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Chronic urticaria in the real-life clinical practice setting in the UK: results from the non-interventional multicentre AWARE study

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Running head: CU in the clinical practice setting in the UK

Abstract

Background. Chronic urticaria (CU) is a skin condition characterised by repeated occurrence of itchy wheals and/or angioedema for >6 weeks.

Aim. To provide data demonstrating the real-life burden of CU in the UK.

Methods. This UK subset of the worldwide, prospective, non-interventional AWARE study included patients aged 18–75 years diagnosed with H1-antihistamine (H1-AH)-refractory chronic spontaneous urticaria (CSU) for >2 months. Baseline characteristics, disease activity, treatments, comorbidities and healthcare resource use were documented. Quality of life, work productivity and activity impairment were assessed.

Results. Baseline analysis included 252 UK patients. Mean age and body mass index were 45.0 years and 29.0 kg/m², respectively. Most patients were female (77.8%) and had moderate/severe disease activity (mean Urticaria Activity Score over 7 days, 18.4) and a ‘spontaneous’ component to their CU (73.4% CSU; 24.6% CSU and chronic inducible urticaria). Common comorbidities included depression/anxiety (24.6%), asthma (23.8%) and allergic rhinitis (12.7%). A previous treatment was recorded for 57.9% of patients. Mean Dermatology Life Quality Index score was 9.5 and patients reported impairments in work productivity and activity. Healthcare resource use was high. Severity of CSU was associated with gender, obesity, anxiety and diagnosis. Only 28.5% of patients completed all nine study visits, limiting analysis of long-term treatment patterns and disease impact.

Conclusions. Adult H1-AH-refractory CU patients in the UK reported high rates of healthcare resource use and impairment in quality of life, work productivity and activity at baseline. The differing structures of UK healthcare may explain the high study discontinuation rates versus other countries.

Introduction

Chronic urticaria (CU) is a group of skin conditions that include chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU) characterised by the recurrence of itchy wheals and/or angioedema for >6 weeks, with (CIndU) or without (CSU) the need for provoking stimuli.¹⁻

⁴ The estimated worldwide prevalence of CU is up to 1% in the general population.⁴ However, direct information on CSU prevalence in the general population is not available due to difficulties in classification, identification and diagnosis of CU.²

The ASSURE study found considerable delay in diagnosis and specialist referral and inadequate knowledge about CSU among medical staff in primary and secondary care.⁴ Incorrect and ineffective treatment patterns were identified, and poor compliance with guidelines resulted in unnecessary investigations and delayed treatments, highlighting many unmet needs in CSU.⁴

Moreover, data on real-life consequences of CU are still limited and little is known about the disease burden, healthcare resource use and socioeconomic impact on H1-antihistamine (H1-AH)-refractory CU patients treated by general practitioners.

The non-interventional AWARE (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) study collected data from a representative sample of CU patients across the world to document real-life treatment scenarios, burden of disease and use of clinical resources in patients with H1-AH-refractory CU.⁵⁻⁹ Our paper reports the UK-specific analysis of baseline demographics of patients with CU, disease characteristics in CSU patients refractory to H1-AHs, as well as healthcare use and impairment in quality of life (QoL), work productivity and activity.

Methods

UK data were collected as part of the non-interventional, multinational, umbrella-design AWARE study. Patients were enrolled between September 2014 and August 2017 from specialised secondary/tertiary dermatology and/or immunology centres across the UK (Salford, Poole, London, Manchester, Chester, Sheffield, Coventry and Warwickshire, Durham, Leeds, Cardiff, Plymouth, Kent and Canterbury, Lewisham, Belfast, Hull, Leicester, Middlesbrough and Liverpool). Centres were selected according to whether they routinely treat CU patients refractory to at least one H1-AH.

Study objectives

The overall primary objective of the worldwide AWARE study, designed before widespread use and approval of omalizumab, was correlation of patient-reported outcomes with treatment options in patients with H1-AH-refractory CU. The study was designed to give a 2-year clinical ‘snapshot’ of patients with CU.

This analysis reports baseline demographics of patients with CU in the UK and analysis of disease characteristics including disease activity/progression over 24 months in patients completing the study.

Study population

CU patients refractory to recommended H1-AH therapy were eligible for enrolment. Inclusion criteria included age ≥ 18 years, medically confirmed diagnosis of CU present for >2 months and refractory to treatment with at least one H1-AH (licensed dose). Patients were informed about the study and provided written consent.

Study design

Patients were observed for 2 years, with eight follow-up visits in quarterly intervals after the baseline visit (Visit 1) (Fig. 1). Variables assessed included demographic data (including height, weight, age and gender), disease activity, current angioedema or angioedema since last visit (skin examination and patient report), comorbidities, current pharmacological treatment, satisfaction with current treatment (visual analogue scale [VAS]) and health-related QoL. Patients also reported how frequently they had missed work (sick leave) and visited additional healthcare resources (including emergency services, hospitalisations, general practitioners, specialised urticaria centres, dermatologists, allergists, ear, nose and throat specialists, dentists and alternative practitioners) since their urticaria symptoms first appeared.

Patient-reported outcomes

Four patient-reported outcomes (Dermatology Life Quality Index [DLQI],¹⁰ Urticaria Activity Score over 7 days [UAS7],¹¹ EuroQol five-dimensions instrument¹² and Work Productivity and

Activity Impairment questionnaire [WPAI]¹³) were offered and used to assess disease control and impact of CSU on patients' QoL.

Statistical analysis

Descriptive analyses were performed to gain an understanding of the qualitative and quantitative nature of the data collected and characteristics of the sample studied. Continuous variables were reported as mean (and standard deviation) or median, minimum and maximum, where appropriate. Categorical variables were reported as counts and proportion of the total study population, where appropriate.

Multivariate analysis was performed using a model based on backward selection. Dependent variables were UAS7 or DLQI. All respective variables with $\leq 10\%$ missing values and a frequency of $\geq 5\%$ were used.

Results

Study population

A total of 265 patients were registered from 21 centres across the UK – 252 patients with CU met all study criteria, of whom 126 were enrolled in a dermatology centre and 126 were enrolled in an immunology and allergy centre. The majority of CU patients included in the study were diagnosed with CSU (n=185; 73.4% [Table 1]). The number of patients with any CSU was 247. Overall, 28.5% of all study patients completed the study. Reasons for discontinuation were lost to follow-up (72.1%), spontaneous remission of CU (20.3%), withdrawal of informed consent (6.4%), relocation (0.6%) and death (0.6%). When compared to patients who discontinued the study, patients who completed the study were older (mean age [SD] 50.02 years [15.01] vs 43.6 years [15.08]; p=0.005) and tended to have more comorbidities such as atopic dermatitis (15.4% vs 5%; p=0.096) and food allergy (9.6% vs 3%; p=0.0375). Patients who remained in the study were also more likely to be on therapy, including “any treatment” (75% vs 53.5%; p=0.0051), omalizumab (7.7% vs 0.5%; p=0.0009) and ciclosporin (23.1% vs 7%; p=0.0007). Patient numbers per visit are shown in Fig. 1.

Baseline demographics and disease characteristics

Baseline demographics and disease characteristics for the overall population and according to enrolment centre specialty are presented in Table 1. Overall, 57.9% of patients reported using treatments for CU. Depression/anxiety disorder (24.6%), asthma (23.8%) and allergic rhinitis (12.7%) were the most frequently reported comorbidities. Asthma ($p=0.0078$), allergic rhinitis ($p=0.0007$), other type of eczema ($p=0.0006$), food allergy ($p=0.0055$) and obesity ($p=0.0098$) were more frequently reported in patients enrolled at immunology/allergy centres. Patients from immunology/allergy centres also reported more angioedema ($p=0.0004$) and angioedema of greater severity ($p=0.0099$) compared to patients enrolled at dermatology centres.

Occurrence of itchy wheals and angioedema

At baseline, wheals on presentation or in the preceding 6 months were reported in 79.4% of patients (Table 1). Individual lesions were reported as lasting for >24 hours for 40.7% of patients. Skin biopsy to look for evidence of vasculitis had been performed in 10.4% of cases. The frequency of flare-ups with wheals declined during the study period from 73.5% (Visit 5) to 69.0% (Visit 9).

Angioedema was reported by 55.9% of patients in the 6 months preceding the initial study visit, with 88.2% of these cases occurring in association with wheals, and 77.3% of these patients reporting moderate or severe angioedema intensity. According to disease activity (UAS7 0–15, 16–27 and 28–42), average duration of angioedema (hours) at Visit 1 was 69.7 (range 5.0–72.0), 34.3 (range 4.0–48.0) and 34.0 (range 8.5–48.0), respectively. Occurrence of reported angioedema decreased to 47.6% (Visit 5) and 27.3% (Visit 9) over the study period.

Patient-reported outcomes

At baseline, mean UAS7 was 18.4, with 42.9%, 26.7% and 30.4% of patients reporting mild (UAS7 0–15), moderate (UAS7 16–27) and severe (UAS7 28–42) disease severity, respectively. Mean DLQI score was 9.5, with 41.8% of patients reporting a large or extremely large impact on QoL (DLQI total score ≥ 11). Overall mean value of the VAS, assessing satisfaction with therapy, was 6.6 (VAS range: 0 [not at all satisfied] to 10 [very satisfied]). Percentage of work impairment as assessed by the WPAI was 28.8%.

Mean total activity impairment was 34.1%, and 32.9% of patients reported at least one sick leave due to urticaria since time of diagnosis; cumulatively, patients were sick for an average of 17.5 weeks. Changes in DLQI, VAS, WPAI and total activity impairment over the study period are presented in Table 2.

Use of medical and clinical resources

Use of medical and clinical resources at baseline and over the study period are presented in Table 3. 33.8% of patients visited an emergency physician or accident and emergency (A&E) department, of whom 68.2% reported angioedema. 12.3% were hospitalised for CU symptoms at least once before enrolment into the study. 84.1% had visited a general practitioner, 41.0% had visited an additional dermatologist or allergist and 25.1% had visited a specialised urticaria centre (Table 3). The average number of visits was 7–13 before study enrolment.

Multivariate analysis

Severity of CSU (UAS7 score) was associated with gender (female), obesity, anxiety disorder and diagnosis (for both CSU and CIndU). Analysis revealed significant positive correlations between UAS7 and gender (female) ($p=0.0014$). A positive correlation was observed for anxiety disorder, but this was not significant. There was a significant negative correlation between UAS7 and obesity ($p=0.0166$) and UAS7 and diagnosis for both CSU and CIndU ($p=0.0245$).

QoL (DLQI score) was associated with gender (female), age, obesity, anxiety disorder and diagnosis (for both CSU and CIndU). Significant positive correlations were observed for gender (female) ($p=0.0056$) and anxiety disorder ($p=0.0054$). A negative correlation was observed for age ($p=0.008$). A trend for negative correlation of DLQI score for obesity was reported ($p=0.0690$).

Discussion

We present baseline disease characteristics and demographics from a study of 265 H1-AH-refractory CU patients referred to specialised urticaria centres in the UK. Notably, only 28.5% of patients completed all nine visits. This may be due to a large number of patients achieving remission and the nature of the UK healthcare system where availability and access to specialist secondary and tertiary care vary between regions, with patients largely managed within the primary care system. As such, the high rate of study discontinuation may be largely due to patients

returning to primary care management following resolution of initial symptoms and associated problems. This is consistent with the most frequently stated reasons for early study discontinuation ('lost to follow-up' and 'spontaneous remission of CU'), as well as the value of adequate knowledge of the importance of adherence to treatment guidelines in the management of CU, which would have been high in these specialised secondary and tertiary centres.

The baseline characteristics reported in this study of UK patients are generally comparable with previously published literature, with the majority of patients being female, and similar reported mean age and body mass index.^{2,4,5,7-9,14,15} Psychiatric comorbidities (depression/anxiety) were the most frequently reported comorbidities; this was unsurprising given the large psychological impact of CU. In the UK, a primary care physician may have a choice of referring a patient with suspected urticaria to an allergist/immunologist or a dermatologist. Differences were observed depending on the specialty of the recruiting physician (allergy/immunology vs dermatology), with patients at an allergy centre reporting a greater prevalence and intensity of angioedema, as well as a higher number of comorbidities. Prior medication history was relatively similar, although patients enrolled at a dermatology centre were more likely to have received sedative H1-AH.

These findings partly reflect referral criteria/patterns in the UK since, for example, patients with angioedema are typically referred to immunology centres in the first instance. Coexistence of these two conditions in the same patient might imply to a referring physician that the urticaria may be allergic in origin and subsequently be more frequently referred to an allergist/immunologist.

Previous publications report that CU is associated with poor QoL, increased healthcare use and increased absenteeism, presenteeism and work impairment.^{2,4,16-18} Consistent with this, a moderate impact (at least) of CU on QoL was reported, and impairments in work productivity and activity were reported in almost one third of patients. Angioedema was reported in >50% of patients, with >75% reporting at least moderate disease intensity, which is likely to have an additional negative impact on QoL, work productivity and activity. Furthermore, presence of wheals for >24 hours was reported in approximately 40% of patients. While these results may be due to patients over-reporting the presence of symptoms, it is also indicative of the impact of disease patients with CU feel. The economic burden of CU in the UK was also evident, with a third of patients reporting A&E department attendance since symptom start, and a higher rate of A&E attendance in patients reporting angioedema. CSU should almost never require A&E attendance or admission since it is not life-threatening, and A&E attendance rates may reflect the difficulty some patients experience

in seeing their primary care physician urgently and a general lack of understanding of the condition, highlighting the need to ensure patients are managed appropriately to optimise their QoL and reduce the socioeconomic burden of CU.

The correlation between QoL and age (negative) and QoL and anxiety disorder (positive) provides an insight into the impact of CSU on younger patients and reflects the social, physical, emotional and psychological status. Although body mass index has been suggested as a risk factor for CSU,^{15,19} we found a significant negative correlation between disease severity and obesity. This is consistent with results in a French cohort reporting lack of association between obesity and severe CSU.²⁰ Additional research is required to investigate any causal relationship between obesity and CSU.

One limitation is the potential for selection bias as patients were recruited from specialised urticaria centres, biasing recruitment towards patients with more severe CU. Additionally, high rates of study discontinuation limit analysis of disease activity, long-term treatment patterns and disease impact. Finally, patients may over-report certain symptoms based on current feelings of discomfort or misunderstanding of how to quantify the presence of symptoms. Further studies exploring management of patients within the UK healthcare system may provide further insight.

Conclusion

These data highlight the disease burden and impact of H1-AH-refractory CU on patients treated in specialised centres in the UK. Patients have impaired health-related QoL, high usage of healthcare resources and impaired work productivity. Further investigation into management of CU patients outside secondary and tertiary care is needed to ensure patients are managed appropriately to optimise their QoL and reduce the socioeconomic burden of CU.

What is already known about this topic?

- CU remains uncontrolled in approximately half of patients, despite the use of licensed doses of H1-AHs
- Previous studies have established unmet needs in the treatment and management of patients with H1-AH-refractory CU, including delays in diagnosis and specialist referral,

inadequate knowledge among medical staff, incorrect treatment patterns and poor compliance with guidelines and best practices

What does this study add?

- The study demonstrates the significant impairments in QoL and work productivity and high healthcare resource use in many patients with H1-AH-refractory CU in the UK
- These findings suggest that patients presenting with both urticaria and angioedema were more frequently referred to an allergist/immunologist, rather than a dermatologist
- The data reflect clinical practice for CU in the UK and demonstrate the disease burden and unmet needs of patients with CU, highlighting the need to ensure appropriate management to optimise patient QoL and reduce the socioeconomic burden of CU in the UK

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19

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20

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Table 1 Baseline demographics and disease characteristics, both overall and according to centre of specialty enrolment

	Allergy centre (n=126)	Dermatology centre (n=126)	All patients (N=252)
Age (years), mean (SD)	43.8 (14.2)	46.1 (16.3)	45.0 (15.3)
Sex, n (%)			
Male	25 (19.8)	31 (24.6)	56 (22.2)
Female	101 (80.2)	95 (75.4)	196 (77.8)
Diagnosis, n (%)			
CSU	90 (71.4)	95 (75.4)	185 (73.4)
CIndU	1 (0.8)	4 (3.2)	5 (2.0)
CSU + CIndU	35 (27.8)	27 (21.4)	62 (24.6)
Duration of disease (years), mean (SD)	4.8 (7.1)	5.0 (7.9)	4.9 (7.5)
Family-related history of urticaria, n (%)	11 (8.7)	6 (4.9)	17 (6.8)
Systolic blood pressure (mmHG), mean (SD)	131.3 (16.0)	127.5 (15.8)	129.6 (16.0)
Diastolic blood pressure (mmHG), mean (SD)	81.2 (10.9)	77.3 (11.0)	79.5 (11.1)
Body mass index (kg/m ²), mean (SD)	30.1 (6.4)	27.6 (5.0)	29.0 (5.9)
Prior medications, n (%)			
Any treatment	69 (54.8)	77 (61.1)	146 (57.9)
Non-sedative H1-AH	53 (42.1)	51 (40.5)	104 (41.3)
Sedative H1-AH	12 (9.5)	25 (19.8)	37 (14.7)

Ciclosporin	15 (11.9)	11 (8.7)	26 (10.3)
Corticosteroid	13 (10.3)	12 (9.5)	25 (9.9)
Montelukast	10 (7.9)	12 (9.5)	22 (8.7)
Omalizumab	5 (4.0)	0	5 (2.0)
Other	26 (20.6)	28 (22.2)	54 (21.4)
Comorbidities, n (%)			
Depression/anxiety	32 (25.4)	30 (23.8)	62 (24.6)
Asthma	39 (31.0)	21 (16.7)	60 (23.8)
Allergic rhinitis	25 (19.8)	7 (5.6)	32 (12.7)
Hypertension	15 (11.9)	11 (8.7)	26 (10.3)
Other type of eczema	20 (15.9)	4 (3.2)	24 (9.5)
Atopic dermatitis	11 (8.7)	7 (5.6)	18 (7.1)
Obesity	13 (10.3)	3 (2.4)	16 (6.3)
Food allergy	10 (7.9)	1 (0.8)	11 (4.4)
Type 1 diabetes	2 (1.6)	1 (0.8)	3 (1.2)
Vitiligo	0	3 (2.4)	3 (1.2)
Hashimoto thyroiditis	2 (1.6)	0	2 (0.8)
Other psychosomatic disease	0	1 (0.8)	1 (0.4)
Lupus erythematosus	0	0	0
Hypertriglyceridaemia	0	0	0
Other comorbidities	68 (54.0)	58 (46.0)	126 (50.0)

Current wheals or wheals during the last 6 months, n (%)	97 (78.2)	99 (80.5)	196 (79.4)*
Wheals present for >24 hours	36 (38.3)	41 (43.2)	77 (40.7)†
Biopsy performed to rule out vasculitis	9 (9.5)	11 (11.3)	20 (10.4)‡
Angioedema during the last 6 months, n (%)	83 (66.9)	55 (44.7)	138 (55.9)*
Angioedema in relation to urticaria	68 (82.9)	52 (96.3)	120 (88.2)§
Angioedema in relation to medical treatment	6 (7.3)	7 (13.0)	13 (9.6)§
Hereditary angioedema	2 (2.4)	1 (1.9)	3 (2.2)§
Based on an acquired C1 esterase inhibitor deficiency	0	0	0§
Other common underlying cause	10 (12.2)	5 (9.3)	15 (11.0)§
ACE inhibitors during the last 12 months	1 (1.2)	5 (9.4)	6 (4.5)¶
Average intensity of angioedema, n (%)			
Negligible	0	0	0#
Mild	19 (23.5)	11 (21.6)	30 (22.7)#
Moderate	33 (40.7)	33 (64.7)	66 (50.0)#
Severe	29 (35.8)	7 (13.7)	36 (27.3)#
Average duration of angioedema (hours), mean (SD)	39.2 (44.9)	71.5 (130.2)	51.2 (87.7)**

ACE, angiotensin-converting enzyme; CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; H1-AH, H1-antihistamine; SD, standard deviation. *Based on n=247 (five patients missing data); †Based on n=189 (seven patients missing data); ‡Based on n=192 (four patients missing data); §Based on n=136 (two patients missing data); ¶Based on n=134 (four

patients missing data); #Based on n=132 (six patients missing data); **Based on n=97 (41 patients missing data).

Bold values indicate $p < 0.05$, for comparison between patients enrolled in allergy versus dermatology centres.

Table 2 Patient-reported outcomes

	Baseline (Visit 1)		Year 1 (Visit 5)		Year 2 (Visit 9)	
	N		N		N	
UAS7, mean (SD)	161	18.4 (13.2)	74	13.4 (12.3)	39	11.3 (10.7)
VAS, mean (SD)	241	6.6 (3.1)	78	8.1 (2.1)	36	7.8 (2.6)
WPAI score, mean (SD)	140	28.8 (27.4)	49	15.1 (20.9)	26	11.5 (17.7)
EQ-5D score, mean (SD)	244	0.66 (0.36)	86	0.73 (0.31)	51	0.78 (0.26)
Total activity impairment, mean (SD)	238	34.1 (31.2)	80	18.6 (25.9)	47	14.7 (22.2)
DLQI score, mean (SD)	237	9.5 (8.0)	87	6.1 (7.0)	48	5.0 (6.3)
Effect on patient's life, n (%)	237		87		48	
No effect at all (0–1)		47 (19.8)		26 (29.9)		22 (45.8)
Little effect (2–5)		46 (19.4)		26 (29.9)		10 (20.8)

Moderate effect (6–10)		45 (19.0)		20 (23.0)		8 (16.7)
Large effect (11–20)		73 (30.8)		10 (11.5)		6 (12.5)
Extremely large effect (21–30)		26 (11.0)		5 (5.7)		2 (4.2)
Sick leave, n (%)	252	3 (1.2)	92	5 (5.4)	51	1 (2.0)
Duration of sick leave (weeks), mean (SD)	70	17.5 (61.9)	4	1.2 (1.9)	1	0.6 (–)
Duration of sick leave due to angioedema (weeks), mean (SD)	30	6.6 (18.9)	1	0.9 (–)	–	–

DLQI, Dermatology Life Quality Index; EQ-5D, European Quality of Life – 5 Dimensions; SD, standard deviation; UAS7, Urticaria Activity Score over 7 days; VAS, visual analogue scale; WPAI, Work Productivity and Activity Impairment.

Table 3 Use of medical and clinical resources

n (%)	Baseline (Visit 1)*	Year 1 (Visit 5)†	Year 2 (Visit 9)‡
Visit to an emergency physician or A&E department	66 (33.8)	2 (3.8)	2 (7.4)
Hospitalisation	24 (12.3)	2 (3.8)	1 (3.7)
Visit to a specialised urticaria centre	49 (25.1)	7 (13.2)	2 (7.4)
Visit to a GP/family physician	164 (84.1)	27 (50.9)	12 (44.4)
Visit to an additional dermatologist/allergist	80 (41.0)	6 (11.3)	1 (3.7)
Visit to an ENT specialist	6 (3.1)	3 (5.7)	0
Visit to a dentist	56 (28.7)	33 (62.3)	16 (59.3)
Visit to a pharmacy	53 (27.2)	7 (13.2)	3 (11.1)
Visit to an alternative practitioner	14 (7.2)	2 (3.8)	3 (11.1)
Use of other resources	–	7 (13.2)	7 (25.9)

A&E, accident and emergency; ENT, ear, nose and throat; GP, general practitioner. *Based on n=195 (57 patients missing data); †Based on n=53 (40 patients missing data); ‡Based on n=27 (25 patients missing data).

Figure legend

Figure 1 Study design and patient disposition.

ASST, autologous serum skin test*; DLQI, Dermatology Quality of Life Index; EQ-5D, EuroQol five-dimensions instrument; UAS7, Urticaria Activity Score over 7 days; VAS, visual analogue scale; WPAI, work productivity and activity impairment.

*Not part of routine clinical practice – only used occasionally.

Figure 1

