
Germany

Tel +49 30 450 518 043

Fax +49 30 450 518 972

Email: marcus.maurer@charite.de

Abstract

Background: Most data on chronic spontaneous urticaria (CSU) originate from highly selected patient populations treated at specialized centers. Little is known about CSU patient characteristics and the burden of CSU in routine clinical practice. AWARE (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) is an ongoing global study designed to assess chronic urticaria in the real-life setting.

Objective: To describe the baseline characteristics of the first 1,539 German AWARE patients with H1-antihistamine-refractory CSU.

Methods: This prospective non-interventional study included patients (18 to 75 years) with a diagnosis of H1-antihistamine-refractory CSU for >2 months. Baseline demographic and disease characteristics, comorbidities, and pharmacological treatments were recorded. Quality of life (QoL) was assessed using the dermatology life quality index (DLQI), chronic urticaria QoL questionnaire (CU-Q₂oL), and angioedema QoL questionnaire (AE-QoL; in cases of angioedema). Previous healthcare resource utilization and sick leave data were collected retrospectively.

Results: Between March and December 2014, 1,539 patients were assessed in 256 sites across Germany. The percentage of females, mean age, and mean body mass index was 70%, 46.3 years, and 27 kg/m², respectively. The mean UCT score was 7.9, 1 in 2 patients had angioedema, and the most frequent comorbidities were chronic inducible urticaria

(CIndU; 24%), allergic rhinitis (18.2%), hypertension (18.1%), asthma (12%), and depression (9.5%). Overall, 57.6% of patients were receiving at least one pharmacological treatment including second generation H1-antihistamines (46.3%), first generation H1-antihistamines (9.1%), and corticosteroids (15.8%). The mean DLQI, total CU-Q₂oL, and total AE-QoL scores were 8.3, 36.2, and 46.8, respectively. CSU patients reported frequent use of healthcare resources, including emergency services (29.7%), general practitioners (71.9%), and additional allergists or dermatologists (50.7%).

Conclusion & Clinical Relevance: This study reveals that German H1-antihistamine-refractory CSU patients have high rates of uncontrolled disease, angioedema, and comorbid CIndU, are undertreated, have impaired QoL, and rely heavily on healthcare resources.

Introduction

Chronic urticaria (CU), one of the most frequent skin disorders, is defined as the repeated occurrence of red, swollen, itchy and sometimes painful hives (wheals), and/or angioedema (swellings in the deeper layers of the skin), for more than 6 weeks [1, 2]. CU has an estimated worldwide prevalence of approximately 1% [3], which includes spontaneous and inducible types. In chronic spontaneous urticaria (CSU), the most common type of CU, symptoms occur without a specific trigger [1, 3]. In contrast, in chronic inducible urticaria (CIndU), symptoms occur in response to specific stimuli, such as exposure to cold, heat or pressure [4]. Patients may suffer from CSU and CIndU in parallel [2].

Most previously published data on CSU patients originate from highly selected patient populations treated at specialized centers, which tend to treat patients who suffer from severe disease, and may not reflect the average patient [5, 6]. Thus, little is known about the burden of disease, the use of healthcare resources and the socio-economic burden of the majority of H1-antihistamine-refractory CSU patients treated by office-based physicians. Previous publications have shown that, despite the available S3-CU guidelines [1, 3, 7], in

routine clinical practice CU is perceived as hard to treat, cost intensive, time-consuming, and problematic [8].

Many questions remain unanswered and need to be addressed in the broader H1-antihistamine-refractory CSU population: What is the average disease activity? How frequently does angioedema occur in CSU patients? How often do CSU and CIndU occur in the same patient? Is the treatment of patients in line with the current guidelines? How are CSU patients affected in their daily lives, and what impact does CSU have on patient quality of life (QoL)? How do CSU patients use the available healthcare resources? These questions must be answered to improve the treatment and management of CSU patients in routine clinical practice.

AWARE (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) is an ongoing prospective non-interventional study (NIS) that assesses the therapy regimens, burden of disease and rates of healthcare resource utilization of H1-antihistamine-refractory CU patients treated by office-based dermatologists or specialized urticaria centers. Here, we report the baseline characteristics, disease activity, frequency of angioedema and other comorbidities, pharmacological treatment, QoL, and the rates of healthcare resource utilization of more than 1,500 German AWARE patients.

Methods

Patients and Study Design

AWARE is an ongoing prospective NIS that will follow CU patients, who are refractory to at least the approved dose of one H1-antihistamine, for two years. The present study reports on German H1-antihistamine-refractory patients who were enrolled in urticaria centers and office-based dermatological practices between March 2014 and December 2014. Urticaria centers and office-based dermatologists were initially informed about the trial via a letter;

study sponsor Medical Scientific Experts also informed urticaria centers in person. Any center or dermatologist that indicated interest in participating was subsequently visited before beginning the trial. In Germany, 56% of office-based dermatologists (IMS OneKey, The Worldwide Healthcare Professional Database) and virtually all dermatologists at urticaria centers are also allergists or allergists in training.

Patients who received a medically confirmed diagnosis of CSU that had been present for longer than 2 months, who were refractory to treatment with H1-antihistamines (evidence of failed labelled dose or up-to 4 fold labelled dose), ≥ 18 years and able to provide informed consent were eligible for inclusion in this study. Patients were excluded from the study if difficulties were anticipated with patient follow-up or if they were participating in a CU indication (or similar) clinical trial.

Patients were informed about the study, and written consent was obtained from each patient at the first visit. During the first visit, demographic data (including height, weight, age, and gender), disease activity, comorbidities, current pharmacological treatment, satisfaction with current treatment (using a visual analog scale [VAS]), and health-related QoL were assessed. Patients also reported how frequently they had missed work (sick leave) and how frequently they had visited additional healthcare resources (including emergency services; hospitalizations; general practitioners; specialized urticaria centers; dermatologists; allergists; ear, nose, and throat specialists; dentists; and alternative practitioners) since their urticaria symptoms first appeared.

Patient-reported outcomes

Four patient-reported outcomes (PROs: urticaria control test [UCT], dermatology QoL index [DLQI], chronic urticaria QoL questionnaire [CU-QoL] and, for patients with angioedema, the angioedema QoL questionnaire [AE-QoL]) were offered and used to assess disease control and the impact of CSU on patients' QoL. UCT is a new PRO tool, which

retrospectively assesses patients' burden of disease over the previous four weeks. UCT consists of four questions that cover disease activity, QoL, disease control, and therapy. A UCT score of ≥ 12 points (range from 0 to 16 points) indicates that a patient's urticaria is controlled and a score of < 12 points indicates that the urticaria is uncontrolled [9]. The DLQI consists of 10 items covering six subdomains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. An overall DLQI score (range from 0 to 30 points) of 0-1, 2-5, 6-10, 11-20 and 21-30 indicates that CSU is having no effect, a small effect, a moderate effect, a very large effect, or an extremely large effect on a patient's QoL, respectively [10]. The CU-Q₂oL is a self-administered 23-item questionnaire used to assess CSU-specific QoL. Using a 5-point Likert scale (1 = not at all; 5 = very much) patients indicated how much CSU affects their overall functioning, sleep, itching/embarrassment, mental status, swelling/eating, and limits looks [11]. Finally, the AE-QoL (developed for patients with angioedema) consists of 17 items covering four subdomains: functioning, fatigue/mood, fears/shame, and nutrition [12]. The total scores of the CU-Q₂oL and AE-QoL questionnaires range of from 0 to 100, with higher scores reflecting greater impairment in QoL.

Statistical Analysis

Only descriptive methods were used for statistical analysis. Means, medians, standard deviation (SD), min and max are stated for quantitative and absolute and relative frequencies for categorical measurements.

Ethical Approval

Ethical approval for the AWARE study was obtained from Charité Ethikkommission in Berlin, Germany (September, 2013; approval number EA1/243/13) and from urticaria specialist centers where needed according to local regulations.

RESULTS

Demographic characteristics and disease activity

A total of 1,577 H1-antihistamine-refractory CSU patients were documented in 256 sites across Germany between March 2014 and December 2014; 1,539 patients met all the inclusion criteria (n = 38 were excluded; n = 19 patients were missing a core variable [age, gender, or time of diagnosis], n = 16 did not meet all inclusion criteria [n = 2 <18 years, n = 10 were diagnosed <2 months, and n = 4 did not have evidence of being H1-antihistamine-refractory], n = 4 patients were participating in another CU trial, and difficulties with follow-up were anticipated for n = 3 patients) and were included in this analysis. This included patients who had CSU only (n = 1,170; 76% of total) and patients with CSU and CIndU concomitantly (n = 369; 24% of total). Overall, 73.9% and 26.1% of patients were treated by office-based dermatologists and urticaria hospital centers, respectively. Seventy percent of patients were female and the mean (SD) age was 46.3 (15.6) years, with a peak prevalence in patients aged 45 to <55 years (23.9%; 18 to <25 years, 9.0%; 25 to <35 years, 17.8%; 35 to <45, 18.8%; 55 to <65 years, 17.4%; 65 to <75 years, 9.1%; ≥75 years, 4.0%). The mean (SD) time since CSU was diagnosed was 4.8 (7.2) years and the mean (SD) body mass index (BMI) was 27 (5.4) kg/m² (Table 1).

The mean (SD) UCT score was 7.9 (4.3). Overall, 77.5% of patients scored <12 at baseline, indicating uncontrolled urticaria. Similarly, the VAS score for patient satisfaction with current therapy was low (mean, 5.4; SD, 3.1).

Approximately 27% of patients reported sick leave due to urticaria. The mean (SD) duration of sick leave was 9.1 (11.7) weeks since symptoms first appeared. Additionally, for patients with angioedema, the mean (SD) duration of sick leave was 9.3 (8.7) weeks since symptoms first appeared.

Angioedema is frequent in H1-antihistamine-refractory CSU patients

Overall, 55.2% of H1-antihistamine-refractory CSU patients were classified as having CSU without angioedema, 46.1% as having CSU with angioedema, and 2.9% as having angioedema without wheals. These percentages add up to slightly more than 100% due to a small number of cases when physicians classified a patient who exclusively develops angioedema but not wheals as both, “CSU with angioedema” and “angioedema without wheals”, which is in line with the guidelines.

Angioedema had occurred during the previous 6 months in 43.4% of patients. The average intensity of angioedema during this time was rated as severe, moderate, mild, and negligible by 31.3%, 46.4%, 20.5%, and 1.8% of patients, respectively. The mean (SD) number of days with angioedema during the previous 6 months was 33.5 (64.0). In 90% of patients who had wheals and angioedema, the development of wheals and angioedema coincided.

Inducible urticaria is a common comorbidity of H1-antihistamine-refractory CSU

CIndU was the most common comorbidity of H1-antihistamine-refractory CSU, occurring in 24% of CSU patients. CIndU was the secondary diagnosis for 86.4% of CSU patients with comorbid CIndU; only 11.1% had a primary diagnosis of CIndU. Symptomatic dermographism (12.3%), delayed pressure urticaria (6.1%) and heat urticaria (4.3%) were the most common types of CIndU reported.

Other frequently reported comorbidities included allergic rhinitis (18.2%), hypertension (18.1%), asthma (12%), depression (9.5%), obesity (8.1%), food allergies (7.9%), atopic dermatitis (6.8%), Hashimoto’s thyroiditis (5.9%), nut allergies (5.8%), and anxiety (4.7%; Table 2).

H1-antihistamine-refractory CSU patients are undertreated

Only 57.6% of patients were receiving treatment for CSU at this baseline assessment (58.8% of patients with UCT scores <12 and 56.1% of patients with UCT scores ≥12): 46.3% of patients were receiving the recommended first line treatment for CSU, i.e. second generation H1-antihistamines, 9.1% were receiving first generation H1-antihistamines and 15.8% were receiving corticosteroids (including prednisolone; Table 3).

Rates of pharmacological treatments were usually higher in hospital center compared to local dermatologist treated patients: any treatment, 65.8% versus 54.7%, respectively; second generation H1-antihistamines, 55.9% versus 42.9%; ranitidine, 5.7% versus 1.1%; montelukast, 11.2% versus 1.0%; omalizumab, 6.0% versus 0.8%; and cyclosporine, 2.7% versus 0.9%. Rates of treatment with prednisolone (11.7% versus 11.6%, respectively), dapsone (2.2% versus 1.1%), and other corticosteroids (3.2% versus 4.6%) were similar in both treatment settings,

CSU frequently leads to a marked impairment in QoL

Analysis of PROs revealed that CSU negatively impacts patient QoL. The mean (SD) DLQI score was 8.3 (6.9; n = 1489), and for 32.8% of patients the symptoms of CSU had a very large or extremely large impact on their QoL. For a further 29.2%, symptoms had a moderate impact on QoL.

The mean (SD) total score for the CU-Q₂oL was 36.2 (20.1; n = 1468). The most severely impaired subdomains of the CU-Q₂oL were itching/embarrassment (mean, 48.2; SD, 26.1), sleep (mean, 45.2; SD, 27.3) and mental status (mean, 41.4; SD, 26.5). Mean scores for overall functioning (mean, 32.2; SD, 25.8), swelling/eating (mean, 22.6; SD, 22.1) and limits looks (mean, 26.4; SD, 27.1) indicated lower levels of impairment (Figure 1A).

In CSU patients with angioedema, the mean (SD) total AE-QoL score was 46.8 (22.2; n = 612). The most severely impaired subdomains were 'fears/shame' and 'fatigue/mood' with a

mean (SD) score of 54.5 (27.1) and 46.0 (26.0), respectively. The overall functioning (mean, 42.0; SD, 29.3) and nutrition (mean, 34.4; SD, 33.0) subdomains were less severely impacted (Figure 1B).

H1-antihistamine-refractory CSU patients frequently use several healthcare resources

H1-antihistamine-refractory CSU patients reported frequent use of healthcare resources: 29.7% of CSU patients had visited emergency services, on average (SD) 3 times (6.4) since their CSU started; 30.3% reported hospitalization, on average (SD) 2.3 times (3.9); 71.9% had visited a general practitioner, on average (SD) 7.9 times (12.5); 50.7% had visited a dermatologist or allergist other than the study-enrolling dermatologist, on average (SD) 8.1 times (24.6); and 32.5% of patients had visited specialized urticaria centers, on average (SD) 7.2 times (12.5). Patients also reported visiting ear, nose and throat specialists (35.3% of patients; 1.7 visits), dentists (35.7% of patients; 1.7 visits), alternative practitioners (4% of patients; 8.9 visits) and using other healthcare resources (19.7% of patients; 2.8 visits).

Discussion

The AWARE study will eventually present a comprehensive real-life data collection describing the impact of available CSU therapies over time and their impact on health-related QoL, as well as the economic burden of CSU patients. This initial analysis reveals that German H1-antihistamine-refractory CSU patients, treated by office-based dermatologists or urticaria centers, display high rates of angioedema and comorbid CIndUs, are undertreated, have impaired health-related QoL and frequently use multiple healthcare resources.

The demographic characteristics reported in this observational study are comparable to previously published expert [13, 14] and trial data [15-17]; a higher proportion of patients were female, and age and BMI values were similar to those in previous literature [15, 16, 18-21]. Angioedema is a major burden for affected patients and can severely impact patient QoL [12]. The exact proportion of CSU patients who experience angioedema remains unclear, with previous publications reporting rates ranging from 33% [13] to 55% [15-18]. In this AWARE patient cohort, over 40% of patients experienced angioedema, of which 77.7% were rated to be of severe or moderate intensity. This data confirms that a high proportion of H1-antihistamine-refractory CSU patients experience angioedema, which is likely to have an additional negative impact on patient QoL.

While previous literature suggests that CSU and CIndU can occur in parallel [2], the frequency of such an occurrence had until now remained largely unknown. This study indicates that approximately 25% of H1-antihistamine-refractory CSU patients have comorbid CIndU. Consistent with previous publications, other comorbidities in this patient population included asthma, allergic rhinitis, atopic dermatitis, allergies, and autoimmune diseases [13, 22-28].

Patients with CSU and other dermatological conditions are often reported to have an increased risk of psychiatric comorbidities, with rates of depression and anxiety ranging between 11-21% and 25-30% in CSU patients, respectively [21, 29-33]. In this AWARE patient cohort, the rates of diagnosed anxiety (4.7%) and depression (9.5%) were only slightly higher than prevalence rates previously reported in the German population [31, 34, 35]. A possible explanation for the lower rates of psychiatric comorbidities in this study may be that different definitions of depression or anxiety were used. Furthermore, only patients with an existing diagnosis of depression or anxiety were reported in this study, whereas other studies have used validated psychometric tests, which can reveal previously undiagnosed conditions [29]. The high proportion of CSU patients who are female and over 40 years may also represent a confounding factor when comparing the prevalence of

psychiatric comorbidities in CSU patients to that of the general population [36]. The patient population may also differ from previously published CSU data, as patients were treated by office-based dermatologists or urticaria centers.

The current urticaria guidelines recommend that physicians should aim for complete symptom control when treating CSU [1]. Second generation H1-antihistamines are recommended as the first-line treatment, increasing doses of second generation H1-antihistamines as the second-line treatment, and finally the approved omalizumab and off-label options ciclosporine A or montelukast as the third-line treatment [1]. These guidelines also recommend against the long-term use of corticosteroids or the use of first generation H1-antihistamines. In the current study, only 58% of patients were receiving pharmacological treatment for CSU at the time of baseline documentation, despite having been diagnosed with H1-antihistamine-refractory CSU for an average of 4.8 years and continuing to experience symptoms. Moreover, less than 50% of patients were receiving the recommended first-line treatment (second generation H1-antihistamines). Nearly 10% of patients were receiving first generation H1-antihistamines, which are not recommended for the treatment of CU. Furthermore, 15.8% were receiving corticosteroid treatment, which is only recommended for a short course (maximum 10 days) treatment if exacerbations demand it [1]. As it was unexpected that CSU-patients would be without any treatment, no item was included in the structured data acquisition on why they were not taking any medication at the time of enrollment. Therefore, we can only hypothesize that this is due to lack of efficacy with previous H1-antihistamine treatment or is a result of treating physicians avoiding off-label therapies.

In line with low rates of treatment, approximately 75% of patients had uncontrolled urticaria (UCT score < 12), mean patient-reported satisfaction with current therapy was low (5.4 points out of 10 using VAS), and CSU had a negative impact on the patients QoL. A high proportion of patients also reported absence from work due to uncontrolled CSU since symptoms first appeared, which further highlights the burden of CSU for patients. These high

rates of under treatment, high rates of non-recommended treatment usage, low levels of symptom control, and low levels of patient satisfaction highlight the need for improved patient care and adherence to the current S3-CU guidelines.

In line with this above observation, healthcare resource usage was high in the AWARE population; roughly 30% of CSU patients had visited the emergency room and 30% required hospitalization since their symptoms first started. Increased rates of healthcare resource utilization have recently been reported for CU patients from the United States and Europe [19, 37]. In addition to the discomfort associated with these visits, the economic burden to the healthcare services is likely to be considerable.

Limitations of the data are mainly driven through the nature of a NIS design. Data completeness and quality as well as questionnaires filled out by patients are highly dependent on the documentation accuracy of participating patients and physicians. As no control population was included in the study, rates of healthcare resource use and comorbidities can only be compared to previously reported rates. This somewhat limits the strength of conclusions, as confounding factors cannot be accounted for. However, the relatively large number of patients, from both specialized centers and office-based dermatologists, included in this assessment provides an unmatched insight into the baseline clinical characteristics of German adult patients with H1-antihistamine-refractory CSU. Prospectively, this NIS will also allow us to gather data on the efficacy of different therapy schedules used and their impact on the socio-economic burden of controlled versus uncontrolled CSU patients.

In summary, the initial baseline analysis from the AWARE study reveals a high unmet need of H1-antihistamine-refractory CSU patients in specialized CU centers as well as the office-based dermatology space. The majority of CSU patients were undertreated, had uncontrolled urticaria and moderately or largely affected QoL. This study highlights the impact of CSU on patient QoL and the need for improved patient care and adherence to the latest treatment guidelines.

Statement of Contributions

NCR, KC, MM, PS, UR, and GRH participated in the design of this study, interpretation of results and drafted the manuscript. VM, ASY, NW, FR, UL, UH, AB, TJ, MP, NB and AS contributed substantially to data generation and revised the manuscript. All authors approved the final version of the manuscript.

Acknowledgements

The authors thank the investigators who participated in this study, including Dr. Tobias Schadeck, Dr. Stefan Golsch, Dr. Alla Schuller, Dr. Udo Amann, Dr. Berardi Monica Quack, Dr. Alex Rothhaar, and Annette Herpich who contributed substantially to data generation. They also thank Aine Abautret-Daly and Gillian Brodie of Novartis Ireland Ltd. for providing writing and editorial assistance with this manuscript. The study was sponsored by Novartis Pharma GmbH.

Conflicts of interest statement

MM has acted as a paid consultant for Novartis and Genentech, has received honoraria for lectures from Novartis and has received research funding by Novartis to his department. PS has received fees for consulting, organizing education, funds for research, reimbursement for attending a symposium and fees for consulting from Novartis GmbH Germany. UR has received fees for consulting and funds for research from Novartis Pharma GmbH. AB is a member of the Novartis urticaria board, received reimbursement for attending a symposium, fees for organizing education, fees for speaking and funds for research. FR has received financial support for the organization of a training course, a speaker's fee and has received

Accepted Article

funding for research from Novartis. TJ has received speaker's honorarium, travel support and consulting fees from Novartis GmbH, Germany. ASY has received a fee for speaking at a symposium and members of his staff are funded by Novartis. VM reports reimbursements to the Department of Dermatology, for patient inclusion to the AWARE registry, from Novartis Pharma GmbH, during the conduct of this study; personal fees (speaker's honoraria on the topic of urticaria and reimbursement for attending a symposium) and funds for research from Novartis Pharma GmbH, outside the submitted work. NW has acted as a paid speaker for company neutral medical education and the clinical center she is employed at has received funding for research carried out in this work. UL has received reimbursement for attending symposia, fees for speaking and consultation from Novartis Pharmaceuticals. UH has received fees from Novartis for speaking, organizing education and consulting. KC and NCR are employees of Novartis Pharma AG Basel. NB, MP, AS, and GRH have no conflicts of interest to declare.

References

1. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69(7):868-87.
2. Grattan C. The urticarias: pathophysiology and management. *Clinical medicine*. 2012;12(2):164-7.
3. Maurer M, Magerl M, Metz M, Zuberbier T. Revisions to the international guidelines on the diagnosis and therapy of chronic urticaria. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*. 2013;11(10):971-8.
4. Magerl M, Borzova E, Gimenez-Arnau A, Grattan CE, Lawlor F, Mathelier-Fusade P, et al. The definition and diagnostic testing of physical and cholinergic urticarias--EAACI/GA2LEN/EDF/UNEV consensus panel recommendations. *Allergy*. 2009;64(12):1715-21.
5. Weller K, Schoepke N, Krause K, Ardelean E, Brautigam M, Maurer M. Selected urticaria patients benefit from a referral to tertiary care centres--results of an expert survey. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2013;27(1):e8-16.
6. Weller K, Viehmann K, Brautigam M, Krause K, Siebenhaar F, Zuberbier T, et al. Management of chronic spontaneous urticaria in real life--in accordance with the guidelines? A cross-sectional physician-based survey study. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2013;27(1):43-50.
7. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Gimenez-Arnau AM, et al. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. *Allergy*. 2009;64(10):1427-43.

8. Weller K, Viehmann K, Brautigam M, Krause K, Siebenhaar F, Zuberbier T, et al. Cost-intensive, time-consuming, problematic? How physicians in private practice experience the care of urticaria patients. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*. 2012;10(5):341-7.
9. 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. *The Journal of allergy and clinical immunology*. 2014;133(5):1365-72, 72 e1-6.
10. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clinical and experimental dermatology*. 1994;19(3):210-6.
11. 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(6):927-36.
12. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development and construct validation of the angioedema quality of life questionnaire. *Allergy*. 2012;67(10):1289-98.
13. Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M. Epidemiology of urticaria: a representative cross-sectional population survey. *Clinical and experimental dermatology*. 2010;35(8):869-73.
14. Kulthanan K, Jiamton S, Thumpimukvatana N, Pinkaew S. Chronic idiopathic urticaria: prevalence and clinical course. *The Journal of dermatology*. 2007;34(5):294-301.
15. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Bulbul Baskan 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. *The Journal of investigative dermatology*. 2015;135(1):67-75.
16. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *The Journal of allergy and clinical immunology*. 2013;132(1):101-9.
17. Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368(10):924-35.
18. Sanchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Subtypes of chronic urticaria in patients attending allergy clinics in Venezuela. *Eur Ann Allergy Clin Immunol*. 2014;46(6):210-5.
19. Balp MM, Vietri J, Tian H, Isherwood G. The Impact of Chronic Urticaria from the Patient's Perspective: A Survey in Five European Countries. *Patient*. 2015;8(6):551-8.
20. Maurer M, Church MK, Goncalo M, Sussman G, Sanchez-Borges M. Management and treatment of chronic urticaria (CU). *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2015;29 Suppl 3:16-32.
21. Maurer M, Weller K, Bindslev-Jensen C, Gimenez-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(3):317-30.
22. Broder MS, Raimundo K, Antonova E, Chang E. Resource use and costs in an insured population of patients with chronic idiopathic/spontaneous urticaria. *American journal of clinical dermatology*. 2015;16(4):313-21.
23. Zazzali JL, Broder MS, Chang E, Chiu MW, Hogan DJ. Cost, utilization, and patterns of medication use associated with chronic idiopathic urticaria. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2012;108(2):98-102.
24. Ban GY, Kim MY, Yoo HS, Nahm DH, Ye YM, Shin YS, et al. Clinical features of elderly chronic urticaria. *The Korean journal of internal medicine*. 2014;29(6):800-6.
25. Sugiyama A, Nishie H, Takeuchi S, Yoshinari M, Furue M. Hashimoto's disease is a frequent comorbidity and an exacerbating factor of chronic spontaneous urticaria. *Allergologia et immunopathologia*. 2015;43(3):249-53.

26. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. *The Journal of allergy and clinical immunology*. 2012;129(5):1307-13.
27. Sanchez Borges M, Tassinari S, Flores A. [Epidemiologic features in patients with antihistamine-resistant chronic urticaria]. *Rev Alerg Mex*. 2015;62(4):279-86.
28. Verneuil L, Leconte C, Ballet JJ, Coffin C, Laroche D, Izard JP, et al. Association between chronic urticaria and thyroid autoimmunity: a prospective study involving 99 patients. *Dermatology*. 2004;208(2):98-103.
29. Staubach P, Eckhardt-Henn A, Dechene M, Vonend A, Metz M, Magerl M, et al. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *The British journal of dermatology*. 2006;154(2):294-8.
30. Picardi A, Abeni D, Melchi CF, Puddu P, Pasquini P. Psychiatric morbidity in dermatological outpatients: an issue to be recognized. *The British journal of dermatology*. 2000;143(5):983-91.
31. Busch MA, Maske UE, Ryl L, Schlack R, Hapke U. [Prevalence of depressive symptoms and diagnosed depression among adults in Germany: results of the German Health Interview and Examination Survey for Adults (DEGS1)]. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz*. 2013;56(5-6):733-9.
32. 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 dermato-venereologica*. 2011;91(5):557-61.
33. Uguz F, Engin B, Yilmaz E. Axis I and Axis II diagnoses in patients with chronic idiopathic urticaria. *Journal of psychosomatic research*. 2008;64(2):225-9.
34. Wittchen HU, Krause P, Hoyer J, Beesdo K, Jacobi F, Hofler M, et al. [Prevalence and correlates of generalized anxiety disorders in primary care]. *Fortschritte der Medizin Originalien*. 2001;119 Suppl 1:17-25.
35. Jacobi F, Wittchen HU, Holting C, Hofler M, Pfister H, Muller N, et al. Prevalence, co-morbidity and correlates of mental disorders in the general population: results from the German Health Interview and Examination Survey (GHS). *Psychological medicine*. 2004;34(4):597-611.
36. Pratt LA, Brody DJ. Depression in the U.S. household population, 2009-2012. *NCHS Data Brief*. 2014(172):1-8.
37. Vietri J, Turner SJ, Tian H, Isherwood G, Balp MM, Gabriel S. Effect of chronic urticaria on US patients: analysis of the National Health and Wellness Survey. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2015.

Figure Legend

Figure 1: Box and whisker plots of (A) CU-Q₂oL scores (functioning, n = 1,433; sleep, n = 1,436; itching/embarrassment, n = 1,439; eating/swelling, n = 1,438; mental status, n = 1,434; limits looks, n = 1,429; and total, n = 1,468) and (B) AE-QoL scores (functioning, n = 592; fatigue/mood, n = 592; fears/shame, n = 593; nutrition, n = 594; and total, n = 612). The boxes represent the interquartile range (25th and 75th percentile) and the mid-lines represent the median. The bottom and top of the whiskers represents the minimum and maximum scores, respectively.

Tables

Table 1: Baseline demographic and clinical characteristics of H1-antihistamine-refractory CSU patients

Demographics	
Age (years)	46.3 ± 15.6
Female, n (%)	1078 (70)
Height (m)	1.70 ± 0.09
Weight (kg)	78.2 ± 17.5
BMI (kg/m ²)	27.0 ± 5.4
Time since diagnosis (years)	4.8 ± 7.2
Sick leave	
Patients, n (%)	411 (26.8)
Duration (weeks)	9.1 ± 11.7
Duration due to AE (weeks)	9.3 ± 8.7
Satisfaction with current therapy^a	
VAS score	5.4 ± 3.1
Disease activity^b	
UCT score	7.9 ± 4.3 ^c

N = 1,539 patients with H1-antihistamine-refractory CSU. Data are presented as mean ± SD, unless otherwise stated. AE, angioedema; BMI, body mass index; CSU, chronic spontaneous urticaria; SD, standard deviation; UCT, urticaria control test; VAS, visual analog scale score. ^aData are from n = 1358. ^bData are from n = 1,488.

^c77.5% of patients had uncontrolled chronic urticaria.

Table 2: Comorbidities in patients with H1-antihistamine-refractory CSU

^a Comorbidity	n (%)
CIndU	
Any ^b	369 (24)
Symptomatic dermographism	189 (12.3)
Delayed pressure urticaria	94 (6.1)
Heat urticaria	66 (4.3)
Cholinergic urticaria	60 (3.9)
Cold urticaria	45 (2.9)
Allergies	
Allergic Rhinitis	280 (18.2)
Asthma	184 (12)
Food allergy ^c	122 (7.9)
Atopic dermatitis	104 (6.8)
Nut allergy	90 (5.8)
Other type of eczema	67 (4.4)
Autoimmune disorders	
Hashimoto's thyroiditis	91 (5.9)
Psychosomatic disorders	
Depression	146 (9.5)
Anxiety	72 (4.7)
Other disorders	
Hypertension	279 (18.1)
Obesity	124 (8.1)
Hypercholesterolemia	70 (4.5)

N = 1,539 patients with H1-antihistamine-refractory CSU. CIndU, Chronic Inducible Urticaria, CSU, chronic spontaneous urticaria.

^aIncludes comorbidities that occurred in greater than 2.0% of patients.

^bIncluding: symptomatic dermographism (12.3%), delayed pressure urticaria (6.1%), heat urticaria (4.3%), cholinergic urticaria (3.9%), cold urticaria (2.9%), aquagenic urticaria (1.4%), light / solar urticaria (0.8%), and contact urticaria (0.7%). No patients reported vibratory urticaria / vibration induced angioedema. Treating physicians diagnosed CIndUs using the provocation

test which they deemed most appropriate. Overall, 36.8% of patients had been exposed to a dermatographism test, 19.4% to a pressure test, 11.6% to a cold provocation test, 10.8% to a heat provocation test, 5.0% to a contact test, and 4.3% to UV and/or visible light test. Prick testing (39.9%), oral provocation testing (3.8%), and epicutaneous testing (17.5%) were also reported.

^cOverall, 46 (3.0%) patients reported nut allergy only, 78 (5.1%) patients reported food allergies only, and 44 (2.9%) patients reported both nut and food allergies.

Table 3: Treatment for CSU

	CSU treatment ^a n (%)
Second generation H1-antihistamine ^b	712 (46.3)
Corticosteroids ^c	244 (15.9)
First generation H1-antihistamine	140 (9.1)
Montelukast	56 (3.6)
Omalizumab	33 (2.1)
Ranitidine	35 (2.3)
Dapsone	22 (1.4)
Ciclosporine	21 (1.4)

N = 1,539 patients with H1-antihistamine-refractory CSU. ^aIncludes any treatment received by more than 0.5% of patients. Patients may have been receiving more than one treatment. 57.6% of patients (n = 886) were receiving any treatment for urticaria.

^bOverall, 388 (25.2%) patients reported using high dose, 381 (24.8%) patients reported using low dose, and/or 97 (6.3%) patients reported using unknown doses or as needed doses of second generation H1-antihistamines.

^cCorticosteroids refers to any corticosteroid, including prednisolone.

