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Clinical characteristics and management of chronic spontaneous urticaria in patients refractory to H_1-Antihistamines in Asia, Middle-East and Africa: Results from the AWARE-AMAC study

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ABSTRACT

Background: Chronic urticaria (CU) is a condition characterized by recurrent itchy hives and/or angioedema for ≥6 weeks. Most of the data about CU come from western countries with very little information available about CU in Asia, Africa, and the Middle East.

Methods: AWARE-AMAC is a 24-month prospective, observational, real-world, non-interventional study in patients aged ≥18 years from Asia, the Middle East, and Africa (AMAC) with CU refractory to H1-antihistamines (H1-AH). The main objective was to describe the real-world experience with CU, including clinical characteristics, presence of angioedema, treatment patterns (shifts between treatment classes and changes within a treatment class), investigator-assessed disease control, and the impact on quality of life. Subgroups of interest were type of CU at Baseline and treatment class (based on 2013 urticaria guidelines). There were no mandatory visits and diagnostic/monitoring procedures additional to routine practice, except the patient diary (7-day Urticaria Activity Score) and patient reported outcome assessments.

Results: The focus of the current manuscript is on patients with chronic spontaneous urticaria (CSU), who formed 98% of the sample. Patients were predominantly female (69.6% female, mean age ± SD 39.8 ± 13.29 years). Time since current diagnosis (Mean ± SD) was 28.6 ± 49.06 months. Amongst patients with CSU, 31.0% had comorbid chronic inducible urticaria (CINDU) and 46.4% had a history of angioedema. 91.9% received H1-AH therapy (±other treatments). The most frequently prescribed treatment classes at Baseline were any/combination of medications, not classified under the other 7 treatment classes, named "Others" (30.5%) followed by, omalizumab (OMA; 23.6%) and second-generation H1-AH monotherapy (sgAH; 15.1%). At Month 12, the most prescribed treatment classes (>15%) for patients were OMA (23.5%) and "Other" (21.3%); 19.7% received "No drug". At Month 24, OMA (22.5%), and "Other" (17.9%) were most frequently prescribed; 28.6% received "No drug". Overall, 79.5% of patients had some type of change in

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treatment. Over the study period, improvement in self-reported QoL increased, which was mirrored by better disease control.

Conclusion: In AMAC countries, the non-recommended "Other" treatment class played a major role in the initial management of CU patients. High usage of H1-AH (±other treatments) and OMA was observed. Treatment changes were observed in a majority of patients. Treatment escalation from sgAH was mostly via OMA. Improvement of disease control and QoL was achieved during the study period.

Trial registration: Observational study (NA).

Keywords: Chronic spontaneous urticaria, Second-generation antihistamines, Omalizumab, Efficacy, Quality of life

INTRODUCTION

Chronic urticaria (CU) is a condition characterized by the development of wheals (hives), and/or angioedema, for longer than 6 weeks.[1] The estimated prevalence of CU is up to 1% in the general population worldwide,[1] with those aged between 30 and 50 years most commonly affected, and females affected approximately twice as often as males.[2–5] The prevalence of CU in Asia has shown an increasing trend, with recent reports of 3.08% in Korea, and 0.79% in Taiwan.[6,7] CU is divided into two types: chronic spontaneous urticaria (CSU), in which symptoms occur without specific identifiable external triggers, and chronic inducible urticaria (CINDU), in which symptoms are induced and where types include cold, heat, solar, delayed pressure, vibratory, dermographism, aquagenic, cholinergic, and contact urticaria.[1,8] CSU is more common than CINDU and accounts for about two-thirds of all CU cases.[1] Patients may concurrently experience CSU and CINDU in approximately 20% of cases.[3] CSU is unpredictable and debilitating with a significant negative impact on patients' quality of life (QoL), including work productivity loss and absenteeism, interference with sleep and daily activities, and high levels of anxiety and psychological distress.[2,9–11] Furthermore, angioedema associated with CU may result in significant QoL impairment,[9,10] due to greater CSU activity, health-related quality of life (HRQoL) and productivity impairment, and resource utilization.[12,13]

In 2013 and 2017, revisions and updates of the international EAACI/GA^{2}LEN/EDF/WAO consensus guideline on urticaria were published.[14,15] According to the 2013 EAACI/GA^{2}LEN/EDF/WAO guideline (relevant at the time of the present study), all CSU patients with symptoms insufficiently controlled by the approved dose of H1-AH (first-line) for 2–4 weeks should be up-dosed to 2–4x the approved dose (second-line), followed by add-on therapy with omalizumab, montelukast or cyclosporine (third-line).[16] H1-antihistamines (H1-AH) have long been the standard of care in CSU,[14,16,17] but up to 60% of patients remain uncontrolled at the approved dose.[18] Nearly half remain symptomatic even on 4x the approved dose of second-generation H1-AH, implying that a significant proportion of the patient population are negatively impacted despite being treated.[19] To improve symptom control and minimize disease burden among CU patients, the international guidelines recommended a stepwise treatment approach.[14,15] Poor adherence to urticaria treatment guidelines has been reported, suggesting that patients may be sub-optimally managed.[20–22] Understanding disease burden and treatment patterns in patients with urticaria in real-world settings is critical in enabling measures to mitigate the impact of urticaria.

The majority of published data on H1-refractory CU are limited to patient populations derived from specialized urticaria centers and thus may not be representative of the general population of

patients with CU. To collect data on the management of a representative sample of CU patients across the world, the AWARE – (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) program through non-interventional, prospective observational studies – was designed. The studies were independently conducted in Europe, Latin America, and, Asia, the Middle East, and Africa (AMAC). AWARE-AMAC was a 24-month prospective, observational, real-world, non-interventional study in H1-AH refractory CU (HRCU) patients in the AMAC region. Here we present key results from AWARE-AMAC pertaining to clinical characteristics, role of angioedema, treatment patterns, investigator-assessed disease control, and impact on QoL at Baseline. While the study included both CSU and CINDU patients, the current publication focuses on data from H1-AH refractory CSU patients due to the small number of CINDU patients included.

METHODS

Study design

Enrollment of patients in the AWARE-AMAC study occurred between 25 October 2014 and 30 September 2015 from 14 countries (Algeria, Bangladesh, Egypt, Indonesia, Israel, Jordan, Lebanon, Oman, Saudi Arabia, South Africa, Taiwan, Thailand, Turkey, and UAE). Patients were included if they had a confirmed diagnosis of CU, defined as recurrent episodes of wheals (hives), angioedema, or both, for at least 2 months and if they showed a presence of signs and/or symptoms of CU that were not controlled by at least 2 weeks treatment with H1-AH. Patients were also required to be $\geq$ 18 years of age and to have provided informed consent. Patients were excluded if they were participating, or planning to participate, in an interventional clinical study for CU. The selection of the treatment for CSU was clearly separated from the decision to include patients in the study, and was made at the discretion of the treating physician in accordance with local standard medical practice and the investigator's clinical judgment. Information on angioedema episodes was collected by the investigators at each visit and reported in the eCRF with intensity of mild/moderate or severe. As the study is an observational one, no diagnostic or monitoring procedures additional to standard care and routine practice were performed for the purpose of the study, except for the patient's diary (7-day Urticaria Activity Score - UAS7) and patient-reported outcome (PRO) assessments. In order to prevent selection bias, investigators had to offer enrollment to all consecutive patients who met study criteria, were likely to be available for the full duration of the follow-up period, and who were willing to participate in the study. The majority of the treating physicians were allergologists or dermatologists. Study visit intervals were not fixed per protocol but adhered to the site's regular practice in this indication. A patient was considered to have completed the study if they were followed for at least the planned 24 months ($\pm$6 weeks); otherwise, they were considered as having prematurely discontinued.

Outcomes

The main objectives of AWARE-AMAC were to describe the clinical characteristics of H1-antihistamines refractory chronic urticaria (HRCU) patients in the AMAC region: type of urticaria, presence of angioedema/comorbidities, diagnostic procedures performed, treatment patterns of HRCU, including the classes of prescribed treatments, initial doses & dose adjustments, treatment duration, and shifts between treatment classes; shifts from one treatment class to another, changes in medication (dose/frequency changes within the same treatment class). The assessments included clinical evolution of HRCU patients, assessed in terms of symptom control (Physician Global Assessment of disease control (PhyGA-VAS), angioedema episodes, and spontaneous remission; clinical evolution in the cohort of patients with the diagnosis of CSU – including CSU with concomitant CINDU; and impact of HRCU on QoL measured with the Dermatology Life Quality Index (DLQI). Four subgroups were defined based on Baseline CU diagnosis: CiNDU, total CSU, which was further divided into CSU with angioedema and CSU without angioedema. Patients who had experienced angioedema due to CU either in the past or at Baseline were included in the CSU with angioedema subgroup, while the CSU without angioedema subgroup consisted of patients who had not experienced angioedema due to CU either in the past or at Baseline. Seven treatment

classes were defined to reflect treatment guidelines in effect at the time of the study in the following order (Fig. 1): (1) second-generation H1-AH (sgAH) - monotherapy approved dose: once daily or as needed; (2) updosed second-generation H1-AH (sgAHUP) - monotherapy updosed, i.e. not taken once daily or as needed; (3) first-generation AH, (fgAH) - monotherapy, or in combination with sgAH; (4) cyclosporine A (CsA) - monotherapy, or in combination with any H1-AH, with or without steroids; (5) omalizumab (OMA) - monotherapy, or in combination with any H1-AH, with or without steroids; (6) montelukast (MONT) - monotherapy, or in combination with any H1-AH, with or without steroids; (7) systemic glucocorticosteroids (SGC) - monotherapy, or in combination with any H1-AH.[14] There were a further 2 treatment classes defined as "Other" and "No drug". The "Other" treatment class consisted of any other medication, or combination of medications, not classified in the 7 treatment classes defined above, and "No drug" refers to patients not on any CU-related treatment.

Statistical analysis

Results are reported as observed. Descriptive statistics (mean, median, standard deviation (SD), lower and upper quartiles, minimum and maximum) are provided for continuous values, and absolute and relative frequencies for categorical values.

Study oversight

The study protocol was approved by the institutional review board of each participating center. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) and in compliance with all federal, local, or regional requirements. The AWARE-AMAC study was sponsored by Novartis Pharma AG, who is also the manufacturer of omalizumab. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

RESULTS

Baseline demographics and disease characteristics

Overall, 919 patients who presented with HRCU were analyzed for the purpose of this study: 18 patients with CINDU alone and 901 patients with CSU; 31.0% of CSU patients had concomitant CINDU. Of the 901 CSU patients analyzed, 69.6%

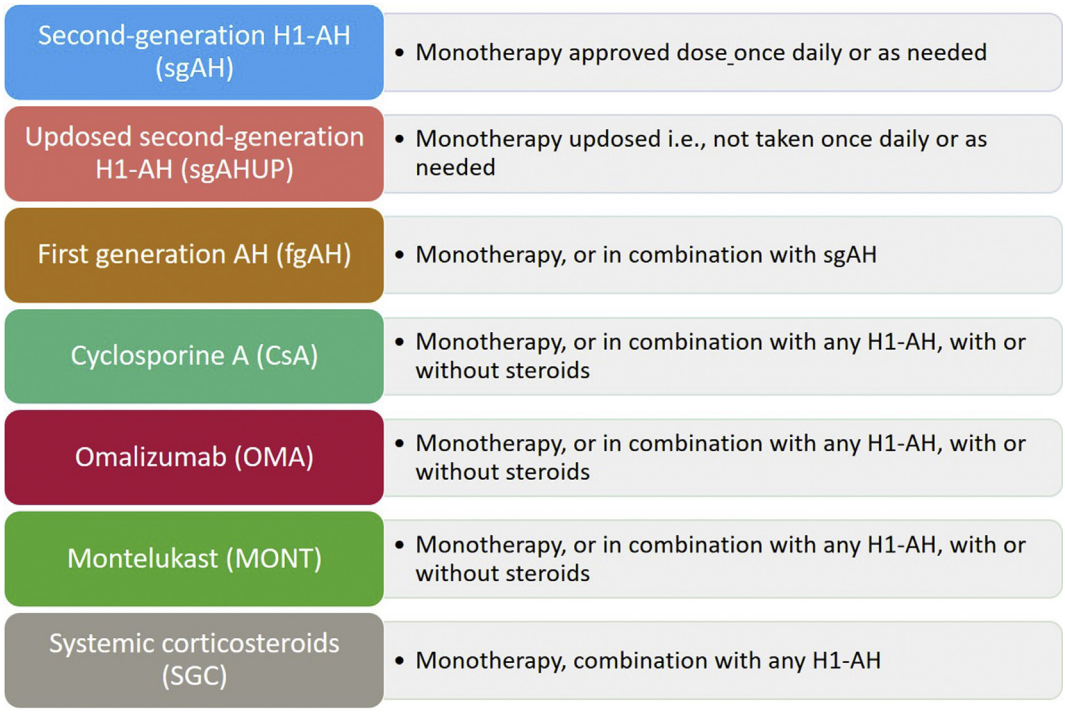

Fig. 1 Pre-defined treatment classes analyzed in AWARE-AMAC study

(627/901) were female, with a mean ± SD age of 39.8 ± 13.29 years. Unless otherwise mentioned, the results presented are for CSU patients. As expected for the region, most patients were either of Caucasian (53.1%; 478/901) or Asian origin (38.3%; 345/901). The average time since diagnosis of disease prior to enrollment was 6.6 ± 7.73 years, with the mean ± SD time since current diagnosis 28.6 ± 49.06 months. In total, 45.4% (409/901) had a diagnosis of CSU with angioedema at Baseline and 54.6% (492/901) had a diagnosis of CSU without angioedema at Baseline. At Baseline, 46.4% (418/901) CSU patients had a past occurrence of an angioedema episode, with 11.4% (103/901) of patients experiencing angioedema of severe intensity (Table 1).

Treatment patterns associated with urticaria therapy

At Baseline, nearly all CSU patients were on treatment (99.9%); only 1 patient was not on treatment, having stopped previous treatment 1 day prior to Baseline and initiated a new treatment on day 1 of the study and was therefore included in the analysis. Most (91.9% [828/901]) CSU patients received H1-AH (either as monotherapy or in

	Overall HRCU	CSU		
		TOTAL	With angioedema	without angioedema
	N = 919	N = 901	N = 409	N = 492
Age (years)				
Mean (SD)	39.6 (13.29)	39.8 (13.29)	39.7 (12.57)	39.8 (13.87)
Sex, n (%)				
Female	640 (69.6)	627 (69.6)	303 (74.1)	324 (65.9)
Race, n (%)				
Caucasian	490 (53.3)	478 (53.1)	254 (62.1)	224 (45.5)
Black	3 (0.3)	3 (0.3)	2 (0.5)	1 (0.2)
Asian	348 (37.9)	345 (38.3)	105 (25.7)	240 (48.8)
Unknown	8 (0.9)	8 (0.9)	4 (1.0)	4 (0.8)
Other	70 (7.6)	67 (7.4)	44 (10.8)	23 (4.7)
Time since diagnosis of current urticaria (months)				
Mean (SD)	28.3 (48.68)	28.6 (49.06)	26.9 (44.92)	30.0 (52.25)
Family-related history of urticaria				
n (%)	139 (15.1)	137 (15.2)	56 (13.7)	81 (16.5)
Occurrence of angioedema episodes in the past				
Yes	421 (45.8)	418 (46.4)	398 (97.3)	20 (4.1)
No	498 (54.2)	483 (53.6)	11 (2.7)	472 (95.9)
Average intensity of angioedema				
Mild	137 (14.9)	136 (15.1)	129 (31.5)	7 (1.4)
Moderate	177 (19.3)	177 (19.6)	171 (41.8)	6 (1.2)
Severe	105 (11.4)	103 (11.4)	96 (23.5)	7 (1.4)
Missing	2 (0.2)	2 (0.2)	2 (0.5)	0
Average duration (days) of angioedema				
< 1	131 (14.3)	129 (14.3)	122 (29.8)	7 (1.4)
1	111 (12.1)	111 (12.3)	103 (25.2)	8 (1.6)
2	80 (8.7)	79 (8.8)	76 (18.6)	3 (0.6)
> 2	96 (10.4)	96 (10.7)	94 (23.0)	2 (0.4)
Missing	3 (0.3)	3 (0.3)	3 (0.7)	0

Table 1. Baseline demographics and disease characteristics of patients in the AWARE-AMAC study (full analysis set). *CSU, Chronic spontaneous urticaria; HRCU, Histamine refractory chronic urticaria; SD, Standard deviation*

combination) at some point during the study, of which 74.8% (674/901) were on sgAH (monotherapy or in combination with another therapy). At Baseline, the predominant treatment classes (≥20% of all CSU patients) were "Other" (30.5 [275/901]), and OMA (23.6% [213/901]). Only 15.1% (136/901) and 12.4% (112/901) received sgAH and sgAHUP monotherapy, respectively. The most common treatments in the treatment class "Other" were H1-AHs taken in conjunction with other medications, which excluded them from the monotherapy treatment classes. These combinations included, H1-AH combined with: H2-antihistamines (approximately 23%); topical treatments (approximately 16%), other therapies (approximately 15%). Of the individual medications which contribute to the "Other" treatment class at Baseline, the most common were ranitidine, cetirizine, fexofenadine, desloratadine and whole blood.

At Month 12, 12.8% (106/826) of CSU patients received sgAH, and 11.5% (95/826) received sgAHUP, respectively. The most common treatment class at Month 12 was OMA with 23.5% (194/826) followed by "Other" treatment (21.3% [176/826]), as opposed to Baseline, where "Other" was the most common treatment class (Fig. 2). Consistent with the trend at Month 12, at Month 24, OMA remained the most common treatment class (22.5% [161/717]), followed by "Other" (17.9% [128/717]). It is noteworthy that during the study, the proportion of CSU patients in the "No drug" treatment class increased from 0.1% (1/901), to 19.7% (163/826) at Month 12, and to 28.6% (205/717) at Month 24. These changes may be explained by an improvement in CSU symptom control of CSU patients in the population.

The longest total mean duration of use for CSU patients of a drug class during the study was for OMA (458.6 ± 261.90 days since Baseline). Prolonged use (mean ± SD duration of use: 194.3 ± 255.07 days since Baseline) of SGC was observed. sgAHUP was associated with a duration of use (mean ± SD) of 273.2 ± 237.58 (Table 2). During the study, 34.0% CSU patients (306/901) did not shift treatment class, and in the OMA treatment class 47.4% (101/213) did not shift treatment class (Table 3). Amongst patients who shifted, 13.2% (18/136) of patients on sgAH and

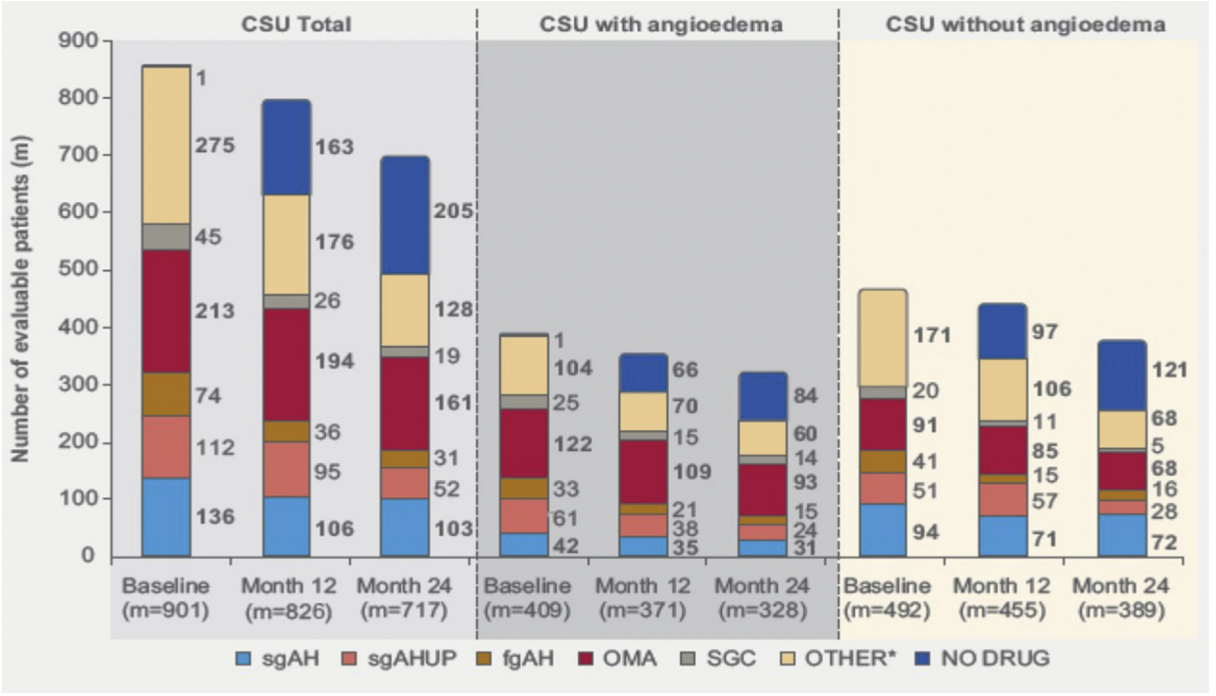

Fig. 2 Urticaria-related Treatment Class during the Study. fgAH, first-generation H1-antihistamine; OMA, omalizumab; sgAH, second-generation H1-antihistamine (approved dose); sgAHUP, second-generation H1-antihistamine (up-dosed); SGC, systemic steroids; OTHER, any other medication or combination not classified under the other subgroup categories. During the study only 1% and 2% of patients were treated with cyclosporine and montelukast respectively (not displayed)

Treatment Class	n	Mean	SD
sgAH	313	270.5	241.89
sgAHUP	256	273.2	237.58
fgAH	123	224.7	242.21
OMA	310	458.6	261.90
MONT	68	220.1	231.21
CsA	32	166.0	199.06
SGC	98	194.3	255.07
OTHER	420	313.1	276.12
NO DRUG	320	336.3	215.50

Table 2. Total Treatment Duration (in Days) during the Study in CSU Patients (Full analysis set). *CsA, cyclosporine; fgAH, first-generation H1-antihistamine; MONT, montelukast; OMA, omalizumab; SD, standard deviation; sgAH, second-generation H1-antihistamine (approved dose); sgAHUP, second-generation H1-antihistamine (up-dosed); SGC, systemic glucocorticosteroids*

18.8% (21/112) of patients on sgAHUP shifted to OMA. Most CSU patients who were shifted to another treatment class were shifted to "Other" or OMA and no CSU patients were shifted to MONT, while all the CSU patients on CSA at Baseline were shifted to other therapies. The majority of CSU patients on sgAH and sgAHUP stayed on them. For those who shifted, most were shifted to "No drug" (41.9% and 29.5% respectively), and fewer than 18.4% of patients on sgAH were up-dosed.

CSU patients were most often reported to have had a change in treatment regimen (dose or frequency of administration), because of lack of efficacy (39.6%; 357/901), if the medication was no longer required (31.9%; 287/901), due to disease improvement (28.5%; 257/901), or other reasons (28.6%; 258/901).

	No shift n (%)	sgAH n (%)	sgAHUP n (%)	fgAH n (%)	CsA n (%)	MONT n (%)	OMA n (%)	Other n (%)	SGC n (%)	No drug n (%)
sgAH (m = 136)	31 (22.8)	49 (36.0)	25 (18.4)	11 (8.1)	1 (0.7)	10 (7.4)	18 (13.2)	41 (30.1)	6 (4.4)	57 (41.9)
sgAHUP (m = 112)	41 (36.6)	24 (21.4)	21 (18.8)	6 (5.4)	1 (0.9)	8 (7.1)	21 (18.8)	22 (19.6)	6 (5.4)	33 (29.5)
fgAH (m = 74)	17 (23.0)	28 (37.8)	17 (23.0)	14 (18.9)	0	3 (4.1)	10 (13.5)	27 (36.5)	10 (13.5)	34 (45.9)
CsA (m = 9)	1 (11.1)	3 (33.3)	1 (11.1)	1 (11.1)	2 (22.2)	0	5 (55.6)	3 (33.3)	1 (11.1)	1 (11.1)
MONT (m = 36)	12 (33.3)	9 (25.0)	6 (16.7)	0	1 (2.8)	3 (8.3)	5 (13.9)	13 (36.1)	2 (5.6)	9 (25.0)
OMA (m = 213)	101 (47.4)	31 (14.6)	36 (16.9)	11 (5.2)	10 (4.7)	2 (0.9)	46 (21.6)	23 (10.8)	7 (3.3)	52 (24.4)
OTHER (m = 275)	92 (33.5)	69 (25.1)	50 (18.2)	13 (4.7)	9 (3.3)	6 (2.2)	29 (10.5)	43 (15.6)	21 (7.6)	121 (44.0)
SGC (m = 45)	11 (24.4)	13 (28.9)	9 (20.0)	7 (15.6)	1 (2.2)	3 (6.7)	8 (17.8)	16 (35.6)	8 (17.8)	12 (26.7)
NO DRUG (m = 1)	0	0	0	0	0	0	1 (100)	0	0	0

Table 3. Shifts* in treatment class during the study in CSU patients (full analysis set). *CsA, cyclosporine; fgAH, first-generation H1-antihistamine; MONT, montelukast; OMA, omalizumab; sgAH, second-generation H1-antihistamine (approved dose); sgAHUP, second-generation H1-antihistamine (up-dosed); SGC, systemic glucocorticosteroids. *Shift defined as a shift from one treatment class to another; patient may: a) Contribute to >1 shift across a row; b) Change from one treatment class to another, including back to the former treatment class. Percentages (%) are based on the number of patients in the full analysis set in each respective Baseline treatment class (m) for each respective group of interest*

Disease burden

At Baseline, 16.5% (149/901) of CSU patients had an occurrence of angioedema, which decreased to 13.0% (52/401) at Month 12, and further to 8.8% (25/284) at Month 24. During the entire study duration, 32.1% (289/901) of CSU patients experienced an occurrence of angioedema. In the CSU with or without angioedema subgroups 60.9% (249/409) of patients with a diagnosis of CSU with angioedema at Baseline experienced angioedema during the study and 8.1% (40/492) of CSU patients diagnosed without angioedema at Baseline experienced angioedema during the study period. The number of angioedema episodes, intensity and average duration reduced over time. This was reflected in the improvement the disease control in patients with CSU at Month 12 and further by Month 24 compared to Baseline when measured with PhyGA-VAS, and total in clinic UAS score (henceforth referred to as UAS score). Similar results were seen in the UAS7 scores between Month 12 and Month 24. Overall, the PhyGA-VAS score in patients with CSU increased notably at Month 12 vs. Baseline, indicating that by Month 12 patients experienced improved disease control; this continued from Month 12–24 (Fig. 3). Both sgAH and sgAHUP consistently showed high mean PhyGA-VAS scores ($\geq$80) from Month 12 onwards. SGC were the least effective treatment class in terms of mean PhyGA-VAS score. The total mean UAS score in CSU patients was 2.8 $\pm$ 1.71 at Baseline, 1.2 $\pm$ 1.41 at Month 12 and 1.1 $\pm$ 1.40 at Month 24. Disease severity as assessed with in clinic assessment of hives and pruritus also demonstrated decreasing disease severity in CSU patients. No hives were seen in 54% (211/391) and 65.8% (177/269) by Month 12 and 24 respectively vs. 19.3% (166/860) of patients assessed at Baseline. Similarly, mild-moderate pruritus was seen in 46.8% (183/391) patients at Month 12, and 43.5% (117/269) at Month 24 vs. 66.9% (575/860) at Baseline.

An increase in the proportion of CSU patients remaining asymptomatic without treatment, and an increase in those achieving spontaneous remission demonstrated an improvement in the disease status of CSU patients. None of the CSU patients were asymptomatic without treatment at Baseline. At Month 12 and 24, 12.1% (100/826) and 23.0% (165/717) of CSU patients were asymptomatic without treatment. Spontaneous remission (defined as complete remission of signs and symptoms of CU for a period longer than 6 months as collected in the eCRF) showed an increasing trend through the study. At Months 12 and 24, 5.2% (43/826) and 19.2% (138/717) of CSU patients had achieved spontaneous remission. 0.1% (1/826) CSU patients who had achieved remission had suffered from a recurrence at Month 12, while 1.5% (11/717) patients suffered recurrence of disease at Month 24 (see Fig. 4). Consequent to the improvement in disease control, the impact of CSU on patients' QoL as measured by DLQI, decreased over time, with the individual subscales (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment) also showing a reduction in scores both at Month 12 and Month 24, compared to Baseline (Table 4).

DISCUSSION

The 2-year results from AWARE-AMAC study confirm that CU has a significant impact on the QoL of patients, including impact on work.[23,24] While there is a considerable burden of urticaria, there is an unmet need for real-world clinical data about CU patients from high-quality, large scale, observational studies.[23,24] The demographics of patients analyzed were comparable to those from other CU clinical trials.[18,25,26] A similar proportion of patients were diagnosed as having CSU with angioedema at Baseline (45.4%) to that typically reported [phase III clinical trials: 41.0%[25]; AWARE in Europe: 46.1%; AWARE in Central and South America: 50.8%].[27] A high percentage of CSU patients had concomitant CINDU (31.0%) in the AMAC region. The corresponding proportion was 22.0% in AWARE study in Europe and 30.0% in Central and South America.[27]

According to the 2013 EAACI/GA^{2}LEN/EDF/WAO guideline (relevant at the time of the AWARE-AMAC study), first-line treatment with second-generation H1-antihistamines was recommended, followed by an increase in dose (up to 4-

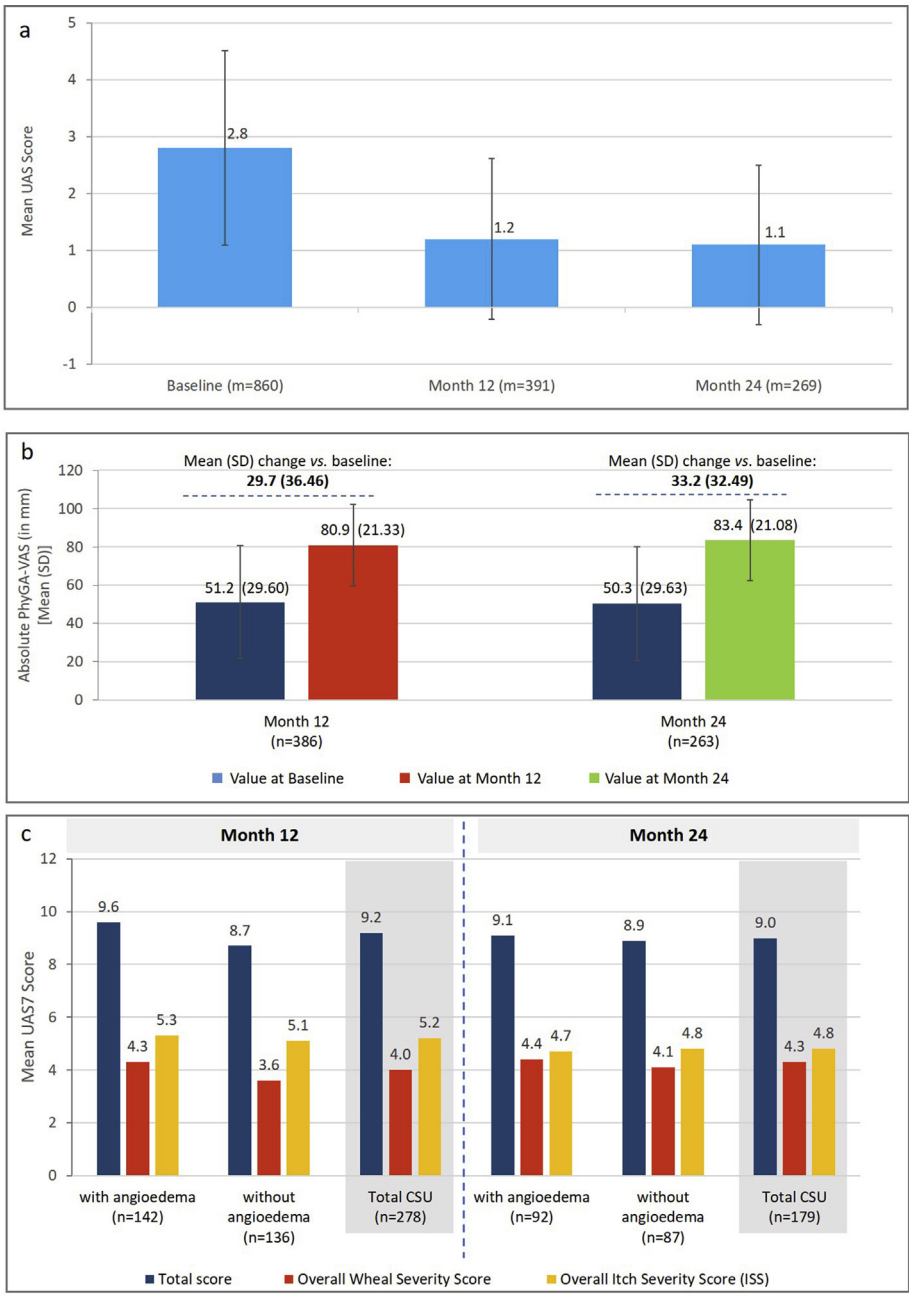

Fig. 3 a) UAS, b) PhyGA-VAS, and c) UAS7 in CSU patients at Month 12 and 24. Error bars represent the standard deviation in (a) and (b). The UAS7 assessment was optional and only conducted where the diary was available in the patient's local language. PhyGA-VAS, Visual Analog Scale Physician Global Assessment of disease control. For post-Baseline visits, only the results for patients with a value for both Baseline and the specific post-Baseline observation time-point are summarized

fold) as second-line treatment and finally the addition of omalizumab, cyclosporin, or montelukast to the second-generation H1-antihistamines as third-line treatment.[14] Many CSU patients in the study received treatments or combinations of treatments not recommended by the 2013 EAACI/GA^{2}LEN/EDF/WAO guideline[14] (classified in the study as "Other") or received steroids for prolonged periods pointing to the possibility of non-adherence to treatment guidelines in a significant subset of patients in the real-world setting. A recent study from Taiwan showed that most CSU patients were unsatisfied with their current treatment as can be expected with sub-optimal treatment.[28] Reports from around the world also point to the fact that the

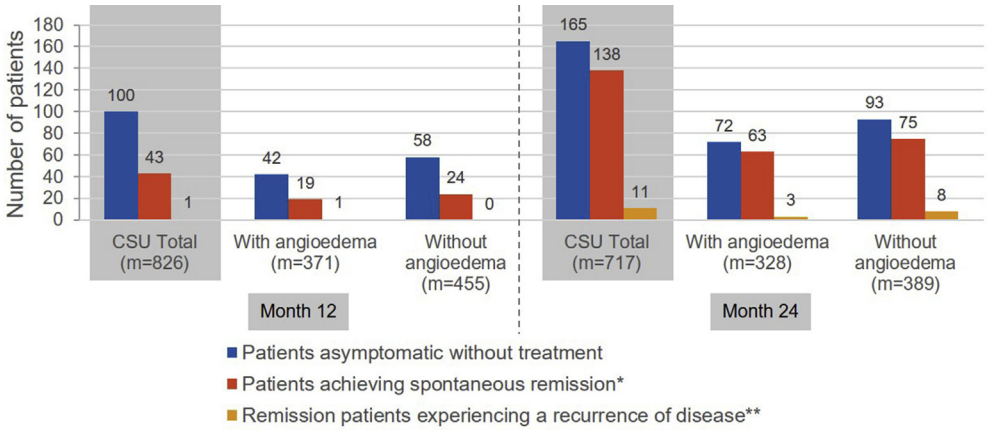

Fig. 4 Disease Status, Spontaneous Remission* and Recurrence of CSU at Month 12 and 24.** * spontaneous remission, defined as complete remission of signs and symptoms of CU for a period longer than 6 months as collected in the eCRF. ** recurrence of disease, defined as those patients who achieved spontaneous remission before experiencing a recurrence of their symptoms or receiving treatment. Percentages (%) are based on the number of patients in the full analysis set with disease status available at the observation time-point of interest (m) for each respective group of interest

management of CSU in real-world settings may not sufficiently comply with guidelines.[20–22,27] Prolonged use of SGC, and use of sgAH (either as monotherapy or in combination) in CSU patients for duration exceeding that recommended by guidelines and relatively high proportions of patients on fgAH in the AMAC region confirms that better awareness of treatment guidelines is required.

Disease severity was assessed using the PhyGA-VAS. Patients with the highest mean PhyGA-VAS scores were frequently not on treatment at the time of the PhyGA-VAS assessment. This could indicate that their previous treatment was highly effective, or, that there was disease disappearance, or, spontaneous remission. At Month 24, spontaneous remission had occurred in nearly 20% of CSU patients, and only 1.5% of CSU patients had relapsed after spontaneous remission. The rate of spontaneous remission must be seen in view of the fact that 135 CSU patients were lost to follow-up, implying the exact rate of spontaneous remission might have been higher. The rate of spontaneous remission in this study is low compared to the literature-reported rate of 30%–50%.[8]

The current study provides a reflection of clinical treatment practices in a real-world practice setting in the included countries. The data are from a well-designed study in a large cohort of patients who were followed up for up to 24 months, thus offering significant scope for recognizing trends in treatment over time, and not just a snapshot of clinical practice at a specific time point. This is especially important, as the data come from a region of the world where scant data about CU treatment in real world practice are published.

The study had a few limitations. The only inclusion criteria applied, next to the patient providing informed consent and age $\geq$18 years, were a medically confirmed diagnosis of CU with symptoms of more than 2 months, and signs and/or symptoms of CU that were not adequately controlled by at least 2 weeks treatment with H1-AHs. It is also worth noting that the presentation of symptoms of CU may lead to visits to physicians, and by extension it is possible for patients not experiencing symptoms being either lost to follow-up or not being assessed at certain timepoints. Thus, outcomes may be affected due to the missing data from this subset of patients. As is generally the case with non-interventional studies, no explicit exclusion criteria apart from simultaneous participation in an interventional clinical study were applied. There was no set visit schedule, therefore the number of assessment points fluctuated during the study. Patients

	Actual value at Baseline[a]	Actual Value At Month 12	Change from BL	Actual value at Baseline[b]	Actual Value at Month 24	Change from BL
Total score						
n	382	382	382	270	270	270
Mean (SD)	10.8 (6.84)	4.8 (5.40)	−6.0 (7.76)	11.1 (6.75)	4.0 (6.02)	−7.2 (8.26)
95% CI	10.1, 11.5	4.3, 5.3	−6.8, −5.2	10.3, 11.9	3.2, 4.7	−8.1, −6.2
Symptoms and feelings						
n	383	383	383	270	270	270
Mean (SD)	3.1 (1.67)	1.5 (1.49)	−1.6 (2.18)	3.3 (1.61)	1.3 (1.60)	−2.0 (2.21)
95% CI	3.0, 3.3	1.4, 1.7	−1.9, −1.4	3.1, 3.5	1.1, 1.5	−2.2, −1.7
Daily activities						
n	383	383	383	270	270	270
Mean	2.3 (1.81)	0.9 (1.36)	−1.5 (2.00)	2.5 (1.81)	0.9 (1.43)	−1.6 (2.19)
95% CI	2.2, 2.5	0.8, 1.0	−1.7, −1.3	2.2, 2.7	0.7, 1.1	−1.8, −1.3
Leisure						
n	382	382	382	270	270	270
Mean	1.7 (1.66)	0.7 (1.24)	−1.0 (1.91)	1.8 (1.67)	0.6 (1.32)	−1.2 (2.05)
95% CI	1.6, 1.9	0.6, 0.9	−1.2, −0.8	1.6, 2.0	0.5, 0.8	−1.4, −1.0
Work and school						
n	382	382	382	270	270	270
Mean	1.3 (1.21)	0.9 (1.21)	−0.4 (1.63)	1.3 (1.21)	0.4 (0.86)	−0.8 (1.36)
95% CI	1.2, 1.4	0.8, 1.0	−0.5, −0.2	1.1, 1.4	0.3, 0.5	−1.0, −0.7
Personal relationships						
n	382	382	382	270	270	270
Mean (SD)	1.4 (1.63)	0.5 (1.05)	−0.9 (1.62)	1.4 (1.63)	0.4 (1.17)	−1.0 (1.64)
95% CI	1.2, 1.5	0.4, 0.6	−1.1, −0.7	1.2, 1.6	0.3, 0.6	−1.2, −0.8
Treatment						
n	382	382	382	270	270	270
Mean (SD)	0.9 (0.96)	0.3 (0.63)	−0.6 (1.04)	0.9 (0.97)	0.3 (0.69)	−0.6 (1.10)
95% CI	0.8, 1.0	0.2, 0.4	−0.7, −0.5	0.8, 1.0	0.2, 0.4	−0.8, −0.5

Table 4. Quality of life (DLQI) during the Study in CSU patients. *a. Baseline value only for the subgroup of patients who had an evaluable value at Month 12. b. Baseline value only for the subgroup of patients who had an evaluable value Month 24*

enrolled in this study might be more severe than the usual CU patients, as the inclusion criteria requested that patients were willing to be followed up for 2 years.

The primary aim of AWARE-AMAC was to collect real-world evidence on disease burden and treatment patterns in patients with HRCU. This goal was achieved by evaluating more than 900 patients across 14 AMAC countries. Although patients with CINDU were also included in the study, this manuscript focuses on patients with a diagnosis of CSU. The study did not scrutinize specific medicinal products, but assessed how patients with HRCU were currently treated in the AMAC region. Over the 24-month study period, the proportion of patients with self-reported improved QoL increased. This was mirrored by positive developments in disease control. Prolonged use of systemic steroid monotherapy, beyond the recommended guidelines for steroid use, was also observed in the region. The non-guideline-recommended "Other" treatment class was used in a considerable proportion of patients. Treatment escalation from the first- and second-line guideline-recommended treatments of

sgAH was mostly performed via OMA, with other third-line treatments being used less frequently. These findings suggest limited adherence to guidelines and highlights the need for better awareness of the guidelines.

CONCLUSIONS

The AWARE–AMAC study shed light on real-world practice regarding the diagnosis and management of CU in >900 patients for 24 months from the AMAC countries for the first time. In the AMAC region, patients were similar to those in other regions from a demographic perspective, and there were a similar percentage of patients with CSU + angioedema compared to other regions. Yet the AMAC region had a higher percentage of patients with comorbid CINDU than other regions. In the AMAC region, limited adherence to CU management guidelines was observed which highlights the need for better awareness of the guidelines. In this study there was a low percentage of spontaneous remission which might be due to high number patients lost to follow-up. The majority of patients had escalation of therapy over the treatment period mostly to omalizumab. There was improvement in disease control reflected in increase QoL scores.

Abbreviations

AMAC: Asia Middle East and Africa; CU: Chronic urticaria; CSU: Chronic spontaneous urticarial; CINDU: Chronic inducible urticarial; CsA: Cyclosporine A; DLQI: Dermatology Life Quality Index; fgAH: First-generation antihistamines monotherapy, or in combination with sgAH; GCP: Good Clinical Practice; H1-AH: H1-antihistamines; HRQoL: Health-related quality of life; HRCU: H1-antihistamines refractory chronic urticarial; OMA: Omalizumab monotherapy, or in combination with any H1-AH, with or without steroids; MONT: Montelukast monotherapy, or in combination with any H1-AH; PhyGA-VAS: Physician Global Assessment of disease control-visual analog scale; PRO: Patient-reported outcomes; QoL: Quality of life; SD: Standard deviation; sgAH: Second-generation antihistamines monotherapy approved dose: once daily or as needed; sgAHUP: Updosed second-generation H1-AH; SGC: Systemic glucocorticosteroids monotherapy, or in combination with any H1-AH; UAS7: 7-day Urticaria Activity Score

Author contributions

All authors contributed to the design and conduct of the trial, and read and approved the final manuscript and its submission.

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Ethics approval and consent to participate

The study protocol was approved by the institutional review board of each participating center. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) and in compliance with all federal, local, or regional requirements. The AWARE-AMAC study was sponsored by Novartis Pharma AG, who is also the manufacturer of omalizumab. Informed consent was obtained from all participants. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

Consent for publication

The authors provide their consent for the publication of the study results.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available. Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit.

Declaration of Competing Interest

C.Y. Chu is a clinical trial investigator for Novartis; has received travel support and consulting fees from Novartis, and payment for lectures from Menarini and Novartis. Kanokvalai Kulthanan has been an educational speaker for MSD and Menarini, and a clinical trial investigator for Novartis. S. Malfait, K. Cooke, and E.L. Dekker are employees of Novartis Pharma AG, Basel, Switzerland. S Crowe is an employee of Novartis Ireland Ltd, Dublin, Ireland. Other authors declare no relevant competing interests.

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