

ORIGINAL ARTICLE

Chronic urticaria in the real-life clinical practice setting in Sweden, Norway and Denmark: baseline results from the non-interventional multicentre AWARE study

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Abstract

Background Chronic urticaria (CU) is characterized by the recurrence of itchy hives and/or angioedema for more than 6 weeks. AWARE (A World-wide Antihistamine-Refractory Chronic Urticaria Patient Evaluation) is a multinational study designed to document the real-life treatment situation, burden of disease and clinical resource usage of H1-antihistamine-refractory CU patients.

Objective To examine baseline data from Scandinavian AWARE patients.

Methods AWARE is a prospective, non-interventional, multinational, umbrella design study, which includes adults (≥ 18 years) with a confirmed CU diagnosis (> 2 months) that is refractory to H1-antihistamines. Baseline patient characteristics, disease activity (urticaria control test [UCT]), pharmacological treatment, comorbidities and healthcare usage were documented by the treating physician. Quality of life (QoL; dermatology life quality index [DLQI]; chronic urticaria quality of life questionnaire [CU-Q2oL; Danish patients only]) and work productivity and activity impairment (WPAI) scores were also assessed.

Results Overall, 158 CU patients from seven centres in Denmark ($n = 80$), Norway ($n = 50$) and Sweden ($n = 28$) were included in this baseline analysis. Mean age and BMI were 40.3 years and 26.5 kg/m², respectively. The majority of patients were female (69.6%), had uncontrolled CU (75.6%; UCT score < 12) and had a 'spontaneous' component to their CU (61.4% CSU; 20.3% both CSU and chronic inducible urticaria). Common comorbidities included asthma (19.6%), allergic rhinitis (16.5%) and food allergies (8.2%). Overall, 60.1% of patients reported using treatments for CU including non-sedative H1-antihistamines (40.5%), corticosteroids (19%), montelukast (14.6%) and omalizumab (8.2%). Pharmacological treatment rates increased to 96.2% during the baseline visit. On average, patient QoL was moderately affected (mean DLQI score 7.7) and healthcare resource usage was high.

Conclusion Adult Scandinavian H1-antihistamine-refractory CU patients reported high rates of healthcare usage and QoL impairment. Rates of pharmacological treatment use were low before study enrolment but increased to almost 100% during the baseline visit.

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Conflicts of interest

Simon Francis Thomsen has received research support, consultancy fees and lecture fees from Novartis. Christian Vestergaard has received consultancy fees and lecture fees from Novartis. Ellen Cathrine Pritzler has received consultancy fees and lecture fees from Novartis. Chris D Anderson has received consultancy fees and lecture fees from Novartis. Nicolas Vaugelade-Baust, Rikke Dodge and Anna-Karin Dahlborn are employees of Novartis.

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Introduction

Chronic urticaria (CU), which includes chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU), is characterized by the recurrence of itchy hives and/or angioedema for more than 6 weeks.¹ CSU can be further divided into CSU due to unknown causes and CSU due to a known cause, e.g. proven autoimmune mediated CSU.^{2–4} The symptoms of CSU develop without any specific physical or external triggers, whereas the symptoms of CIndU develop in response to specific triggers (e.g. heat urticaria, cold urticaria, delayed pressure urticaria, solar urticaria, symptomatic dermographism, cholinergic urticaria, vibratory urticaria and aquagenic urticaria).⁵ The estimated prevalence of CU is up to 1% in the general population,^{4,6–8} with females reported to be affected approximately twice as often as males and the highest incidence between the ages of 20 and 40 years.^{6,9}

International guidelines recommend a stepwise treatment approach to achieve symptom control in CU.^{1,10} These guidelines recommend initial treatment with labelled doses of second-generation non-sedating H1-antihistamines (H1-AH). For patients with an inadequate treatment response within 2 weeks, up-titration of the H1-AH dose up to four times the labelled dose is recommended (high dose). If high dose continues to offer inadequate symptom relief after 4 weeks, guidelines recommend three add-on treatment options: montelukast, omalizumab or cyclosporine.¹ However, the extent to which these guidelines are adhered to in patients from Scandinavian countries remains unclear.

Patients with CU are reported to experience considerable disease burden and quality of life (QoL) impairment, which can include anxiety, economic burden and increased healthcare use.^{6–8,11–14} The burden of disease in Scandinavian patients with H1-AH refractory CU remains unknown. Furthermore, there is no comprehensive Scandinavian CU patient database reviewing H1-AH refractory CU patients. As a result, very little is known regarding the demographics, disease characteristics and prevalence of comorbidities in Scandinavian patients.

The AWARE (A World-wide Antihistamine-Refractory Chronic Urticaria Patient Evaluation) study is a multinational non-interventional study, which has been designed to document the real-life treatment situation, burden of disease and use of clinical resources of patients with H1-AH refractory CU. This interim analysis examines the baseline demographics, disease characteristics, pharmacological treatment and the extent of disease burden in Scandinavian CU patients who are refractory to H1-AHs.

Materials and methods

These baseline data from Denmark, Sweden and Norway were collected as part of the ongoing non-interventional, multinational, umbrella design AWARE study. This study is being conducted in accordance with the Declaration of Helsinki, the principles of Good Clinical Practice, and national laws and

regulations regarding clinical studies. Approval from the Institutional Review Board/Independent Ethics Committee/Research Ethics Board was obtained for each centre, and all participating patients gave written informed consent before any data were recorded.

Study patients

Inclusion criteria were age ≥ 18 years, ability to provide informed consent and a medically confirmed diagnosis of CU for more than 2 months, which is refractory to treatment with H1-AH (refractory disease was defined as evidence of failed labelled dose or up to fourfold labelled dose of H1-AHs). Patients were excluded from the study if they were participating in any other clinical urticaria study or if it was unlikely they would be available for the full duration of the follow-up period of 24 months. A patient evaluation was performed at baseline (visit 1), which included demographic data collection, CU-related medical history (treatment, course of disease, diagnosis and presence of angioedema), details of pharmacological treatment for CU and existing comorbidities. Patients were also asked to indicate whether they had used any additional healthcare resources since their CU symptoms began and, if so, how frequently they had used each resource. During the baseline visit, patients' pharmacological treatment was changed if deemed necessary by the treating physician.

Study objectives

The overall primary objective of the worldwide AWARE study is correlation of patient-reported outcomes (PROs: Dermatology Life Quality Index, DLQI; Chronic Urticaria Quality of Life questionnaire, CU-Q_{2oL}; CU specific Work Productivity and Activity Impairment, WPAI-CU; Urticaria Control Test, UCT and optional Urticaria Activity Score over 7 days, UAS7) with the treatment options used in patients with H1-AH refractory CU. The aim of this baseline evaluation is to document the disease characteristics, the pharmacological treatments used and the burden of CU in patients treated in urticaria centres in the Scandinavian arm of the AWARE study. Furthermore, the influence of disease and patient characteristics on QoL was investigated.

Patient-reported outcomes

Physicians had the option to assess patients using validated disease activity (UCT; UAS7), QoL (CU-Q_{2oL}; DLQI) and work productivity (WPAI-CU) questionnaires. The UCT is a four-item questionnaire for assessing CU disease activity retrospectively over the previous 4 weeks.¹⁵ Each item is rated on a Likert-type scale (0 = very often and 4 = not at all), and a total score is calculated (range, 0–16; higher scores indicate better disease control; scores ≥ 12 are consistent with well-controlled disease). The UAS instrument includes two items: itch intensity (0 = no itch and 3 = severe itch) and number of hives (0 = none and 3 > 50).¹ The sum of both items is calculated daily (UAS; range, 0–6), and the weekly score (UAS7; range,

0–42) is calculated based on seven consecutive days. The CU-Q2oL questionnaire, which was only recorded in Danish patients, includes 23 questions relating to overall functioning (including work, physical, leisure and social activities), sleep, itching/embarrassment, mental status, swelling/eating and limits looks (limitations in choice of clothing or cosmetics used due to urticaria symptoms). Total scores range from 0 to 100, with higher scores indicating worse QoL.¹⁶ The DLQI is a 10-item questionnaire relating to patients' symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. Total DLQI scores range from 0 to 30, with higher scores indicating worse QoL.¹⁷ The WPAI-CU evaluates work productivity and activity impairment due to chronic urticaria with the aid of six short questions relating to absenteeism (the percentage of work time missed due to urticaria), presenteeism (the percentage of impairment experienced while at work), overall work productivity (an overall work impairment estimate based on absenteeism and presenteeism) and overall activity impairment (the percentage of impairment in daily activities) over the previous 7 days.¹⁸ Only employed patients respond to the work-related questions, whereas all patients respond to the activity-related questions.

Data management and statistical analysis

Documentation was performed by the treating physician exclusively online in the electronic case report form, with the exception of the patient questionnaires that were available as hardcopy forms. Data were analysed primarily with descriptive methods using SAS® V 9.2 (SAS Institute, Inc. Cary, North Carolina, US). Means and standard deviations (SD) were calculated for continuous variables, and percentages and frequencies were calculated for categorical variables.

Linear regression analysis, with stepwise backward elimination, was used to select patient characteristics that influence DLQI scores. Potential influencing factors examined were age, gender (male vs. female), time since diagnosis, comorbidities (four variables: metabolic, atopic, autoimmune and psychiatric disease), body mass index (BMI), current hives (yes or no), angioedema (yes or no), UCT score, sick leave (yes or no) and diagnostic group (CSU, CSU and CIndU, or CIndU). Bivariate analysis was used to illustrate and further evaluate the influence of each selected variable; *P*-values of respective statistical tests (ANOVA models and *t*-tests) are provided and values below 0.05 considered as statistically significant. However, these tests only have exploratory character, and therefore, no adjustment for multiple testing has been performed.

Results

Baseline demographics and disease characteristics

Of 161 patients registered from seven specialized urticaria centres across Norway (*n* = 50), Sweden (*n* = 28) and Denmark

(*n* = 83), 158 CU patients met all the study criteria and were included in the final analysis population (two patients were excluded as they were registered after the cut-off date and one patient did not meet all the inclusion criteria). The mean patient age was 40.3 years, with the highest fraction (26.6%) of patients aged 35 to <45. The majority of patients were female, and over 50% of patients were overweight (BMI >25; Table 1).

Over 80% of patients with H1-AH refractory CU had a 'spontaneous' component to their disease (61.4% CSU; 20.2% both CSU and CIndU; and 18.4% had CIndU only). The most common CIndU subtypes were cold urticaria (18.4%), symptomatic dermographism (8.9%) and cholinergic urticaria (7.6%; Table 2). Overall, 85.4% had experienced hives within the previous 6 months and for the majority of patients hives lasted <24 h (94.8%). Angioedema had occurred in 32.9% of patients within the previous 6 months (Table 2); 3.8% rated their angioedema as negligible, 53.8% as mild, 34.6% as moderate and 7.7% as severe.

Pharmacological treatment

The most commonly reported treatments at the baseline visit included non-sedative H1-AH (any dose 40.5%: labelled dose, 12.7%; high dose, 29.1%; unknown dose, 3.2%), corticosteroids (19%), montelukast (14.6%) and omalizumab (8.2%). Denmark had the highest proportion of treated patients, followed by Norway and Sweden (Table 3). During the same visit, if deemed

Table 1 Patient demographics at baseline (analysis population)

Patient demographics	<i>n</i> (%) [*]
Age, mean (SD) [†]	40.3 (13.5)
18 to <25 years	20 (12.7)
25 to <35 years	37 (23.4)
35 to <45 years	42 (26.6)
45 to <55 years	33 (20.9)
55 to <65 years	18 (11.4)
65 to <75 years	8 (5.1)
≥75 years	0 (0.0)
Gender, f (%) [‡]	110 (69.6)
Height (m), mean (SD)	1.71 (0.09)
Weight (kg), mean (SD)	77.7 (17.1)
BMI (kg/m ²), mean (SD)	26.5 (5.0)
≤18.5 kg/m ²	1 (0.6)
>18.5 to ≤25 kg/m ²	68 (43.0)
>25 to ≤30 kg/m ²	58 (36.7)
>30 to ≤40 kg/m ²	27 (17.1)
>40 kg/m ²	4 (2.5)

^{*}Data are presented as *n* (%) unless otherwise stated.

[†]Mean age in Denmark, 42.1 years; Norway, 39.2 years; and Sweden, 37.0 years.

[‡]Percentage females in Denmark, 71.3%; Norway, 68.0%; and Sweden, 67.9%.

Data are based on *N* = 158.

BMI, body mass index; SD, standard deviation.

Table 2 Disease characteristics at baseline (analysis population)

Disease characteristics	n (%) [*]
Diagnostic group	
CSU	97 (61.4)
CIndU	29 (18.4)
CSU and CIndU	32 (20.2)
Years since diagnosis, mean (SD) [†]	6.4 (8.5)
CSU, mean (SD)	5.4 (6.6)
CIndU, mean (SD)	11.9 (13.9)
CSU and CIndU, mean (SD)	4.3 (4.3)
CIndU Subtype [‡]	
Cold Urticaria	29 (18.4%)
Symptomatic dermographism	14 (8.9%)
Cholinergic Urticaria	12 (7.6%)
Delayed Pressure Urticaria	10 (6.3%)
Heat Urticaria	3 (1.9%)
Aquagenic Urticaria	1 (0.6%)
Hives within the last 6 months	135 (85.4)
Duration of hives [§]	
<24 h	128 (94.8)
>24 h	7 (5.2)
Angioedema within the last 6 months	52 (32.9)

^{*}Data are presented as n (%), unless otherwise stated.

[†]Mean time since diagnosis (± SD): Denmark, 5.1 (7.0); Norway, 8.2 (10.5); and Sweden 6.6 (7.8) years.

[‡]No patients had a diagnosis of solar urticaria, vibratory angioedema or contact urticaria.

[§]Includes patients with current hives or hives within the last 6 months (n = 135).

Data are based on N = 158, unless otherwise stated.

CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; and SD, standard deviation.

necessary by the physicians, the patient's treatment was changed (reported as current treatment), with rates increasing to 96.2% for any treatment. Non-sedative H1-AH continued to be the most common treatment prescribed (any dose 87.3%; labelled dose, 8.2%; high dose, 76.6%; unknown, 4.4%), followed by omalizumab (42.4%), montelukast (12.7%) and corticosteroids (12.7%; Table 3). Overall, 100% of Norwegian patients were prescribed non-sedative H1-AHs (80%, Danish; 85.7%, Swedish). However, Danish patients were more commonly treated with omalizumab, montelukast and cyclosporine compared with patients in Norway and Sweden (Table 3).

Comorbidities

The most commonly reported comorbidities were asthma (19.6%), allergic rhinitis (16.5%), food allergies (8.2%) and other eczema (7.6%; Table 4). Other common comorbidities (>5%) included atopic dermatitis, nut allergies, thyroid diseases including Hashimoto's thyroiditis, obesity and hypertension. The proportion of patients with a diagnosis of anxiety (3.2%) or depression (4.4%) was low.

Burden of disease: disease activity, quality of life and work productivity

The mean UCT score (± SD) was 8.3 (4.8), indicating that on average patients' urticaria was not sufficiently controlled; only 44 of 155 patients (24.4%) presented with well-controlled urticaria (UCT score ≥12). Norwegian patients had the lowest mean UCT scores at baseline and were therefore most affected by CU (Table 5). Patients rated their satisfaction with their treatment as 6.1 (mean) on a visual analogue scale (VAS).

Overall, CU had a moderate effect on QoL, with a mean DLQI score of 7.7. Mean DLQI scores were higher in Norway (10.9) than Denmark (6.3) and Sweden (6.0), which indicates worse QoL. In addition to the DLQI score, the CU-Q2oL score was assessed in 77 Danish patients. The most severely affected subdomains of the CU-Q2oL were sleep (mean, 41.2), itching/embarassment (mean, 35.7) and mental status (mean, 30.9). The least affected subdomain of the CU-Q2oL was swelling/eating (mean, 14.7; Table 5).

A total of 155 patients completed the WPAI questionnaire. Employed patients (n = 111) reported missing work during the past 7 days due to their CU, accounting for 3.7% (mean) of their work time (absenteeism). Overall, 20.6% of their work productivity time was lost due to CU (presenteeism) and total work productivity impairment accounted for 23.2% of their time. Outside the workplace, patients (n = 155) reported activity impairment due to CU, accounting for 29.5% of their time (Table 6). Furthermore, 25.9% of patients reported sick leave, since urticaria symptoms began, due to urticaria (Table 6).

Healthcare resource utilization

Rates of healthcare utilization were high amongst these Scandinavian AWARE patients: 72.5% had visited a general practitioner (GP), 68.6% had visited another dermatologist or allergist, 42.5% had visited specialized urticaria centres, and 27.5% had visited an emergency physician or the emergency room due to urticaria since their urticaria symptoms started. The frequency of visits to healthcare resources ranged from a mean number of visits of 1.0 (pharmacy) to 10.5 (alternative practitioner). Other healthcare resource utilization reported included, dentists, ear–nose–throat specialists and hospitalization (Table 7).

Factors affecting DLQI scores

Disease severity (UCT scores) was the most significant influencer of DLQI scores, whereby patients with better disease control (UCT scores ≥12) had lower mean DLQI scores than patients with UCT scores <12 (n = 44; 2.52 vs. 9.80, respectively; P < 0.0001). Patients with sick leave had higher mean DLQI scores (10.11 [n = 38]) than patients without sick leave (6.97 [n = 117]; P = 0.0088). Patients with CIndU had the highest mean DLQI scores and patients with CSU only had the lowest scores (CIndU, 11.38 [n = 29]; CIndU and CSU, 7.65 [n = 31];

Table 3 Baseline treatment and treatment prescribed during the baseline visit (current treatment; analysis population)

	Baseline treatment				Current treatment			
	Total (N = 158)	Denmark (N = 80)	Norway (N = 50)	Sweden (N = 28)	Total (N = 158)	Denmark (N = 80)	Norway (N = 50)	Sweden (N = 28)
Any treatment	95 (60.1)	59 (73.8)	26 (52.0)	10 (35.7)	152 (96.2)	76 (95.0)	50 (100.0)	26 (92.9)
Non-sedative H1-AH*	64 (40.5)	37 (46.3)	21 (42.0)	6 (21.4)	138 (87.3)	64 (80.0)	50 (100.0)	24 (85.7)
Corticosteroid†	30 (19.0)	25 (31.3)	3 (6.0)	2 (7.1)	20 (12.7)	11 (13.8)	6 (12.0)	3 (10.7)
Montelukast	23 (14.6)	20 (25.0)	1 (2.0)	2 (7.1)	20 (12.7)	9 (11.3)	0 (0.0)	11 (39.3)
Omalizumab	13 (8.2)	12 (15.0)	1 (2.0)	0 (0.0)	67 (42.4)	55 (68.8)	10 (20.0)	2 (7.1)
H2-AH‡	7 (4.4)	0 (0.0)	6 (12.0)	1 (3.6)	12 (7.6)	0 (0.0)	6 (12.0)	6 (21.4)
Dapsone	6 (3.8)	5 (6.3)	0 (0.0)	1 (3.6)	1 (0.6)	1 (1.3)	0 (0.0)	0 (0.0)
Sedative H1-AH	5 (3.2)	2 (2.5)	1 (2.0)	2 (7.1)	4 (2.5)	2 (2.5)	0 (0.0)	2 (7.1)
Cyclosporine	4 (2.5)	4 (5.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (1.3)	0 (0.0)	0 (0.0)
Mycophenolate mofetil	2 (1.3)	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hydroxychloroquine	1 (0.6)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Methotrexate	1 (0.6)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
UVB-therapy	1 (0.6)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adrenaline§	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.9)	0 (0.0)	3 (6.0)	0 (0.0)
Other¶	9 (5.7)	9 (11.3)	0 (0.0)	0 (0.0)	1 (0.6)	1 (1.3)	0 (0.0)	0 (0.0)

*Patients receiving one daily dose were recorded as 'labelled dose' (12.7% at baseline, 8.2% after the first visit); patients receiving more than one daily dose were recorded as 'high dose' (29.1% at baseline, 76.6% after the first visit); patients reporting 'treatment as needed' were recorded as 'unknown' (3.2% at baseline, 4.4% after the first visit).

†Systemic corticosteroids including prednisolone; physicians were not required to specify whether oral or intramuscular corticosteroids had been prescribed, the reason or the duration of corticosteroid treatment.

‡H2-AH including cimetidine and ranitidine.

§Three patients, with a risk/history of severe angioedema, were prescribed adrenalin in case of emergency.

¶Other therapies were not specified by the treating physician.

Data are presented as, n (%).

AH, antihistamine.

CSU, 6.65 [n = 95]; $P = 0.0022$). No statistically significant association between DLQI outcomes and age, gender, BMI, time since diagnosis, comorbidities, current hives and presence of angioedema was seen (data not shown).

Discussion

Here, we present baseline disease characteristics and demographics from a study of 158 H1-AH refractory CU patients who have been referred to specialized urticaria centres in Denmark, Sweden and Norway. The baseline characteristics of this Scandinavian patient cohort are generally consistent with previous publications.^{6–9,19} The majority of patients experienced hives that lasted for less than 24 h and almost one-third of patients reported experiencing angioedema, which is within the previously published range.^{9,19} The mean patient age was 40.3, over two-thirds of patients were female, and over half of all patients in this cohort were overweight (BMI >25). An association between obesity and risk of urticaria has recently been suggested by Lapi *et al.*³ Similarly, CU patients from the EU (France, Germany, Italy, Spain and the UK) had a significantly higher average BMI than the control population.⁸

The most common diagnosis was CSU. However, these Scandinavian AWARE results provide new insight into the rates of

co-occurrence of CSU and CIndU (20.3%) in CU patients. Symptomatic dermographism has previously been reported to be the most common of the physical urticarias; however, in this patient cohort, rates were lower than previously reported.^{20,21} This may be due to selection bias, as patients with symptomatic dermographism may be referred to specialized clinics less frequently. The data also indicate that in this Scandinavian AWARE patient cohort, cold urticaria is the most commonly diagnosed CIndU subtype (18.4%). It has previously been suggested that cold urticaria is more common in colder climates,^{22,23} but studies involving structured provocation have not been performed. It is also possible that due to the colder climate in Norway, Sweden and Denmark, patients with cold urticaria have more severe or more persistent symptoms than patients in warmer climates, and they are more likely to be referred to specialized centres for treatment. Future results from other countries involved in the AWARE study will provide further insight into any geographical or climate differences associated with the rates of specific CIndU subtypes.

Despite pharmacological therapies being recommended as the first line treatment for CU, in this study, only 60.1% of patients reported baseline treatment. These data suggest that a large proportion of patients are not receiving adequate pharmacological

Table 4 Rates of comorbidities in patients with chronic uricaria

Comorbidity	n (%)
Atopic disease	
Asthma	31 (19.6)
Allergic rhinitis	26 (16.5)
Atopic dermatitis	10 (6.3)
Food allergy	13 (8.2)
Other eczema	12 (7.6)
Nut allergy	9 (5.7)
Psychiatric disease	
Depression	7 (4.4)
Anxiety	5 (3.2)
Psychosomatic disease	0 (0.0)
Autoimmune disease	
Thyroid disease*	8 (5.1)
Type 1 diabetes	1 (0.6)
Vitiligo	0 (0.0)
Metabolic disease	
Obesity	11 (7.0)
Hypertension	11 (7.0)
Hyperlipidaemia	3 (1.9)
Other comorbidities†	29 (18.4)

*Thyroid diseases: hypothyroidism, Hashimoto's thyroiditis, Grave's disease, myxoedema and unspecified thyroid disease.

†Other comorbidities reported were back pain, wasp allergy, type 2 diabetes, omega-5 gliadin allergy, Borrelia infection, multiple sclerosis, haemochromatosis, attention-deficit/hyperactivity disorder, fibromyalgia, migraine, mononucleosis, psoriasis vulgaris, polycystic ovarian syndrome, irritable colon, mitral valve stenosis, tachycardia, gastric ulcer, gastritis, birch allergy, prostate hypertrophy, hip arthrosis, menorrhagia, cholecystectomy and biliary colic.

Data are based on $N = 158$.

treatment. Moreover, only 40.5% of patients reported non-sedative H1-AH use at baseline. As patients did not specify why they were not receiving H1-AH treatment, we can only speculate that this may be due to two major factors: firstly, the referring medical practitioner may not have been up to date with the latest CU treatment guidelines and did not recommend the appropriate H1-AH treatment regimen after initial lack of response; secondly, patients were treated per the guidelines and stopped H1-AH treatment before the baseline visit due to lack of response.

The rates of treatment increased to 96.2% at the first visit; the most commonly prescribed treatment continued to be non-sedative H1-AHs; however, 42.4% of patients were now treated with omalizumab. At baseline, more Danish patients reported pharmacological treatment compared to Swedish and Norwegian patients. Furthermore, Danish patients had the highest rates of third-line treatments at baseline and at the end of the first visit.

The most common comorbidities were atopic diseases: asthma, allergic rhinitis, food allergies, eczema and atopic dermatitis. The rates of the majority of these comorbidities were lower than previously reported in German CU patients (allergic rhinitis, 41.9%; atopic dermatitis, 18.9%; allergic asthma,

Table 5 Patient-reported outcomes at baseline

	n	mean (SD)
Patient Satisfaction with therapy (VAS)	98	6.1 (3.4)
CU-Q ₂ oL*		
Functioning	76	27.9 (27.2)
Sleep	77	41.2 (29.6)
Itching/Embarrassment	77	35.7 (28.6)
Mental status	76	30.9 (26.1)
Swelling/Eating	76	14.7 (16.7)
Limits Looks	77	28.7 (26.8)
Total	77	29.6 (21.4)
DLQI score†	155	7.7 (6.5)
UCT‡§	157	8.3 (4.8)
UAS7	37	15.6 (11.5)

*CU-Q₂oL was only investigated in Danish patients ($N = 80$).

†mean (SD) DLQI score in Denmark, Norway and Sweden were 6.3 (6.2), 10.9 (6.5) and 6.0 (5.1), respectively.

‡UCT score <12, $n = 111$; UCT score ≥ 12 , $n = 44$.

§mean (SD) UCT scores in Denmark, Norway and Sweden were 8.7 (5.1), 6.9 (4.2) and 9.6 (4.3), respectively.

CU-Q₂oL, chronic urticaria quality of life questionnaire; DLQI, dermatology life quality index; SD, standard deviation; UAS7, urticaria activity score over 7 days; UCT, urticaria control test; and VAS, visual analogue score.

Table 6 Sick leave and 'Work productivity and activity impairment' in patients with chronic urticaria

WPAI	n = 155
Percentage presenteeism, mean (SD)	20.6 (22.6)*
Percentage absenteeism, mean (SD)	3.7 (11.9)*
Percentage total work productivity impairment, mean (SD)	23.2 (24.0)*
Percentage total activity impairment, mean (SD)	29.5 (28.3)†
Sick leave	n = 158
Sick leave due to Urticaria, n (%)	41 (25.9)
Duration of sick leave, mean weeks/year (SD)	3.8 (6.3)‡

* $n = 111$ were in paid employment and answered questions relating to presenteeism, absenteeism and work productivity.

† $n = 155$ provided responses for the percentage total activity impairment.

Sick leave was based on patient recall since symptoms began.

‡Based on $n = 20$ (21 patients missing data).

WPAI values (range: 0–100%) are based on the seven previous days; higher scores indicate lower productivity.

WPAI, work productivity and activity impairment; SD, standard deviation.

17.6%).²⁴ However, the German study was a cross-sectional sample of 13 300 inhabitants of Berlin ($n = 4053$ respondents; $n = 189$ with confirmed current urticaria); therefore, the results are not directly compared to this AWARE patient cohort being treated at specialized urticaria centres. Similarly, the rates of psychiatric comorbidities were lower than recent estimates of major depression and general anxiety disorder in the Swedish general population²⁵ and rates of depression were in line with reported estimates for Nordic countries – between 3.5% and 5% for depression.²⁶ These rates are lower than expected, as previous

Table 7 Additional healthcare utilization due to urticaria since symptoms began

	Number of patients with visits, n (%)	Frequency of visits, mean (SD)
GP/family physician	111 (72.5)	8.3 (14.0)*
Further dermatologist/allergist	105 (68.6)	6.4 (7.8)*
Specialized urticaria centres	65 (42.5)	8.4 (11.7)
Emergency physician/emergency room	42 (27.5)	2.5 (2.6)
Hospitalization	19 (12.4)	1.5 (0.9)
Dentist	4 (2.6)	1.5 (0.7)†
Pharmacy	4 (2.6)	1.0 (0.0)†
Ear–Nose–Throat specialist	2 (1.3)	3.5 (3.5)
Alternative practitioner	2 (1.3)	10.5 (13.4)
Other healthcare resources	3 (2.0)	2.0 (0.0)‡

*Frequency data missing for $n = 3$.

†Frequency data missing for $n = 2$.

‡Frequency data missing for $n = 1$.

Data are based on $N = 153$.

GP, general practitioner; SD, standard deviation.

studies have reported higher rates of psychiatric disorders in CSU patients.²⁷ Furthermore, two recent studies in the USA and EU have reported increased rates of both anxiety and depression in patients being treated for CU compared with matched comparisons.^{7,8} Inconsistencies in our data may be due to differences in the diagnostic criteria used, due to heterogeneous patient populations examined or due to selection bias. The lack of matched patient controls makes it difficult to interpret this depression and anxiety data, and further research is required to fully understand the link between psychological comorbidities and CU.

The burden of CU is considerable; previous publications report that CU is associated with poor QoL, increased healthcare use, and increased absenteeism, presenteeism and work impairment.^{7,8,28–30} The mean UCT scores were lowest in the Norwegian patient cohort than in the Danish and Swedish cohorts; in line with this observation, DLQI scores were higher in the Norwegian patient group than in the other two groups, indicating lower QoL. However, the low patient numbers preclude drawing any further conclusions regarding why differences between the three countries might be seen.

In this patient group, average DLQI scores indicate that patients were moderately affected by their CU and that poor disease control (UCT score <12) was associated with poor QoL, which is in line with previous CU studies.¹⁶ Comorbidities, current hives and presence of angioedema did not influence DLQI in these patients. CU-Q2oL scores were only available for the Danish patients in this AWARE study. Our results indicate that sleep, itching/embarrassment and mental status were the most severely affected subdomains of patient QoL. Similarly, Mlynec *et al.* reported that sleep, itching/embarrassment and mental status were the most affected subdomains in 157 German CU patients.¹⁶

Healthcare resource utilization was common in this patient cohort. Similarly, healthcare use in the previous 6 months was significantly higher in CU patients vs. matched controls.^{7,8} Furthermore, the rates of work absenteeism and presenteeism were high in this AWARE patient group and patients with sick leave reported significantly worse DLQI scores. Previous publications also suggest that mean levels of absenteeism, presenteeism and overall work impairment are significantly higher in patients currently treated for CU than matched controls.^{7,8}

This study has a number of strengths. We included patients from three countries with similar healthcare systems, which should allow for a good cross section of the CU patient population to have been examined. We also provide new insight into the disease burden and impact of CU in Scandinavian patients and the variables that influence health-related QoL. Furthermore, the patients included in this AWARE study were treated in specialized urticaria centres; this ensures that CU has been correctly diagnosed. Limitations of the study include the small sample size and potential for selection bias as patients were only recruited from specialized urticaria centres. Although access to the clinics is not dependent on private insurance, which should allow for all patients to access the highly specialized clinics, the recruitment may be biased towards patients with more severe CU. This may have led to overestimation of the rates of cold urticaria and other CIndUs, corticosteroid treatment, angioedema and/or the extent of disease burden.

Conclusions

These data highlight the unmet treatment needs for adult H1-AH refractory CU patients in Scandinavia. A large proportion of patients are not treated even with the most basic pharmacological therapies. Additionally, patients have health-related QoL impairment, high usage of healthcare resources and impaired work productivity. These burdens are likely to be associated with an additional economic burden to society. Improved education and dissemination of knowledge and the guidelines is urgently required to improve patients care.

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