



Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: <https://www.tandfonline.com/loi/icmo20>

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To cite this article: Ben Hoskin, Benjamin Ortiz, Brandee Paknis & Abhishek Kavati (2019) Exploring the real-world profile of refractory and non-refractory chronic idiopathic urticaria in the USA: clinical burden and healthcare resource use, Current Medical Research and Opinion, 35:8, 1387-1395, DOI: [10.1080/03007995.2019.1586222](https://doi.org/10.1080/03007995.2019.1586222)

To link to this article: <https://doi.org/10.1080/03007995.2019.1586222>



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Accepted author version posted online: 22 Feb 2019.
Published online: 28 Mar 2019.



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ORIGINAL RESEARCH



Exploring the real-world profile of refractory and non-refractory chronic idiopathic urticaria in the USA: clinical burden and healthcare resource use

Ben Hoskin^a, Benjamin Ortiz^b, Brandee Paknis^b and Abhishek Kavati^b

^aAdelphi Real World, Bollington Macclesfield, UK; ^bHealth Economics and Outcomes Research, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

ABSTRACT

Introduction: Chronic idiopathic/spontaneous urticaria (CIU/CSU) is a debilitating skin condition that is burdensome for patients and healthcare providers. We aimed to describe clinical characteristics, consultation patterns and healthcare resource utilization in real-world US patients with refractory and non-refractory CIU/CSU.

Methods: Data was collected from the Adelphi Real World 2015 Urticaria Disease Specific Programme. Physicians completed patient record forms (PRFs) for the next four patients consulting with non-refractory CIU/CSU and the next six with refractory CIU/CSU; patients were considered refractory if symptomatic and on treatment step ≥ 2 . The same patients were asked to complete patient self-completion (PSC) forms describing how CIU/CSU affected them.

Results: Seventeen physicians (15 allergists; 2 dermatologists) completed 184 PRFs (108 refractory CIU/CSU; 76 non-refractory CIU/CSU); 140 patients completed PSC forms (93 refractory CIU/CSU; 47 non-refractory CIU/CSU). Mean time from first consultation to diagnosis was 13.5 (SD 28.3) weeks; mean time from diagnosis to first treatment was 16.0 (SD 37.9) weeks. Patients with refractory CIU/CSU were more likely to initially consult primary care physicians than those with non-refractory CIU/CSU (51% and 28%, respectively). The most common symptoms were itching, sleep problems and anxiety/distress, affecting 75%, 23% and 18%, respectively. Patient-perceived disease severity was greater than physician-perceived severity (refractory CIU/CSU kappa 0.1512; non-refractory CIU/CSU 0.1590).

Conclusions: Patients with CIU/CSU in this real-world study – particularly those with refractory CIU/CSU – were slow to receive specialist care and had substantial symptom burdens; patient–physician perception of disease severity was discordant. Earlier diagnosis of CIU/CSU may lead to timely use of CIU/CSU therapies.

ARTICLE HISTORY

Received 19 November 2018
Revised 8 February 2019
Accepted 20 February 2019

KEYWORDS

Chronic idiopathic urticaria;
chronic spontaneous
urticaria; real-world;
refractory; management

Introduction

Urticaria is a skin condition characterized by pruritic raised wheals that range in size from a few millimeters to several centimeters and occur anywhere on the body¹. Angioedema – a sudden, pronounced swelling of the subdermis and subcutis or swelling of the mucous membranes – may also be present on any part of the body but is most frequently observed on the hands, face and feet². Urticaria is defined as being chronic if it has been continuously or intermittently present for at least 6 weeks^{1,3}. No external stimulus can be identified in 70–80% of patients with chronic urticaria; these patients are said to have chronic idiopathic urticaria (CIU; also known as chronic spontaneous urticaria [CSU])⁴. CIU/CSU is reported to affect 0.5–1.0% of the overall population at any time⁵. Thus, approximately 1.5 million people are estimated to have CIU/CSU in the USA^{5,6}.

Symptoms associated with CIU/CSU are burdensome for patients and healthcare providers. CIU/CSU has been shown

to have a profound impact on quality of life as a result of both the core symptoms and other factors, such as lack of sleep due to itching, treatment-related side effects, and cosmetic disfigurement^{5,7,8}. In addition, a meta-analysis of psychosocial factors indicated that patients with CIU/CSU had significantly higher scores for measures of somatization, obsessive–compulsive disorder, interpersonal sensitivity and depression, anxiety, insomnia and stressful life events than healthy controls, indicating the large adverse impact of their condition; indeed, the pooled prevalence of psychosocial factors was 46% in that analysis⁹.

Current EAACI/GA²LEN/EDF/WAO guidelines recommend second-generation H₁ antihistamines as first-line treatment for patients with CIU/CSU¹⁰, although approximately 50% of patients remain symptomatic despite treatment at approved doses⁵ and require escalation to higher doses of these agents. The anti-immunoglobulin E antibody omalizumab, which is approved for the treatment of patients who remain symptomatic despite H₁ antihistamine treatment^{11–13}, should

CONTACT Abhishek Kavati  abhishek.kavati@novartis.com  Health Economics and Outcomes Research, Novartis Pharmaceuticals Corporation, Building 125, Office 3413B, One Health Plaza, East Hanover, NJ 07936-1080, USA

 Supplemental data for this article is available online at <https://doi.org/10.1080/03007995.2019.1586222>.

be added if the patient's symptoms remain uncontrolled despite these increased doses¹⁰.

The present study was undertaken to describe the clinical characteristics, consultation patterns, disease-management approaches and healthcare resource utilization among patients with CIU/CSU in a real-world clinical setting in the USA. In addition, we aimed to explore differences in characteristics between patients with refractory and non-refractory disease to identify areas of unmet need in both patient groups.

Methods

Data for the present analysis was drawn from the Adelphi Real World 2015 Urticaria Disease Specific Programme (DSP), a cross-sectional survey of physicians and patients in the real-world clinical setting that was conducted in the USA, France, Germany and the United Kingdom between March and July 2015. The DSP methodology has been described in detail elsewhere¹⁴. The survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996¹⁵ and the Health Information Technology for Economic and Clinical Health Act legislation¹⁶. Ethical approval for the study was obtained from the Western Institutional Review Board.

Physicians were recruited from across the USA. The only inclusion criteria were that participating physicians were board-certified allergists or dermatologists, had been qualified for a minimum of 4 years, were actively involved in the management of and made treatment decisions for patients with CIU/CSU, and saw at least three patients with CIU/CSU per month. All physicians included in this analysis were specialists.

Physicians were asked to include only patients currently undergoing treatment for CIU/CSU, specifically those with symptoms of urticaria (hives and itching, with or without angioedema) on a continuous or intermittent basis, lasting 6 weeks or more¹⁷, with no known cause and in line with the guidelines provided in the patient record form. Eligibility of patients was determined by physicians based on their medical expertise and clinical judgement of symptoms.

Patients were defined as having refractory or non-refractory disease, using a pre-programmed research definition in the absence of widely accepted definitions of refractoriness to treatment, in order to examine the characteristics of patients not responding to more advanced treatment regimens. Using treatment steps as defined in the most up to date US guidelines available at the time of the study, i.e. those issued by the Joint Task Force on Practice Parameters guidelines (Figure 1)¹ and the contemporary academic literature, patients were considered to have refractory disease if they were symptomatic and on treatment step 2 or greater. Patients were considered to have non-refractory disease if they were currently asymptomatic on any treatment step or symptomatic on step 1 treatment.

Patients provided written informed consent for use of their anonymized and aggregated data for research and publication in scientific journals. Data was collected in such a way that

patients and physicians could not be identified directly; all data was aggregated and de-identified before receipt.

Data collection

Physicians were asked to take part in an interview assessing their perceptions and attitudes toward the diagnosis, management and treatment of CIU/CSU, and to complete patient record forms for the next four patients with non-refractory CIU/CSU and the next six patients with refractory CIU/CSU. The physician-completed patient record form collected information on patient demographics, clinical characteristics, clinical management and outcomes, and past and current medication and medical resource use, including disease severity and progression, consultation history, laboratory, physical and perception tests/assessments undertaken to establish a diagnosis and/or disease activity, treatment, healthcare provider visits, hospitalizations, and need for care from professional or nonprofessional caregivers. Disease severity and progression were determined by the physician, based on their own judgement and perception of the patient's condition. Disease severity measures, such as the Urticaria Activity Score over 7 days (UAS7), which is widely used in clinical trials, were not used in this study as these are not commonly used in routine clinical practice.

The same patients were invited to participate in an exercise using a patient self-completion form that asked about their diagnosis, current treatment, and ongoing management and clinical burden, as well as perceptual questions relating to satisfaction and attitudes toward their condition. These forms were filled out separately and confidentially, with no influence or input from the physician or nurse, and were based on the patients' own perceptions. Completion of this form was not mandatory.

Statistical analyses

Data was analyzed using descriptive statistics. Continuous variables were reported with mean and standard deviation (SD); categorical variables were reported with frequency and percentage. Comparisons of the cohorts with refractory versus non-refractory disease were performed for all data points, other than basic patient demographics, using bivariate analysis. Differences between patient types were assessed using Mann-Whitney *U* tests for continuous variables or categorical variables with ordered responses, Fisher's exact tests for dichotomized variables and Pearson's chi-squared tests for categorical variables with more than two categories. The significance level was set at 5%; all tests were two-sided. Owing to incomplete data, a level of missingness was expected across variables. The level of missingness was reported for each variable being analyzed. Weighted kappa analyses were performed to assess the agreement between patient and physician ratings of disease severity for patients with refractory and non-refractory disease. Kappa <0 indicates no agreement; 0–0.20 indicates slight agreement, 0.21–0.40 indicates fair agreement, 0.41–0.60 indicates moderate

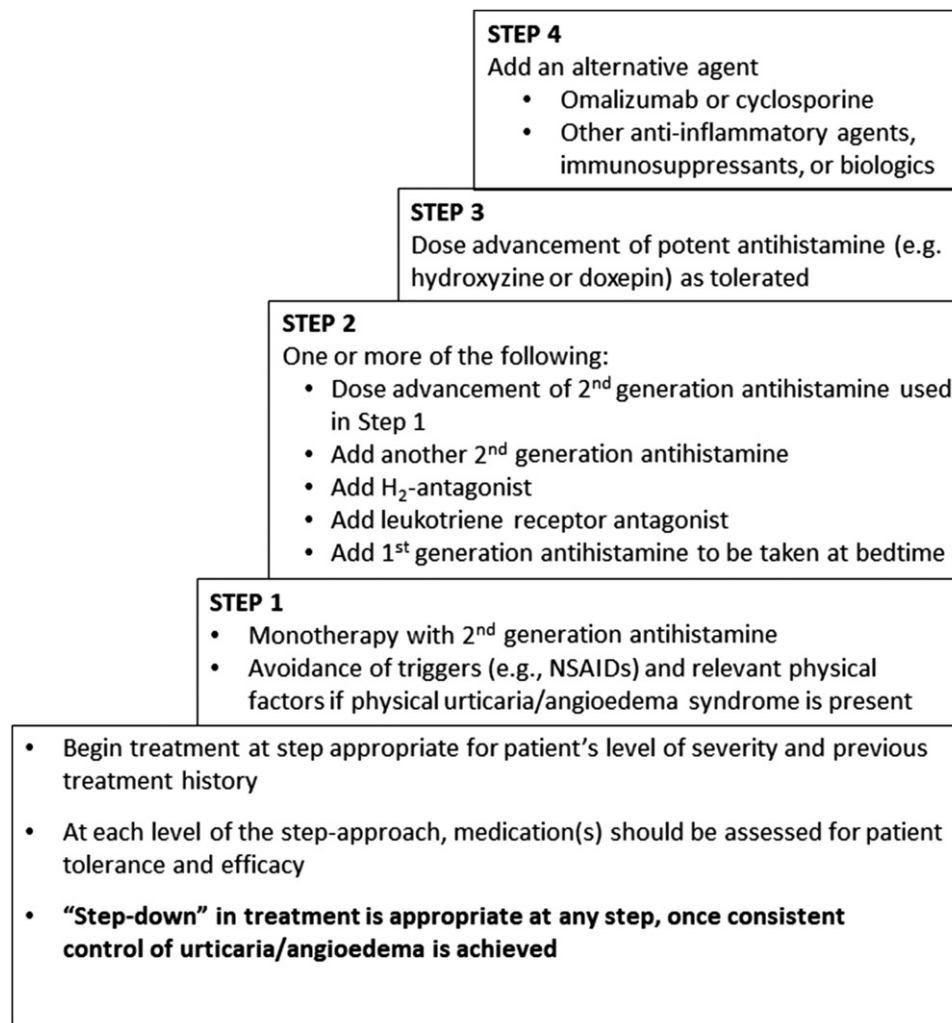


Figure 1. Step-care approach to the treatment of patients with chronic urticaria (supporting the study definition of refractory and non-refractory patients). Abbreviation. NSAID, Nonsteroidal anti-inflammatory drug. Reprinted from J Allergy Clin Immunol, vol. 133/No. 5, J. A. Bernstein et al, The diagnosis and management of acute and chronic urticaria: 2014 update, pp 1270–7, Copyright (2014), with permission from Elsevier.

agreement, 0.61–0.80 indicates substantial agreement and 0.81–1.00 indicates almost perfect agreement^{18,19}.

All statistical analyses were performed using Stata statistical software release 14 (StataCorp LLC, College Station, TX, USA).

Results

A total of 17 physicians across the USA (15 allergists and 2 dermatologists; 13 office-based and 4 hospital-based; 13 male and 4 female) participated in the physician interviews. Physicians were located in eastern ($n=6$; 35%), southern ($n=4$; 24%), midwestern ($n=4$; 24%) and western states ($n=3$; 18%). Physicians completed a total of 184 patient record forms (median 10 per physician; range 2–35), 108 relating to patients with refractory CIU/CSU (median 6 per physician; range 0–19) and 76 relating to patients with non-refractory CIU/CSU (median 4 per physician; range 0–23). In total, 140 of the 184 patients (76%) completed a patient self-completion form: 93 had refractory CIU/CSU and 47 had non-refractory CIU/CSU.

Patient demographics and clinical characteristics are shown in Tables 1 and 2. Patients had a mean age of 47.7 years

(refractory CIU/CSU, 48.0 years; non-refractory CIU/CSU, 47.3 years), 86% were female (refractory CIU/CSU, 87%; non-refractory CIU/CSU, 84%) and 61% were in full- or part-time employment (refractory CIU/CSU, 63%; non-refractory CIU/CSU, 58%). When asked if anyone was responsible for caring for the patient and their daily needs as a consequence of their CIU/CSU, physicians answered yes for 10% of patients with refractory disease and 25% of those with non-refractory disease.

Diagnosis

Many patients reported taking a considerable time to consult a physician after the onset of urticaria symptoms, with only 34% of the overall patient population visiting a physician as soon as they experienced urticaria symptoms (31% of patients with refractory disease and 39% of those with non-refractory disease) and 45% overall waiting >6 weeks to see a physician (46% of patients with refractory disease and 44% of those with non-refractory disease). A total of 82% of patients overall self-medicated with over the counter medication before consulting a healthcare professional (87% of patients with refractory CIU/CSU and 70% of those with non-refractory disease). When asked why they delayed

Table 1. Demographic characteristics of patients with refractory and non-refractory CIU/CSU.

Characteristic	All patients (n = 184)	Refractory CIU/CSU (n = 108)	Non-refractory CIU/CSU (n = 76)
Age, years			
Number of missing entries	0	0	0
Mean (SD)	47.7 (15.3)	48.0 (14.2)	47.3 (16.8)
Sex, n (%)			
Male	26 (14)	14 (13)	12 (16)
Female	158 (86)	94 (87)	64 (84)
BMI, kg/m ²			
Number of missing entries	1	0	1
Mean (SD)	29.8 (7.2)	30.6 (7.7)	28.7 (6.4)
Employment status, n (%)			
Number of missing entries	28	11	17
Working full time	88 (56)	58 (60)	30 (51)
Working part time	7 (4)	3 (3)	4 (7)
Student	6 (4)	2 (2)	4 (7)
Unemployed	9 (6)	8 (8)	1 (2)
Homemaker	19 (12)	10 (10)	9 (15)
Retired	27 (17)	16 (17)	11 (18)
Is anyone responsible for the patient's daily needs?, n (%)			
Yes	30 (16)	11 (10)	19 (25)
No	154 (84)	97 (90)	57 (75)
Healthcare professional initially consulted, n (%)			
Number of missing entries	17	12	5
Allergist/dermatologist ^a	91 (54)	41 (43)	50 (70)
PCP or GP or internist	69 (41)	49 (51)	20 (28)
Other specialist	1 (1)	1 (1)	0 (0)
Other	6 (4)	5 (5)	1 (1)

^aAllergist/dermatologist participating in the survey and other allergists/dermatologists.

Abbreviations. BMI, Body mass index; CIU, Chronic idiopathic urticaria; CSU, Chronic spontaneous urticaria; GP, General practitioner; PCP, Primary care physician; SD, Standard deviation.

Table 2. Clinical characteristics of patients with refractory and non-refractory CIU/CSU.

Characteristic	All patients (n = 184)	Refractory CIU/CSU (n = 108)	Non-refractory CIU/CSU (n = 76)
Mean time since diagnosis, years (SD)	2.6 (5.1)	2.6 (5.6)	2.6 (4.5)
Mean time since first treatment for CIU/CSU, months (SD)	17.5 (25.6)	14.8 (20.3)	20.6 (30.5)
Disease severity at diagnosis, n (%) ^a			
Number of missing entries	19	14	5
Mild	20 (12)	8 (8)	12 (17)
Moderate	82 (50)	42 (45)	40 (56)
Severe	63 (38)	44 (47)	19 (27)
Current disease severity, n (%)			
Number of missing entries	3	2	1
Mild	95 (52)	48 (45)	47 (63)
Moderate	64 (35)	42 (40)	22 (29)
Severe	22 (12)	16 (15)	6 (8)
Disease progression, n (%)			
Number of missing entries	17	10	7
Improving	114 (68)	62 (63)	52 (75)
Worsening	11 (7)	9 (9)	2 (3)
Neither	42 (25)	27 (28)	15 (22)

^aPhysician-assessed.

Abbreviations. CIU, Chronic idiopathic urticaria; CSU, Chronic spontaneous urticaria; GP, General practitioner; PCP, Primary care physician.

consulting a physician, 66% of patients overall answered that they waited to see if their symptoms would go away on their own (69% and 58% for refractory and non-refractory disease, respectively) and 59% said they tried to manage the condition on their own before visiting the doctor (61% and 54% for refractory and non-refractory disease, respectively).

Patients overall were most likely to initially consult an allergist/dermatologist (54%) or a primary care physician (41%). Patterns differed in patients with refractory and non-refractory disease: most patients with refractory CIU/CSU

(51%) first consulted a primary care physician, whereas most of those with non-refractory CIU/CSU (70%) initially consulted an allergist or dermatologist.

The mean time from first consultation to diagnosis of CIU/CSU was 13.5 weeks (SD 28.3 weeks) in the overall population and the mean time from diagnosis to first treatment for CIU/CSU was 16.0 weeks (SD 37.9 weeks). The mean time from first consultation to diagnosis of CIU/CSU was 13.8 weeks (SD 28.9 weeks) for patients with refractory CIU/CSU and 13.0 weeks (SD 27.6 weeks) for those with non-refractory CIU/CSU. The mean time from diagnosis to first treatment for CIU/CSU

was 14.7 weeks (SD 37.5 weeks) for patients with refractory CIU/CSU and 17.5 weeks (SD 38.6 weeks) for those with non-refractory CIU/CSU. Where a delay in diagnosis occurred, the most common reason reported by patients was waiting for a referral to a specialist (45% of patients overall; 36% of patients with refractory CIU/CSU and 63% of patients with non-refractory CIU/CSU).

The first diagnosis was CIU/CSU for 47% of patients overall and acute urticaria was the initial diagnosis for 42% of patients overall. CIU/CSU was the first diagnosis for 36% of patients with refractory disease and 63% of patients with non-refractory disease; acute urticaria was the first diagnosis for 52% of patients with refractory disease and 28% of patients with non-refractory CIU/CSU.

Analysis of patients with refractory disease according to type of physician initially consulted revealed a longer mean time to diagnosis in those who consulted a primary care physician (17.1 [SD 35.6] weeks vs. 11.2 [SD 21.4] weeks) for those who consulted a specialist, and a longer time from diagnosis to consultation with the current managing specialist (73.2 [SD 305.9] weeks vs. 7.9 [SD 32.1] weeks). Once diagnosed, the time to treatment for CIU/CSU was similar in refractory patients consulting a primary care physician or specialist (14.2 and 15.9 weeks, respectively).

Clinical burden of refractory and non-refractory chronic idiopathic/spontaneous urticaria

At the time of diagnosis, physicians classified their patient's CIU/CSU as severe in 38% of patients overall (Table 2). More patients with refractory CIU/CSU had severe disease (47% vs. 27% for those with non-refractory CIU/CSU). At the time of the survey, physicians considered the disease to be severe in 12% of patients overall (15% of patients with refractory disease and 8% with non-refractory disease). Relative to the patient's previous history of CIU/CSU, disease status was reported to be improving in 68% of patients overall (63% in patients with refractory and 75% in those with non-refractory disease).

Patients also rated the severity of their disease. A high level of disconnect between physician- and patient-reported severity was observed in patients with refractory and non-refractory CIU/CSU, as shown in Figure 2. In total, 55% of patients overall considered their disease to be more severe than their physician (52% of refractory patients and 61% of non-refractory patients); 7% of patients overall considered their disease to be less severe than their physician (8% of refractory patients and 7% of non-refractory patients).

The most common physician-reported symptoms at the time of the current consultation were itching (75% of patients

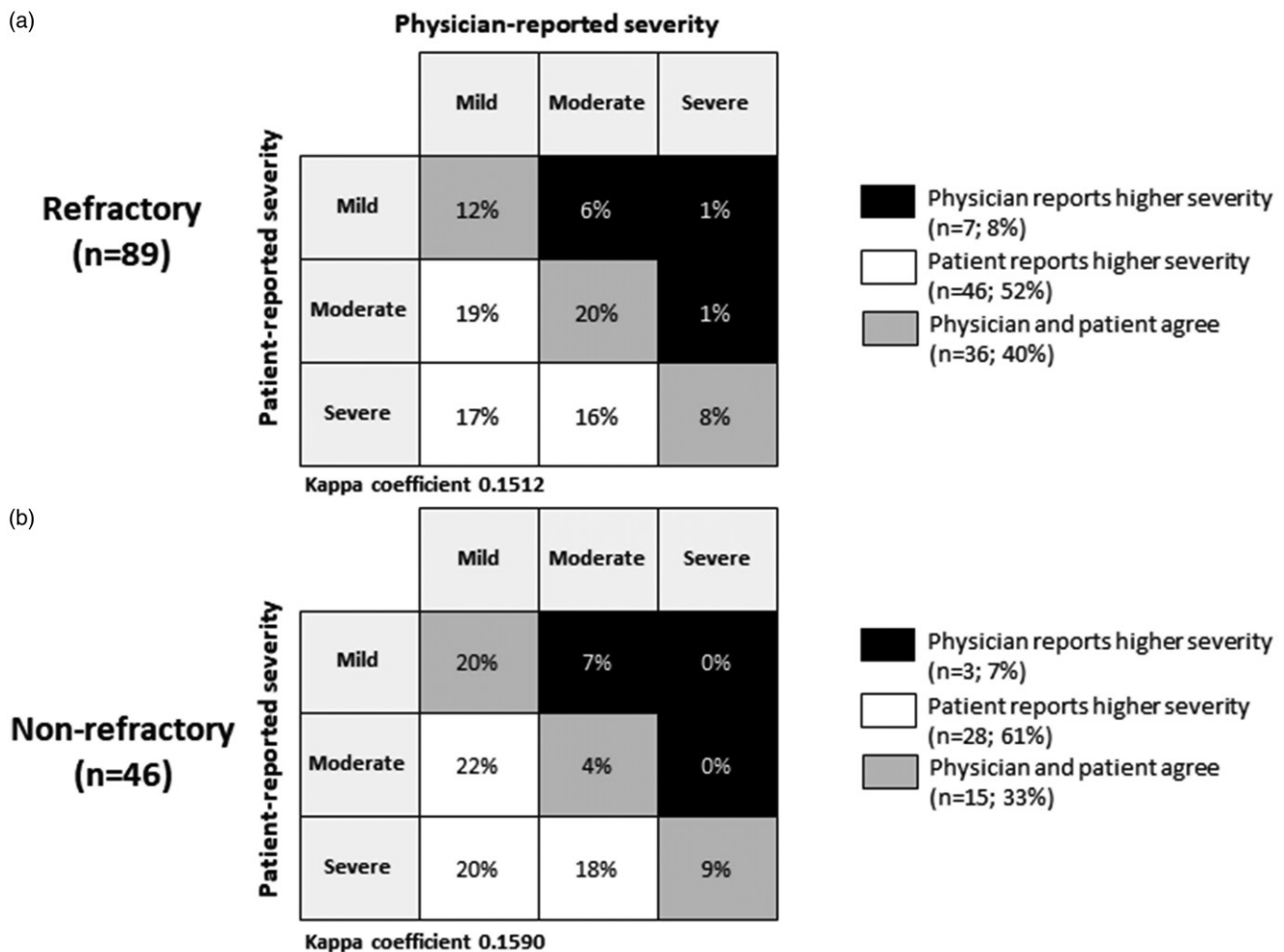


Figure 2. Physician- and patient-reported severity of disease in patients with (a) refractory and (b) non-refractory chronic idiopathic urticaria.

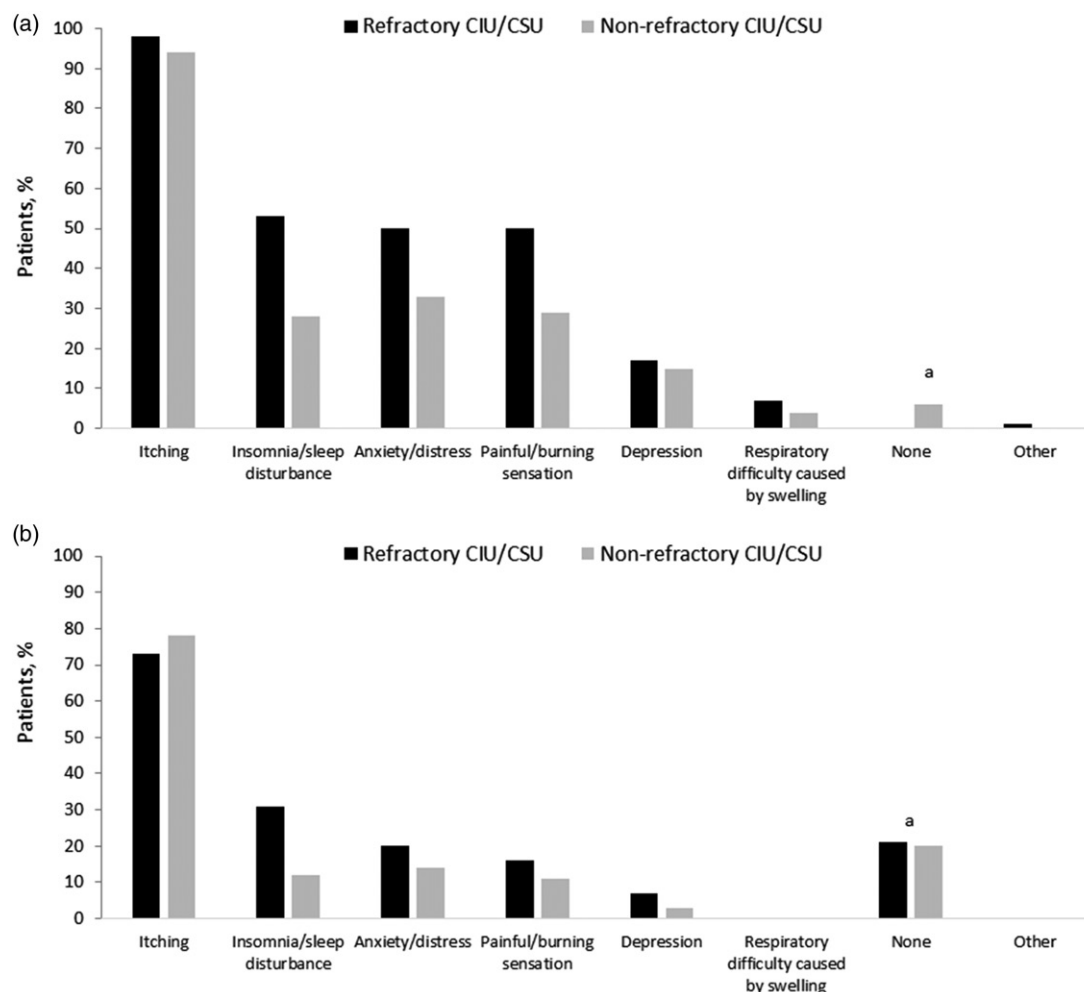


Figure 3. Symptoms reported by physicians: (a) at diagnosis and (b) present at the current consultation or most recent symptomatic period. Abbreviations. CIU, Chronic idiopathic urticaria; CSU, Chronic spontaneous urticaria. ^aPatients could be symptom-free on the day of consultation but have had symptoms in the recent past and still be considered refractory to treatment (see definition in *Methods*).

overall), sleep problems (23%) and anxiety/distress (18%). Symptom profiles for patients with refractory and non-refractory CIU/CSU are shown in Figure 3. The incidences of itching, pain, depression and anxiety were similar in both groups, whereas insomnia/sleep disturbance was more common in patients with refractory versus non-refractory disease ($p = .0024$). Some reduction in physician-reported symptom burden between the time of diagnosis and the current consultation was evident in both groups (Figure 3).

Areas of the body most commonly affected by CIU/CSU included the arms/elbows/wrists, back, legs/knees/ankles and chest/abdomen (Supplementary Figure S1). A similar pattern was observed in refractory and non-refractory patients. The entire body was affected in 37% of patients with refractory disease and 36% of patients with non-refractory disease.

Physicians reported that 10% of patients overall were currently experiencing angioedema and a further 32% had previously experienced angioedema; the typical duration of symptomatic periods was 102 (SD 166.7) days. Similar proportions of patients with refractory and non-refractory CIU/CSU were currently experiencing (9% and 11%, respectively) or had previously experienced angioedema (37% and 24%, respectively). The typical duration of symptomatic periods

was similar in patients with refractory and non-refractory disease (99 and 106 days, respectively).

Physician-reported goals of treatment are shown in Figure 4. Managing itching, reducing the frequency of symptomatic periods and dissipation of hives were the most commonly cited goals overall; managing angioedema was less important to physicians than other goals. Goals that were of greater importance in patients with refractory versus non-refractory disease included reducing the frequency ($p = .0018$ for refractory vs. non-refractory disease), severity ($p = .0036$) and duration ($p = .0161$) of symptomatic periods; improving the patient's ability to perform normal daily activity ($p = .0004$); preventing relapses ($p = .0009$); minimizing adverse events ($p = .0157$); and limiting the psychological impact of the disease ($p = .0168$). Managing itching, dissipation of wheals and reducing hives/angioedema on exposed areas in order to improve the patient's appearance were similarly important goals for patients with refractory and non-refractory disease.

Healthcare resource use

Physicians reported the mean number of consultations relating to CIU/CSU per patient in the last 12 months as 5.6 (SD 4.2) for the overall population; this was higher in patients

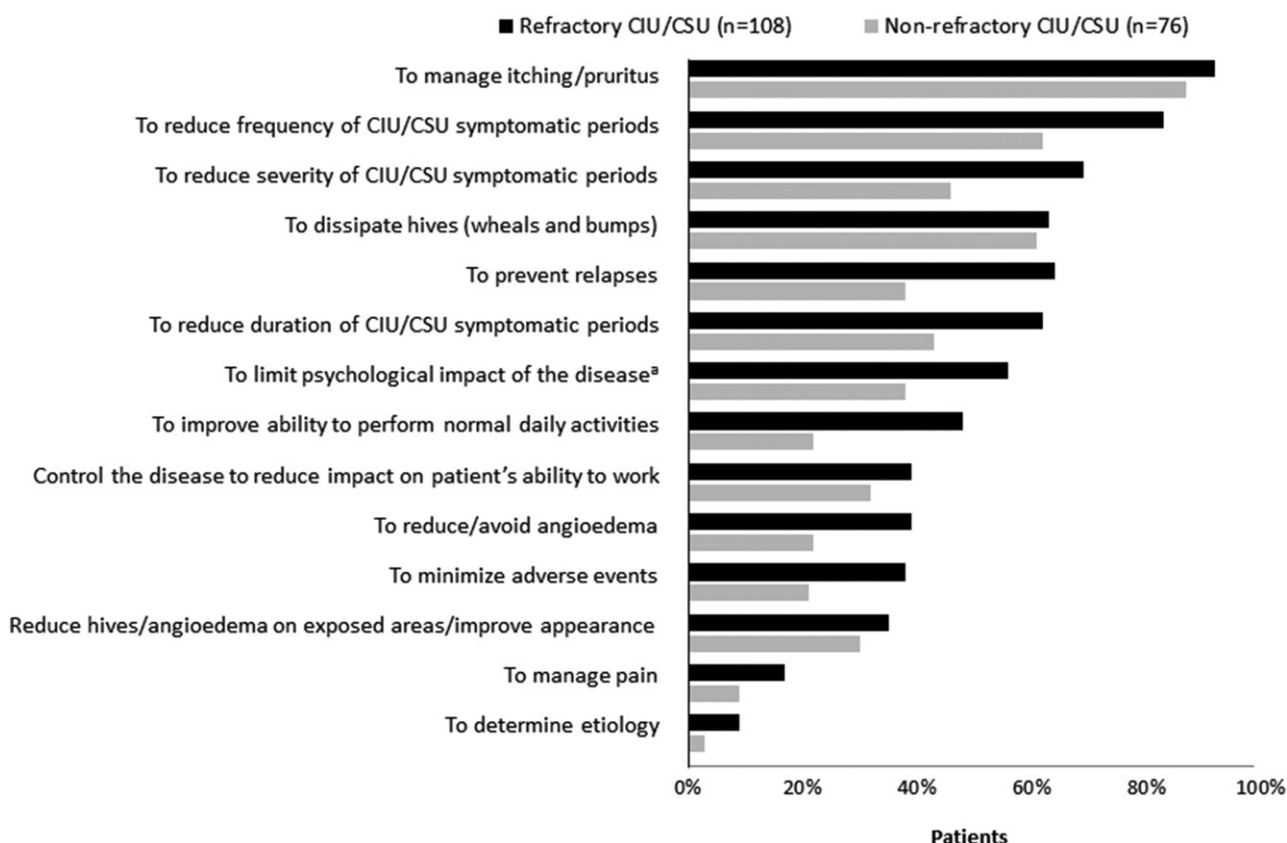


Figure 4. Goals of treatment for patients with CIU/CSU as reported by physicians. ^aEffect on social activities, interpersonal relationships, anxiety/stress, general psychological wellbeing. Abbreviations. CIU, Chronic idiopathic urticaria; CSU, Chronic spontaneous urticaria.

with refractory versus non-refractory CIU/CSU (6.3 [SD 4.7] vs. 4.4 [SD 3.0], respectively; $p = .0036$). Only one patient was hospitalized in the past 12 months as a result of their CIU/CSU. Healthcare professionals consulted are shown in Table 1; patients most commonly consulted their allergist; primary care physicians/general practitioners/internists were consulted less commonly.

Patients had previously undergone a mean of 3.5 (SD 3.9) laboratory, physical and perceptual tests/assessments, performed at any time, for their urticaria. Those with refractory disease underwent more tests than patients with non-refractory CIU/CSU (4.2 vs. 2.6, respectively; $p = .0012$). The most common laboratory tests were complete blood counts, which were performed in 46% of patients overall (54% of patients with refractory CIU/CSU and 34% of those with non-refractory CIU/CSU; $p = .0107$), antinuclear antibody tests (38%, 44% and 29% of patients, respectively; $p = .0447$) and thyroid function measurements (33%, 42% and 20% of patients, respectively; $p = .0023$; Supplementary Figure S2). Overall, disease activity and patient-reported outcomes measures were infrequently reported by the physician. When used, the most common patient-reported outcomes previously administered or recorded were the UAS7 (in 11% of patients overall, 11% of those with refractory CIU/CSU and 11% of patients with non-refractory CIU/CSU; $p = 1.0000$) and the Dermatology Life Quality Index (3%, 5% and 0% of patients, respectively; $p = .0781$). Overall, 33% of patients had undergone no laboratory, physical or perceptual tests/

assessments (22% of patients with refractory CIU/CSU and 47% of those with non-refractory CIU/CSU; $p = .0004$).

Discussion

Information regarding the qualitative burden of CIU/CSU on the US healthcare system has been limited to date. The present study of clinical burden and healthcare resource use in a real-world CIU/CSU population was undertaken to provide an insight into patients with CIU/CSU. Unlike the previous National Health and Wellness Survey (NHWS) of patients with chronic urticaria²⁰, the present study included only those patients with chronic urticaria with no known cause – a little studied group of patients.

Patients in this study took a considerable time to consult a physician and had a time from first consultation to diagnosis of 13.5 weeks and a time from diagnosis to first treatment of 16 weeks. Patients were frequent consulters, with an average of 5.6 visits in the previous 12 months to healthcare providers, in particular allergists and primary care physicians. This is in line with reported healthcare resource use in the NHWS, which identified patients with chronic urticaria as having twice the healthcare resource use of matched control patients²⁰ and comparable resource use to patients with severe psoriasis⁸. A similar level of resource use was observed in patients with CIU/CSU in the ASSURE-CSU study performed in Canada, France, Germany, Italy, Spain, The Netherlands and the UK²¹. Unlike the latter study,

hospitalization due to CIU/CSU was uncommon in the present study, possibly as a result of differences in disease severity in patients in the two studies.

Patients perceived their disease to be more severe than did their physicians. This suggests poor communication by patients or poor understanding and/or appreciation by physicians of the impact of CIU/CSU symptoms on patients and their quality of life. Whatever the reason, discordance in disease-severity perception may affect treatment selection and outcomes. Poor physician–patient concordance has been reported in other diseases, including rheumatoid arthritis²² and psoriasis²³. Physical factors, such as pain and markers of inflammation²⁴, and depression²² have been associated with higher discordance. Possible reasons for discordance were not identified in the present study.

A key feature of this research was the comparison of patients with refractory versus non-refractory CIU/CSU, which enabled identification of differentiating characteristics and inefficiencies in the management of patients with both refractory and non-refractory disease. Patients with refractory CIU/CSU appeared to experience a more complex diagnostic process than those with non-refractory disease. Refractory patients were more likely to initially consult a primary care physician than patients with non-refractory disease, most of whom consulted a specialist at the first instance. This appeared to result in a slower diagnostic process and delayed initiation of effective specialist care.

This is, to the best of our knowledge, the first study to compare symptom burden in patients with refractory and non-refractory CIU/CSU in the USA. Assessment of symptoms showed a greater burden in patients with refractory disease compared with those with non-refractory CIU/CSU, with the potential to impact on patients' quality of life if not adequately treated. Insomnia/sleep disturbance was significantly more common in patients with refractory versus non-refractory disease. Sleep disturbance, which results in impaired quality of life and, in some cases, serious psychopathology, is a key issue for some patients with CIU/CSU²⁵. Results from three placebo-controlled clinical studies have shown that treatment with omalizumab resulted in improvements in sleep, suggesting that this might be an appropriate treatment option for patients whose CIU/CSU is uncontrolled despite H₁ antihistamines²⁶.

Overall, patient-reported outcomes and disease activity measures were infrequently used/documented by physicians in this setting. Patients with refractory disease underwent more laboratory, physical and perceptual tests and had more healthcare practitioner consultations than those with non-refractory disease, suggesting a greater financial burden for both the patient and the healthcare system. This is in agreement with other studies, which have shown a substantial financial burden associated with CIU/CSU^{21,27–29}. These findings underline the importance of improving outcomes in patients with refractory CIU/CSU.

Some limitations of this study warrant consideration. As this was a presenting population of a limited number of patients who consulted a specialist physician, under- and over-representation of various patient groups is possible.

Consequently, our findings may not be generalizable to the broader CIU/CSU population. In addition, physicians were mainly allergists ($n = 15$, vs. dermatologists $n = 2$). As urticaria is a cutaneous disease, patients are managed by dermatologists and allergists; the split of allergists and dermatologists in the current study may therefore not be representative of the proportions of these specialties in the US. Another potential limitation is that as there is no widely accepted definition of refractory urticaria, refractoriness in the present study was a subjective measure of disease status; consequently, other definitions may be considered. Finally, objective measures of disease severity were not widely used in this study. This may lead to misclassification and potential mismanagement of patients.

Conclusion

The present analysis suggests that patients with CIU/CSU may take a long time to receive specialist treatment, and have a high symptom burden and a considerable physician–patient severity perception discordance. Despite guideline recommendations, use of objective measures of disease severity is limited in real-world clinical practice. Additional research into the factors considered by physicians when assessing disease severity would be useful in understanding patient classification and treatment and management practices. Patients with refractory CIU/CSU appear to have a greater symptom burden than those with non-refractory disease. These findings add to the available understanding of the clinical burden associated with CIU/CSU and suggest further areas for research and education, in particular the role of primary care physicians in the diagnosis and management of patients with CIU/CSU.

Transparency

Declaration of funding

Sponsorship for the study and editorial assistance were funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

Author contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, had full access to the data in this study, take responsibility for the integrity of the data and accuracy of the data analysis, and have given their approval for this version to be published.

Declaration of financial/other relationships

B.H. has disclosed that he is employed by Adelphi Real World. B.O., B.P. and A.K. have disclosed that they are employees of Novartis Pharmaceuticals Corporation and own stock or stock options. The authors have indicated that they have no other conflicts of interest regarding the content of

this article. *CMRO* peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgements

The authors thank David Bell and Stuart Blackburn of Adelphi Real World for their contribution to the data acquisition and analysis. Editorial assistance in the preparation of this article was provided by Deirdre Carman, and was funded by Novartis Pharmaceuticals Corporation.

Data availability

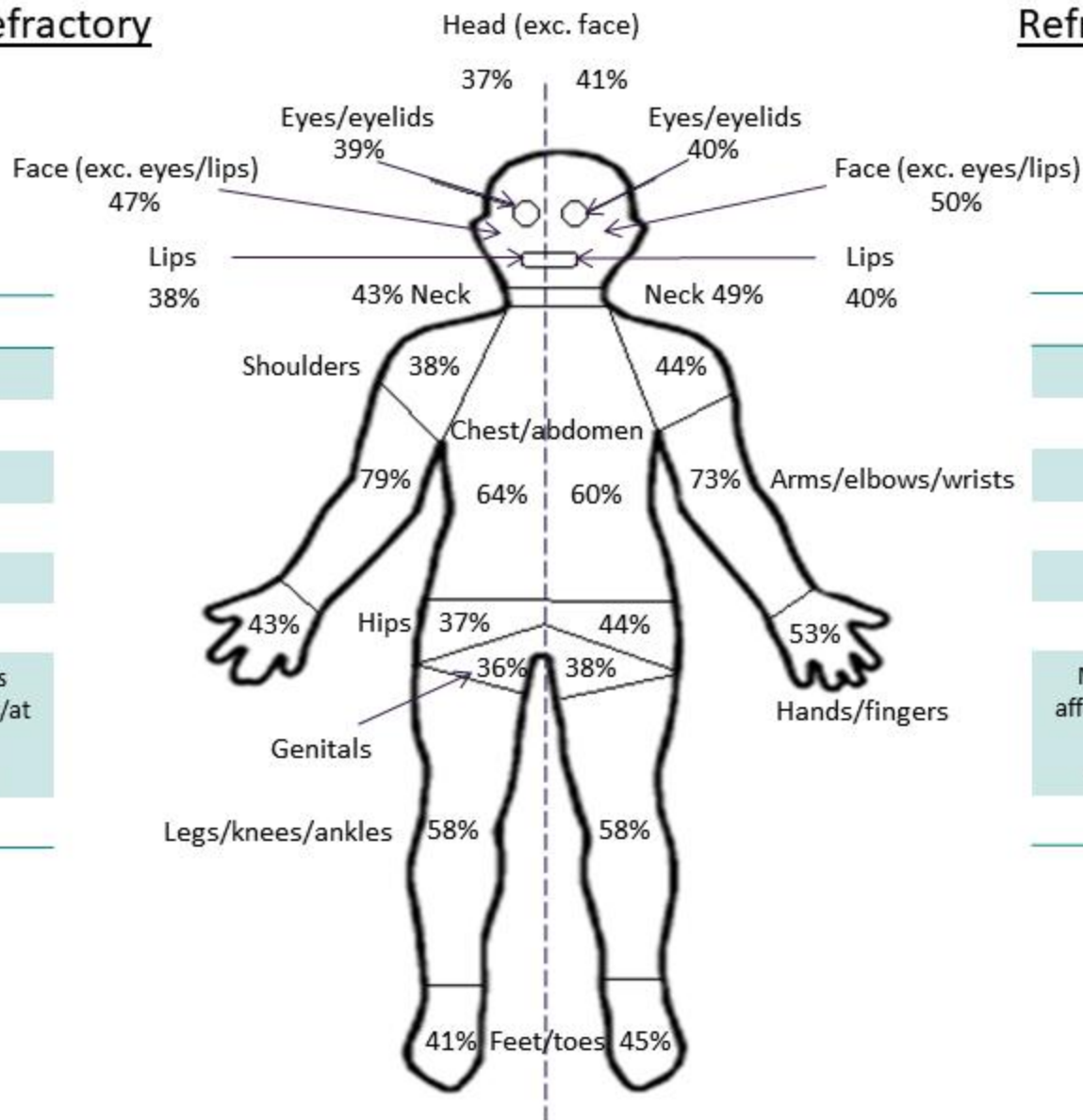
The datasets generated and/or analyzed during the current study are not publicly available as these are proprietary data. All of the conclusions drawn in the manuscript are based on data included in the publication and supporting literature has been provided.

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Non-refractory

Refractory



Not Shown

Back

57%

Buttocks

37%

Entire Body

36%

Mean number of sites affected by hives today/at most recent CSU symptomatic period

7.3

Not Shown

Back

59%

Buttocks

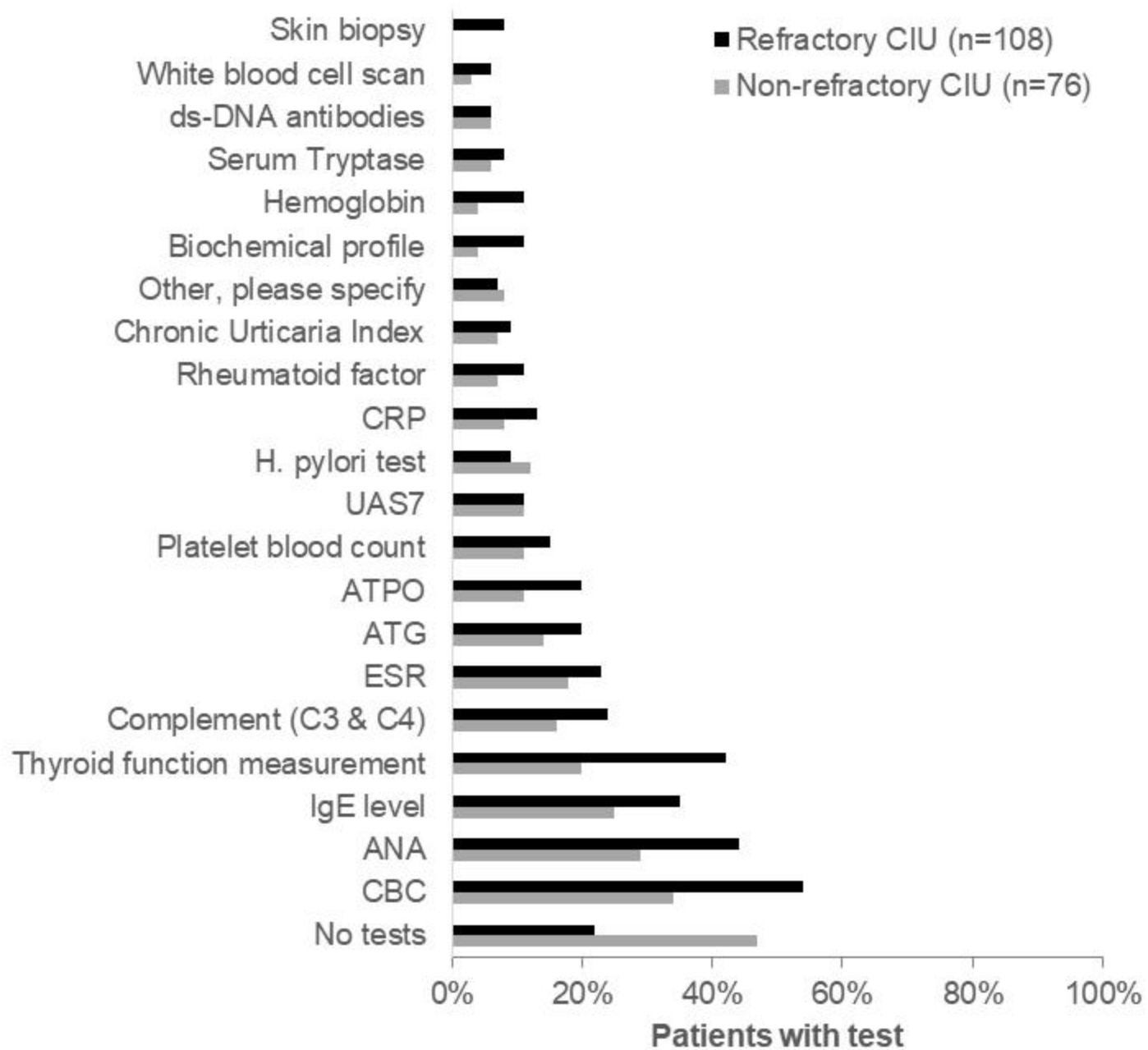
45%

Entire Body

37%

Mean number of sites affected by hives today/at most recent CSU symptomatic period

7.8



Electronic supplementary material

Figure S1 Areas of the body affected in patients with refractory and non-refractory chronic idiopathic urticaria/chronic spontaneous urticaria

Figure S2 Tests performed in patients with CIU/CSU

ANA antinuclear antibody; ATG antithyroglobulin antibody; ATPO antithyroperoxidase antibody; CBC complete blood count; CIU chronic idiopathic urticaria; CSU, chronic spontaneous urticaria; CRP C-reactive protein; ESR erythrocyte sedimentation rate; Ig immunoglobulin; UAS7 Urticaria Activity Score over 7 days.