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Antihistamine-resistant chronic spontaneous urticaria remains undertreated: 2-year data from the AWARE study

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Abstract

Background: Real-world evidence describing the benefits of recommended therapies and their impact on the quality of life (QoL) of chronic urticaria (CU) patients is limited.

Objective: To investigate disease burden, current treatment schedule, and the use of clinical resources by patients with H_1-antihistamine-refractory CU in Europe.

Methods: AWARE (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) is a global, prospective, non-interventional study in the real-world setting, sponsored by the manufacturer of omalizumab. Disease characteristics, pharmacological treatments, and health-related QoL of patients (N = 2727) ≥18 years of age diagnosed with H_1-antihistamine-refractory chronic spontaneous urticaria (without inducible urticaria) for >2 months are reported here.

Results: Of the 2727 patients included, 1232 (45.2%) and 1278 (46.9%) were successfully followed up for any assessment and for the key outcome, the urticaria control test (UCT) score, respectively, and patients with complete remission (14.1%) were excluded from analyses.The proportion of patients with uncontrolled CSU (UCT score <12) dropped from 78% (n/N = 1641/2104) at baseline to 28.7% (n/N = 269/936) after two years of participation in the AWARE study. In addition, the proportion of patients with no impact of CSU on their QoL (assessed by the Dermatological Life Quality Index) increased to 57% (n/N = 664/1164) from 18.7% (n/N = 491/2621) at baseline. Emergency room visits (2.4% [n/N = 7/296] vs 33.5% [n/N = 779/2322]) and hospital stays (1.7% [n/N = 5/296] vs 24.2% [n/N = 561/2322]) reduced at Month 24 vs baseline. Overall, 23.2% (n/N = 26/112) patients on non-sedating H_1-antihistamines (nsAH) and 41.9% (n/N = 44/105) patients on up-dosed nsAH had uncontrolled CSU (UCT <12) at Month 24. In omalizumab-treated patients, 27.1% (n/N = 78/288) had uncontrolled CSU at Month 24.

Conclusion: These data confirm improvements for most patients with CSU over a 2-year follow-up period. Further studies are needed to understand the differences between guideline recommendations and reported management.

KEYWORDS

angioedema, chronic spontaneous urticaria, quality of life, urticaria

1 | INTRODUCTION

Chronic urticaria (CU) is characterized by itching, burning or sometimes painful hives (wheals), and/or angioedema (swelling in the deeper layers of the skin) for at least 6 weeks.[1] The estimated prevalence of CU varies from 0.1% in North America to 1.4% in the Asian population.[2] In patients with CU, symptoms may occur spontaneously without a definite trigger, known as chronic spontaneous urticaria (CSU), or in response to a specific trigger, known as chronic inducible urticaria (CIndU).[3,4] About 20% of CU patients may experience CSU and CIndU concurrently.[5]

Chronic urticaria has a negative impact on the quality of life (QoL) and hampers work productivity and daily activities.[6-8] The international guideline for urticaria (EAACI/GA^{2}LEN/EDF/WAO) recommends a stepwise treatment approach to improve symptom control and reduce disease burden among patients with CU.[1] Second-generation non-sedating H_1-antihistamines (nsAH) at approved doses are the first-line therapy; however, up to 60% of patients do not respond adequately within 2-4 weeks of starting the treatment and require increased doses (upto 4-fold of the licensed dose), which is the second-line recommendation.[1,9] At the time the AWARE study was initiated, the EAACI/GA^{2}LEN/EDF/WAO urticaria guideline recommended third-line add-on therapy with ciclosporin, leukotriene receptor agonists such as montelukast, or omalizumab, if no adequate response was achieved with higher than standard doses of H_1-antihistamines; however, this recommendation was changed in the 2017 update and revision of this guideline.[1,10] The 2017 guideline provides a strong recommendation for the use of omalizumab as third-line add-on therapy to H_1-antihistamines, if no adequate response is observed after 2-4 weeks (or earlier if symptoms are intolerable) of treatment with an up-dosed nsAH. Patients who remain inadequately controlled with omalizumab after 6 months (or earlier if symptoms are intolerable) are recommended to receive add-on therapy with ciclosporin A as a fourth-line agent (off-label).[1]

Real-world evidence on the benefits of the recommended therapeutic medications and their impact on the QoL of CU patients in Europe is limited. Previous reports suggest that physicians show poor adherence to guidelines in the diagnosis and therapeutic management of CSU leading to an unmet need in the CU patient population.[11] Baseline findings of the AWARE study in Europe revealed that CU is largely uncontrolled, undertreated, and associated with a high healthcare resource use burden, and that it has a large effect on QoL, work, and activity.[12] Furthermore, the majority of data on CU that is inadequately controlled with H_1-antihistamines are limited to patient populations derived from specialized urticaria centres such as Urticaria Centers of Reference and Excellence (UCAREs),[13] which may not represent the general CU population.[11,14] AWARE is a prospective, non-interventional study that examines real-world treatment patterns, burden of disease, and rates of healthcare resource utilization of patients with CU that is inadequately controlled with H_1-antihistamines. Here, we report any changes in the treatment regimen, symptoms, and health-related QoL (HR-QoL) throughout the 2-year period of the study with patients with CSU inadequately controlled by H_1-antihistamines in 12 European countries.

2 | METHODS

2.1 | Patients and study design

AWARE was a multicentre, prospective, non-interventional study that followed patients with CU for 2 years, who were inadequately controlled with at least one approved dose of H_1-antihistamine.[15] This report focuses on patients enrolled in urticaria centres and office-based dermatological and allergological practices across 12 European countries (Germany, Spain, the United Kingdom, Italy, Greece, Russia, France, Denmark, Belgium, Portugal, Norway, and Sweden) at 418 sites between March 2014 and October 2015. Patients were included if they had physician-confirmed CU for at least 2 months with inadequate response to standard-doses of H_1-antihistamine treatment. Patients were also required to be ≥18 years of age and be able to provide informed consent. Enrolled patients were followed up for at least 2 years. Patients were excluded from the study if urticaria was present for less than 2 months or due to unanticipated difficulties in the follow-up of the patient in the 2-year study period, or if they were simultaneously participating in any other clinical CU study. All patients met the following criteria: fulfilment of all inclusion criteria, no violation of any exclusion criteria, written informed consent prior to study enrolment, and all core baseline characteristics (gender, age, and diagnosis) available.

Although patients with CIndU were also included in the AWARE study, this manuscript focuses on patients diagnosed with CSU (with or without angioedema). The study protocol was approved by the institutional review board of each participating centre. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) and in compliance with all federal, local, and regional requirements. AWARE was sponsored by the manufacturer of omalizumab.

2.2 | Patient-reported outcome measures

Patient-reported outcome (PRO) measures were used to assess disease activity, to measure the impact on the QoL as recommended by international guidelines and control CU.[10] PROs included the

7-day Urticaria Activity Score (UAS7; weekly diary for disease activity),[16-18] Dermatology Life Quality Index (DLQI; questionnaire for psychosocial effects of chronic skin disease),[19] Chronic Urticaria QoL Questionnaire (CU-Q_2oL),[20] Angioedema QoL Questionnaire (AE-QoL),[21,22] Urticaria Control Test (UCT; to assess urticaria control: UCT ≥12, poorly controlled disease: UCT <12),[23,24] Work Productivity and Activity Impairment Questionnaire (WPAI),[25] and monthly Angioedema Activity Score (AAS).[26] Each patient was observed for a period of 2 years. After the baseline visit (Visit 1), patients had eight follow-up visits in quarterly intervals. The various treatment groups examined are presented in Figure S1.

2.3 | Statistical analysis

All statistical analyses were performed on the analysis population and assessed using descriptive statistics. Means, medians, standard deviation (SD), maximum, and minimum are stated for quantitative, absolute, and relative frequencies for categorical measurements.

3 | RESULTS

3.1 | Demographics and clinical characteristics

Patient disposition and diagnostic groups are shown in Table 1. Of the 3683 patients included in the analysis, 74.0% (n = 2727) had only CSU, 5.3% (196) had only CIndU, and 20.6% (n = 760) had concomitant CSU and CIndU. The mean ± SD age of CSU patients was 46.7 ± 15.7 years, and 70.9% (n = 1933) of patients were female (Table 2). The mean ± SD for total duration of disease was 4.7 ± 7.2 years. In all, 1589 (43.5%) patients discontinued the study. Lost to follow-up (62.9%) of patients was the main reasons for discontinuation, followed by withdrawal of informed consent (20.3%) and spontaneous remission of CU (14.1%). The total patients available for assessment at each visit are described in Table S1.

3.2 | Symptom control (wheals and angioedema) after 2 years in AWARE

At baseline, 89.4% (n/N = 2419/2706) of CSU patients experienced wheals (within the last 6 months before baseline). At Months 3 and 24, 74.3% (n/N = 1529/2058) and 47.5% (n/N = 589/1241) of patients reported wheals (in the 3 previous months), respectively (Figure 1A). Correspondingly, the mean UAS7 score declined over the study period from 17.5 (±12.4) (N = 589) at baseline to 4.5 (±7.5) (N = 724) at Month 24.

At baseline, 45.0% (n/N = 1219/2706) of CSU patients experienced angioedema during the last 6 months; this decreased to 25.8% (n/N = 526/2042) at month 3 and continued to improve across visits. At Month 24, 13.1% (n/N = 162/1232) of CSU patients experienced angioedema (Figure 1B). Substantial improvement in monthly mean (±SD) AAS (baseline: 122.9 ± 111.3 [N = 116], Month 24:83.1 ± 110.9 [N = 42]) was observed (Figure 1D).

TABLE 1 Disposition and diagnostic groups

Disposition	N (%)
Enrolled patients	3741 (100)
Included in the analysis	3683 (98.4)
Excluded[a]	58 (1.6)
Combined diagnostic categories[b]	
CSU	2727 (74.0)
CIndU	196 (5.3)
CSU + CInDU	760 (20.6)
Single diagnoses[b]	
CSU without angioedema, n (%)	1840 (50.0)
CSU with angioedema, n (%)	1704 (46.3)

Abbreviations: CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria.
[a]Patients excluded from the analysis due to missing core variables or a violation of the inclusion/exclusion criteria.
[b]Percentage based on patients included in the analysis (N = 3683).

3.3 | Disease control after 2 years in AWARE

In terms of urticaria control (UCT) at baseline, 78.0% (n/N = 1641/2104) of patients had poorly controlled CSU (UCT <12). At Month 3, 51.3% (n/N = 844/1645) had poorly controlled CSU (Figure 1C) and, the UCT score improved over time, and at Month 24, 28.7% (n/N = 269/936) of CSU patients showed poor disease control.

3.4 | HR-QoL over 2 years in AWARE

Baseline DLQI scores indicated that merely 18.7% (n/N = 491/2621) of CSU patients experienced no impact on their QoL (DLQI band 0-1) (Figure 2A). This markedly improved over the 2-year study period: 50.3% (n/N = 773/1538) of patients reached this goal after 1 year and 57.0% (n/N = 664/1164) after 2 years. At Month 24,

TABLE 2 Demographics and baseline disease characteristics

	CSU patients (N = 2727)
Age (years), mean (SD)	46.7 (15.7)
Sex, n (%)	
Male	794 (29.1)
Female	1933 (70.9)
Duration of disease (years), mean (SD)	4.7 (7.2)
Family-related history of urticaria, n (%)	166 (6.1)
Body mass index (kg/m^2), mean (SD)	26.8 (5.4)

Abbreviations: CSU, chronic spontaneous urticaria; SD, standard deviation.

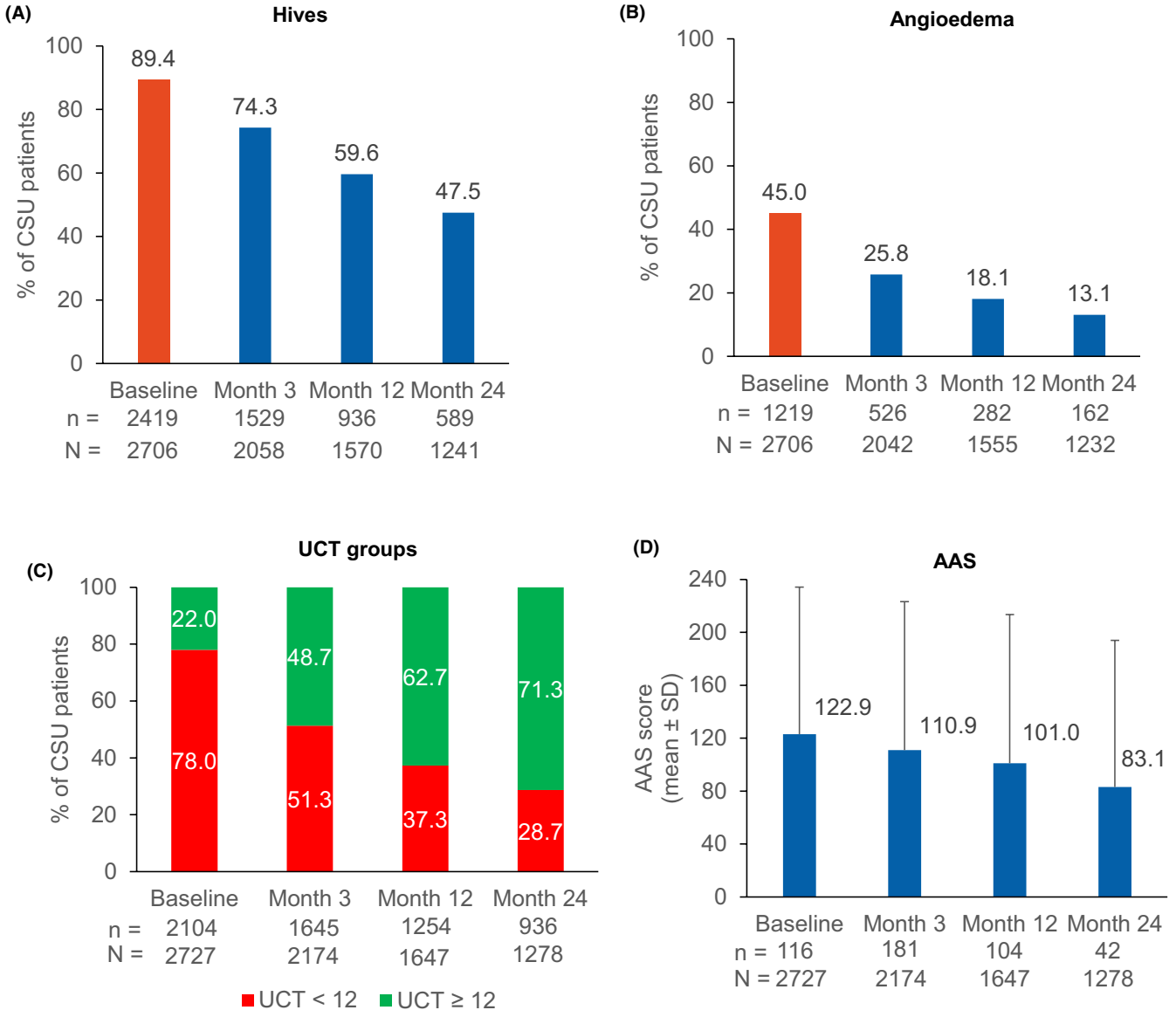

FIGURE 1 Prevalence of (A) hives, (B) angioedema, (C) the proportion of patients with controlled (UCT ≥12) or uncontrolled (UCT <12) disease, and (D) monthly AAS among patients with CSU[a]. n, number of patients where a particular evaluation form was available at each visit; N, total number of patients at each visit. [a]The number of patients with evaluation at each visit varied because of the registry nature of AWARE. AAS, angioedema activity score; CSU, chronic spontaneous urticaria; UCT, urticaria control test [Colour figure can be viewed at wileyonlinelibrary.com]

18.5% (n/N = 216/1164) of CSU patients experienced moderate to extremely large effect on their QoL compared to baseline (54.1%, n/N = 1419/2621). Substantial improvement in mean (±SD) CU-Q_2oL (baseline: 35.1 ± 20.2 [N = 1928], Month 24:16.3 ± 16.1 points [N = 824]) and AE-QoL (42.4 ± 23.6 [N = 1178] to 22.7 ± 19.7 points [N = 409]) was seen (Figure 2B-C).

3.5 | Healthcare resource utilization over 2 years of treatment

Emergency room visits and hospital stays were frequent at baseline and reduced at the end of the study: emergency room visits (33.5%, n/N = 779/2322 at baseline down to 2.4%, n/N = 7/296 at Month 24) and hospital stays (24.2%, n/N = 561/2322 at baseline down to 1.7%, n/N = 5/296 at Month 24). General practitioners and additional visits to dermatologists/allergists were seen for CSU symptoms by 65.0% (n/N = 1510/2322) and 53.1% (n/N = 1232/2322) patients at baseline, respectively. At Month 24, 22.3% (n/N = 66/296) and 23.6% (n/N = 70/296) CSU patients were still consulting additional general practitioners and dermatologists/allergists.

3.6 | Work productivity impairment over 2 years of treatment

A substantial improvement of total activity impairment measured by the WPAI was seen from 32.5 ± 30.1% [N = 2437] at baseline down

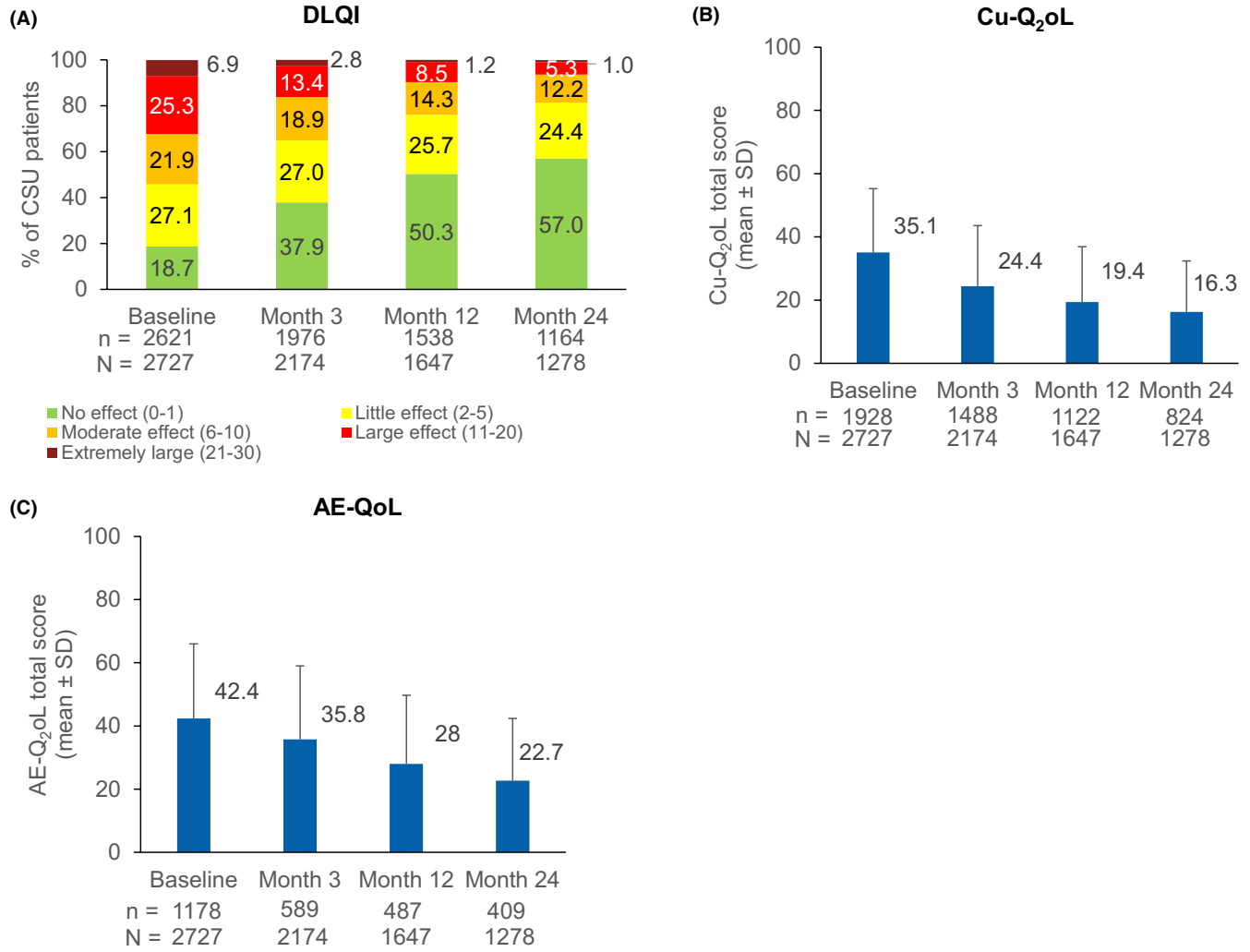

FIGURE 2 QoL measures: (A) DLQI, (B) CU-Q_2oL, and (C) AE-QoL[a]. n, number of patients where a particular evaluation form was available at each visit; N, total number of patients at each visit. [a]The number of patients with evaluation at each visit varied because of the registry nature of AWARE. AAS, angioedema activity score; AE-QoL, angioedema quality of life questionnaire; CU-Q_2oL, chronic urticaria quality of life questionnaire; DLQI, dermatology life quality index [Colour figure can be viewed at wileyonlinelibrary.com]

to 12.3 ± 21.3% [N = 1069] at Month 24 in CSU patients. Similarly, impairment of total work productivity improved from 26.7 ± 27.5% [N = 1321] down to 10.7 ± 18.9% [N = 561] within 2 years. The CSU-induced impairment while working (presenteeism) reduced from 24.5 ± 25.7% [N = 1331] at baseline to 9.4 ± 17.4% [N = 562] at Month 24. The mean (± SD) percentage of work time missed (absenteeism) due to CSU was also reduced from 7.3 ± 19.7% [N = 1360] to 2.1 ± 10.0% [N = 714] at Month 24.

3.7 | Treatment pattern over 2 years in AWARE study

With regard to medication groups, 17.3% (n/N = 473/2727) of CSU patients were treated with approved doses of nsAH (Figure 3), and 23.2% (n/N = 26/112) of these patients had poorly controlled disease (UCT < 12) at month 24. Overall, 22.3% (n/N = 609/2727) of CSU patients used up-dosed nsAH (Figure 3), and 41.9% (n/N = 44/105) of these patients had an uncontrolled form of the disease at Month 24. While 32.3% (n/N = 881/2727) of CSU patients were treated with omalizumab (Figure 3), 27.1% (n/N = 78/288) of CSU patients had uncontrolled disease at Month 24. Of 945 CSU patients who received omalizumab during the study, only 34.4% (n = 325) continuously received the drug prior and during the course of study, 3.1% (n = 29) had only received prior treatment, and 18.3% (n = 173) started treatment during the study (no prior treatment). 44.2% of patients underwent other treatment schemes.

Other treatments, such as ciclosporin and sedating antihistamines (sAH), were rarely used, and none of them were prescribed in more than 5% of patients (Figure 3). Interestingly, the non-recommended use of "on-demand" nsAH increased from 3.1% (n/N = 85/2727) before enrolment to 12.8% (n/N = 163/1278) at Month 24. The number of patients on "no treatment" was small throughout the study and decreased from 37.0% (n/N = 1008/2727) prior enrolment to

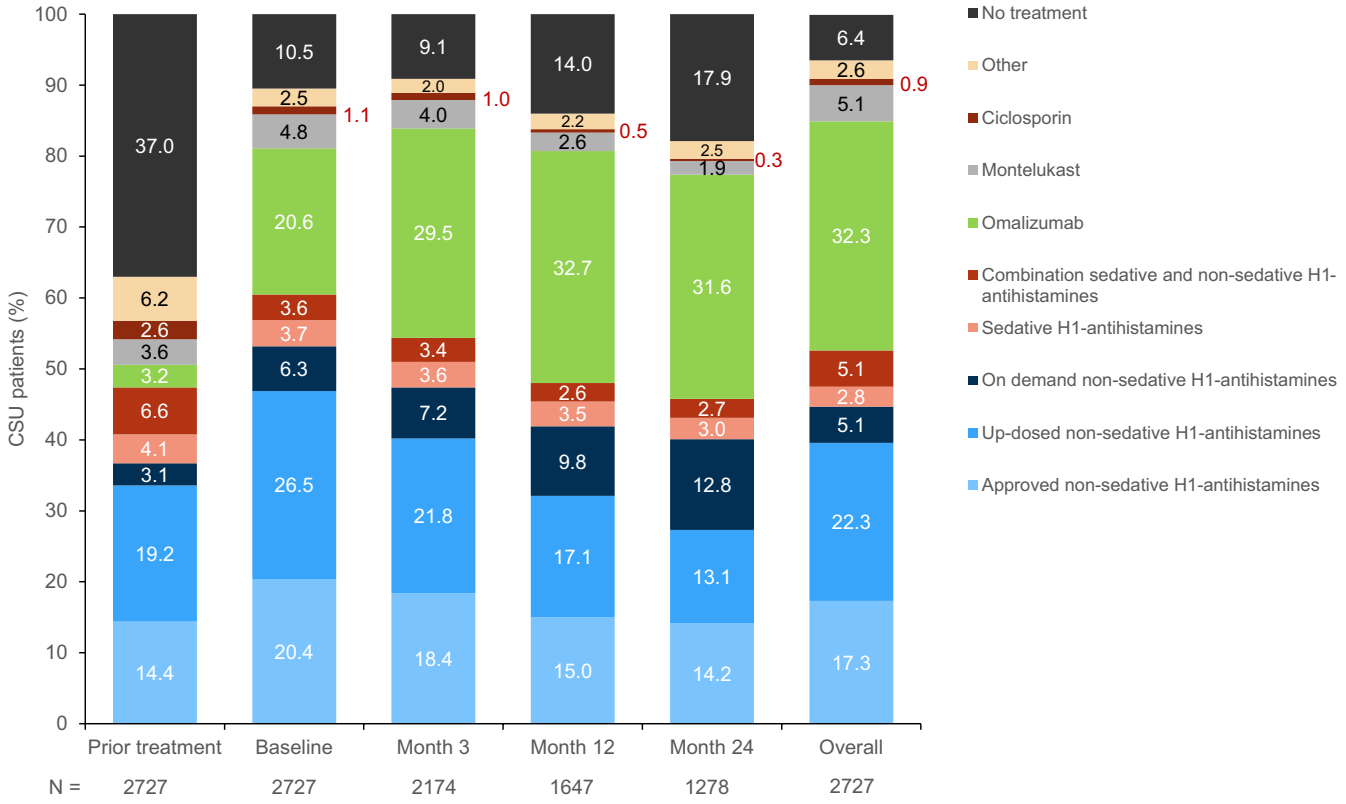

FIGURE 3 Numbers (and percentages) of patients receiving different treatments at each visit. N, total number of patients at each visit. CSU, chronic spontaneous urticaria. Other third-line treatment options (as defined in 2014 guidelines) were rarely used. Prior to AWARE enrolment, ciclosporin was prescribed in 2.6% (n = 71) of patients, which reduced to 0.3% (n = 4) at the end of the observational period. Similarly, montelukast was prescribed for 3.6% (n = 97) of patients with chronic urticaria before enrolment and prescriptions reduced to 1.9% (n = 24) at Month 24 (Figure 4). The non-recommended sedative antihistamines were similarly rarely prescribed, with 4.1% before enrolment reduced to 3.0% (n = 38) after the 2 years of observational period [Colour figure can be viewed at wileyonlinelibrary.com]

17.9% (n/N = 229/1278) at Month 24. As shown in Figure 4, the majority of the patients requiring treatment due to poorly controlled disease at baseline, either continued to receive treatment with nsAH or received no treatment at all during subsequent visits.

In some countries (Greece, Portugal, Belgium, Denmark, and Norway), patients were frequently escalated to up-dosed nsAH (between 12.8% [n/N = 10/78] in Belgium and 22.0% [n/N = 11/50] in Norway) and switched to third-line therapies at high rates (between 79.3% [n/N = 115/145] in Greece and 60.5% [n/N = 46/76] in Portugal) (Figure 5). Non-recommended therapies, such as combination of nsAH and sAH, were rarely used and rates of patients reported as receiving "no treatment" were low to none.

In Germany, the United Kingdom, Spain, and Sweden, patients were frequently up-dosed to nsAH, but a substantial amount of patients were either not up-dosed at all (Germany with 19.4% [n/N = 431/2226]) or escalated to off-label third-line therapies (montelukast: the United Kingdom 19.8% [n/N = 50/252] and Sweden 35.7% [n/N = 10/28]). Escalation to omalizumab varied in this group (United Kingdom 20.2% [n/N = 51/252], Sweden 25% [n/N = 7/28], Germany 30.9% [n/N = 687/2226], and Spain 44.7% [n/N = 122/273]).

In France, Italy, and Russia, relatively high rates of patients remained on approved doses of nsAH, despite the fact that they were inadequately controlled with them, with levels of 23.9% [n/N = 22/92], 27.9% [n/N = 69/247], and 29.1% [n/N = 39/134], respectively. Likewise, up-dosing of nsAH was observed less frequently, with levels ranging between 14.1% [n/N = 13/92] in France and 17.4% [n/N = 43/247] in Italy. Up-dosing to omalizumab occurred in only 14.2% [n/N = 19/134] (Russia) to 22.8% [n/N = 21/92] (France) of cases. The use of montelukast varied between 4.0% [n/N = 10/247] (Italy) and 20.9% [n/N = 28/134] (Russia). Additionally, the non-recommended combination of nsAH and sAH was chosen in 4.3% [n/N = 4/92] (France) up to 12.6% [n/N = 31/247] (Italy) of patients.

4 | DISCUSSION

The present study aims to prospectively collect real-world data to evaluate disease burden and treatment in CU patients inadequately treated with H1-antihistamine. The 2-year results from AWARE in Europe confirm that CSU remains undertreated. The baseline demographics and clinical characteristics of patients with CSU documented in the study, in general, are similar to the patient population included in omalizumab clinical trials.[27-29] Concomitant angioedema was reported in almost half of enrolled CU patients within the last six months. At baseline, 89.4% and 45% of patients reported hives and angioedema, respectively. Although there was improvement in the

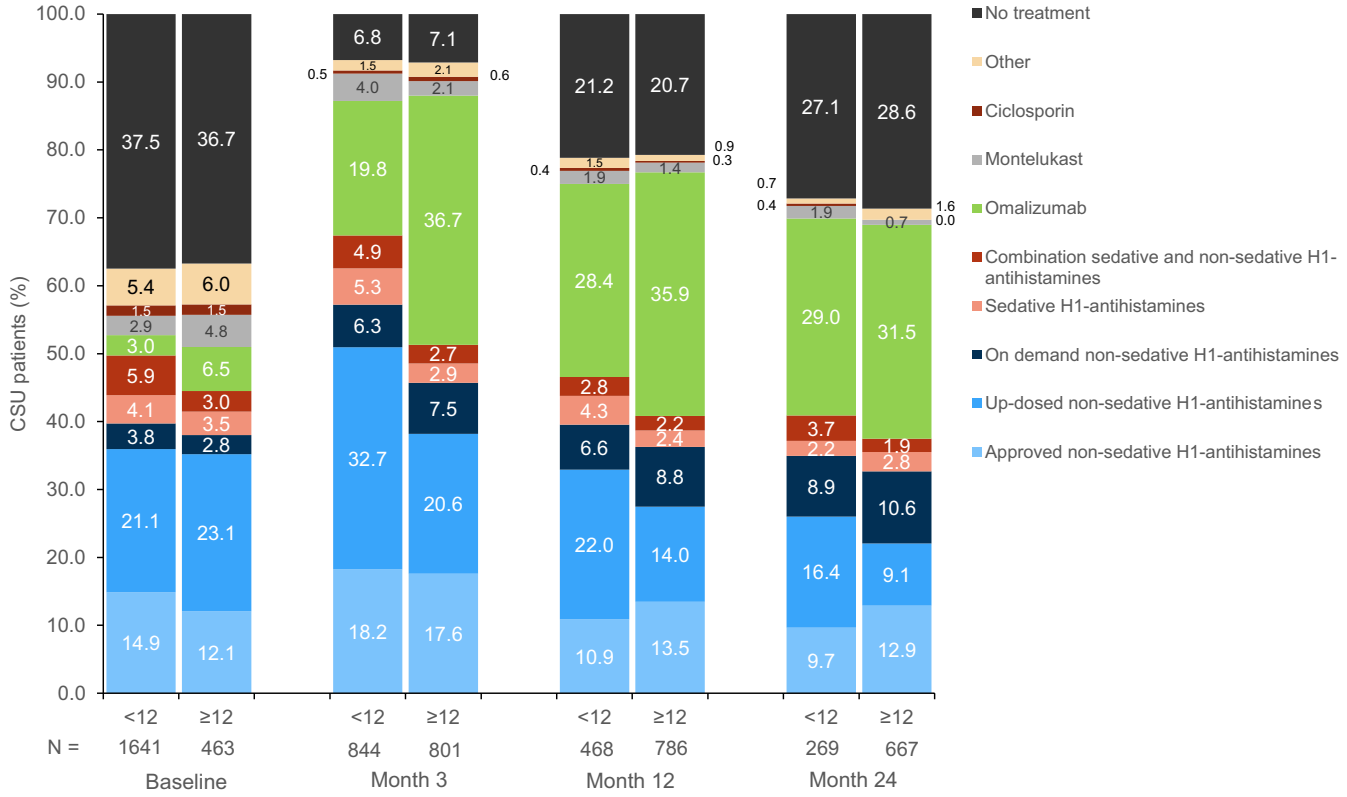

FIGURE 4 Numbers (and percentages) of poorly controlled (UCT <12) well-controlled patients (UCT ≥12) receiving different treatments at each visit. N, total number of patients at each visit. CSU, chronic spontaneous urticaria [Colour figure can be viewed at wileyonlinelibrary.com]

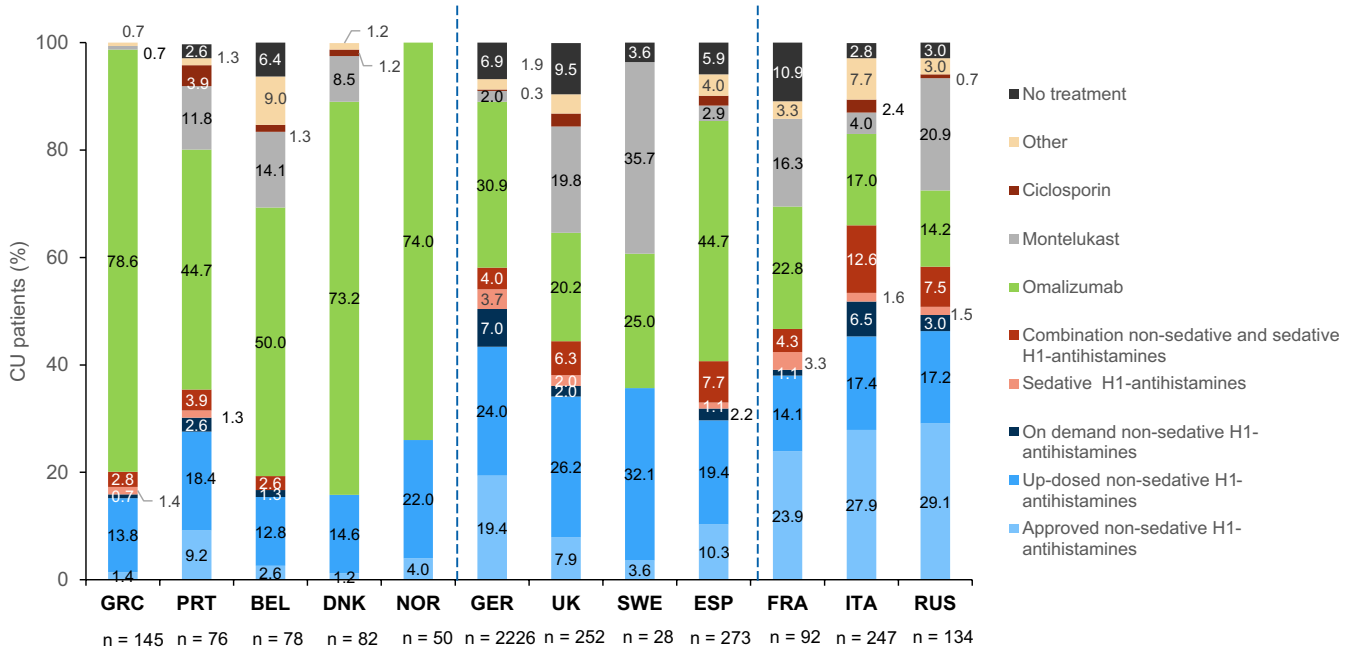

FIGURE 5 Treatment groups (current medication) by country based on escalation to third-line therapies (2014 EAACI/GA^{2}LEN/EDF/WAO guidelines). Results reported for the entire CU population (N = 3683). CU, chronic urticaria. BEL, Belgium; DNK, Denmark; ESP, Spain; FRA, France; GER, Germany; GRC, Greece; ITA, Italy; NOR, Norway; PRT, Portugal; RUS, Russia; SWE, Sweden; UK, United Kingdom [Colour figure can be viewed at wileyonlinelibrary.com]

disease condition over time, a substantial proportion of patients continued to have hives and/or angioedema after 2 years. Angioedema plays a significant role in the burden of CSU, with a negative impact on HR-QoL and is known to drive direct costs.[6] The frequency of CSU with comorbid CIndU has not been well-documented to date; however, in this broad observational study, the rate of comorbid CIndU in these patients with CSU inadequately controlled with H_1-antihistamines was 20.6%.[1,5]

At baseline, patients with CSU were undertreated and had high medical resource utilization. Also, 4 of 5 patients had poorly controlled CSU (UCT <12). Nearly 55% of CU patients had at least a moderate, large, or extremely large impact on their QoL. The CU-Q_2oL score at baseline confirmed a moderate to high impact of urticaria on patients' QoL.

The most frequent medications reported prior enrolment were CU guideline-recommended nsAHs. According to the 2014 urticaria guidelines established at the time of the AWARE study,[10] patients not responding to first-line (approved dose of nsAH) and second-line treatment (up-dosed nsAH) were to be prescribed third-line add-on therapy with omalizumab, montelukast, or ciclosporin. Since individual CSU patients differ in their responses to the recommended treatment algorithm, the focus of the present study was to evaluate the proportion of patients in different treatment groups and their corresponding UCT scores where available. Patients improved substantially over the 2-year observational period as evident by all investigated objectives, with more than 70% of patients with CSU achieving symptom control. A substantial proportion of patients had poorly controlled CSU after the two-year period, and after being seen by a specialist. As with a previous observational study by Curto-Barredo et al[5] where 32.4% and 17.3% of patients with CSU required medical care after 3 and 5 years, respectively, this AWARE study shows the necessity of long-term medical case in CSU.

The burden of CSU on HR-QoL was evident from PROs with high DLQI and CU-Q_2oL scores. Despite treatment and expert care, about one in five patients had moderate to extremely large effects on their HR-QoL after 2 years. Our results are in agreement with previous studies showing that CSU has a significant impact on QoL of patients, with a high rate of emotional burden and psychiatric comorbidities.[30-34] Unsurprisingly, for a 2-year observation period, CSU patients showed high medical resource utilization, with multiple dermatologists and general practitioners being involved with patient care.

Our results show that many patients after two years of expert care, either receive treatment that does not help them control their urticaria or receive no treatment at all. In this study, 23.2% of patients with CSU who remained uncontrolled (UCT < 12) with nsAH should ideally have at least received up-dosed nsAH in an attempt to improve symptoms. Similarly, 41.9% of patients whose symptoms were uncontrolled with up-dosed nsAH should have received further escalation to a third-line treatment option. Such differences in treatments may be attributed to clinicians who do not always follow urticaria treatment guidelines and may require better acceptance of the guidelines for treatment.[35-37] A web-based survey of patients diagnosed with CU in Germany revealed that only 40% of symptomatic patients were under physician care, with the majority of them choosing to stop their consultations, as they felt doctors were unable to help them or that they knew how to treat the CU symptoms themselves.[38] Similar results on survey of patients were reported in Italy.[35] The guidelines recommend omalizumab as an add-on treatment (to H_1-antihistamines) and upon de-escalation patients should stop omalizumab and continue H_1-antihistamines; however, there appears to be a persistence of omalizumab use in patients with withdrawal of other treatments. Omalizumab is shown to be safe and effective across randomized placebo-controlled trials[28,29,39] and several real-world studies,[40-44] with a total patient exposure of 1,328,183 patient years (Novartis data on file, Dec 2019).

The strength of this study as a reflection of real-world practice is also its main limitation. There were no pre-defined or randomized group assessments of patients, instead data describing the treatment strategy of a patient were assessed on an ongoing basis and could also vary during the study. The only inclusion criteria applied, next to the patient providing informed consent and age ≥18 years, were a medically confirmed diagnosis of CU with symptoms of more than 2 months and inadequate control with H_1-antihistamines. No explicit exclusion criteria apart from anticipated difficulties in the follow-up of the patient and simultaneous participation in any other clinical urticaria trial were applied. Number of patients available for assessment decreased over 2 years primarily due to loss of follow-up. The calculation of percentages was based on the valid data per parameter, excluding patients with missing values. Patients with complete remission of urticaria (14.1%) were also excluded from the analysis. Additional factors yielding a selection bias of patients cannot be completely ruled out. The observed frequent lack of treatment escalation might be related to variability in prescription practices across European countries, cost and/or availability of treatment, or tolerability issues—the present study did not systematically collect safety and tolerability data; therefore, these factors cannot be excluded. The European countries included in this study have unique healthcare systems and currently not all guideline-recommended therapies are available; for instance, omalizumab was not available in the UK during the study period or affordable for all patients with CSU. For example, certain countries experience specific reimbursement constraints that make it mandatory to stop third-line treatment (omalizumab) after a certain period of time. The countries may also have local guidelines that can differ from EAACI/GA^{2}LEN/EDF/WAO guidelines. In addition, it is also likely that health economic factors in different countries might affect prescription practices. When interpreting subgroup analyses by country, it has to be considered that patient numbers per country varied significantly: from 28 patients in Sweden up to 2226 patients in Germany. The data obtained within this study were assessed using descriptive statistics and were not used for comparative analysis.

The present data from a large patient population likely reflect the disease burden and treatment regimens of CU patients in Europe. The enormous variability observed in data reflecting healthcare utilization and treatment strategies between countries maybe seen as a result of

different healthcare systems and health economic standards of participating countries. There is a need for improved patient care, physician education, and adherence to treatment guidelines for better management of CU. Further studies are needed to understand the differences between guideline recommendations and reported management.

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CONFLICT OF INTEREST

M. Maurer has received grant/research support and/or honoraria for consulting or lectures from Aralez, Allakos, FAES, Genentech, Merckle Recordati, Moxie, Novartis, Roche, Sanofi, MSD, UCB, Uriach. A. Giménez-Arnau has served as medical advisor for Uriach Pharma, Genentech, Novartis, FAES, GSK, Sanofi; received research grants supported by Uriach Pharma, Novartis, Grants from Instituto Carlos III-FEDER and involved in educational activities for Uriach Pharma, Novartis, Genentech, Menarini, LEO Pharma, GSK, MSD, Almirall and Sanofi. G. Guillet received a grant from Novartis for this study. M. Labrador-Horrillo has received fees for lectures and consulting from Novartis. H. Lapeere received fees for lectures and/or consulting from Novartis, Sanofi, Leo pharma and Janssen. S. Savic reports personal fees from Novartis; grants, personal fees and other from Sobi; grants and personal fees from CSL Behring; personal fees from Shire. N. Chapman-Rothe is an employee of Novartis. C. Costa and R. Meshkova report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data sets generated during and/or analysed 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 the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The data may be requested from the corresponding author of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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