ORIGINAL ARTICLE

A Specialized Therapeutic Approach to Chronic Urticaria Refractory to H1-Antihistamines Improves Disease Burden: The Spanish AWARE Experience

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Abstract

Objective: During its first year, the AWARE study assessed disease activity, patient quality of life (QOL), and treatment patterns in chronic urticaria (CU) refractory to H1-antihistamines (H1-AH) in clinical practice.
Methods: We performed an observational, prospective (24 months), international, multicenter study. The inclusion criteria were age ≥18 years and H1-AH–refractory CU (>2 months). At each visit, patients completed questionnaires to assess disease burden (Urticaria Control Test [UCT]), disease activity (7 day-Urticaria Activity Score [UAS7]), and QOL (Dermatology Life Quality index [DLQI], Chronic Urticaria Quality of Life Questionnaire [CU-Q2oL], and Angioedema Quality of Life Questionnaire [AE-QoL]). We present data for Spain.
Results: The study population comprised 270 evaluable patients (73.3% female, mean [SD] age, 48.9 [14.7] years). At baseline, 89.3% were prescribed a CU treatment. After 1 year, first- and second-line treatments became less frequent and third-line treatments became more frequent. At baseline, 47.0% of patients experienced angioedema; at 1 year, this percentage had fallen to 11.8%. The mean (SD) AE-QoL score decreased from 45.2 (28.7) to 24.0 (25.8). The mean (SD) UCT score decreased from 7.0 (4.5) to 12.1 (4.1). According to UAS7, 38.2% of patients reported absence of wheals and itch in the previous 7 days at 1 year compared with 8.3% at baseline. The mean (SD) DLQI score decreased from 8.0 (7.4) to 2.8 (4.6). At the 1-year visit, the percentage of patients reporting a high or very high impact on QOL fell from 29.9% to 9.6%.
Conclusions: H1-AH–refractory CU in Spain is characterized by absence of control of symptoms and a considerable impact on QOL. Continuous follow-up of CU patients and third-line therapies reduce disease burden and improve patients' QOL.

Key words: Chronic urticaria. Clinical practice. Spain. Quality of life. Angioedema. Urticaria.

Resumen

Objetivo: El estudio AWARE evalúa la actividad de la enfermedad, la calidad de vida (CV) del paciente y los patrones de tratamiento en pacientes con urticaria crónica (UC) refractarios a antihistamínicos H1 (AH-H1) en práctica clínica durante el primer año del estudio.
Métodos: Estudio observacional, prospectivo (24 meses), internacional y multicéntrico. Pacientes ≥18 años con diagnóstico de UC refractarios a AH-H1 (>2 meses). En cada visita, los pacientes completaron cuestionarios para evaluar la carga de la enfermedad (*Urticaria Control Test* [UCT]), actividad de la enfermedad (*7 day-Urticaria Activity Score* [UAS7]), CV (*Dermatology Life Quality index* [DLQI], *Chronic Urticaria Quality of Life Questionnaire* [CU-Q2oL], *Angioedema Quality of Life* [AE-QOL]). Presentamos datos españoles.
Resultados: Se incluyeron 270 pacientes evaluables (73,3% mujeres, edad media [DE] 48,9 [14,7] años). Al inicio del estudio, al 89,3% se le prescribió un tratamiento para la UC. Después de 1 año, los tratamientos de primera/segunda línea tendieron a disminuir y la tercera

línea a aumentar. El 47,0% de los pacientes experimentaron angioedema al inicio del estudio, siendo del 11,8% al cabo de 1 año. La media (DE) de AE-QOL pasó de 45,2 (28,7) a 24,0 (25,8). La media (DE) de UCT pasó de 7,0 (4,5) a 12,1 (4,1). Según UAS7, el 38,2% de pacientes reportaron ausencia de ronchas y prurito en los últimos 7 días al año frente al 8,3% al inicio. El DLQI medio (DE) pasó de 8,0 (7,4) a 2,8 (4,6). En la visita de 1 año, el porcentaje de pacientes que reportaron un impacto en la CV alto/muy alto pasó del 29,9% al 9,6%. *Conclusiones:* Los pacientes españoles con UC refractarios a AH-H1 presentan una falta de control de la sintomatología con un importante impacto en su CV. El seguimiento continuo de los pacientes con urticaria crónica espontánea y las terapias de tercera línea han demostrado una tendencia a reducir la carga de la enfermedad y a mejorar la CV de los pacientes.

Palabras clave: Urticaria crónica. Práctica clínica. España. Calidad de vida. Angioedema. Urticaria.

Introduction

Urticaria is a mast cell– and basophil-driven skin disease characterized by the presence of erythematous, pruritic rash, itchy wheals (hives), and/or angioedema [1]. Between 8% and 20% of the population is susceptible to experiencing at least 1 episode of urticaria during their lifetime [1-3]. Depending on the clinical course, urticaria can be acute (symptoms ≤6 weeks) or chronic (CU, with recurrent episodes lasting >6 weeks) [1,4].

The estimated prevalence of CU in the general population is 0.6% [3]. According to triggering factors, CU is classified into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CINDU) [5]. CSU is the most common nonacute type (about 70%) [6] and occurs without a specific trigger. CINDU appears as a response to specific stimuli (eg, exposure to cold, heat, or sunlight) [2,7]. Clinical CU patterns are broad, and patients often exhibit both subtypes concomitantly [8].

The duration of CU (from months to years) has a negative impact on patients' health-related quality of life (HRQOL) and productivity [2]. Current HRQOL and disease activity questionnaires are useful tools in daily clinical practice and can help physicians to determine the prognosis and severity of CU [9-12].

International clinical practice guidelines recommend individualized management to achieve rapid and complete control of the symptoms of CU based on the most effective and safest medication [1,2]. Current first-line (1L) treatment is with nonsedating H1-antihistamines (NS-H1-AH) at licensed doses. If symptoms persist, the licensed dose may be increased up to 4-fold as second-line (2L) treatment [1,2,4,13]. Omalizumab is recommended as third-line treatment (3L) [1]. While cyclosporine A has also been recommended as third-line treatment, new guidelines consider it to be fourth-line treatment [1]. Similarly, montelukast was recommended as third-line treatment, although not in the updated guidelines owing to the lack of clinical evidence [1]. In addition, systemic corticosteroids can be used for a maximum of 7-10 days in cases of exacerbation [1,13]. It is worth noting that 77.7% of CSU patients are symptomatic despite the use of licensed doses of second-generation H1-antihistamines (H1-AH) and that 63.2% of patients who did not respond to the licensed dose could benefit from increased doses [14].

The main objective of the "A Worldwide Antihistamine-Refractory Chronic Urticaria Patient Evaluation (AWARE)" study was to assess disease activity and HRQOL in patients with CU refractory to at least 1 course of treatment with H1-AH in daily clinical practice in Spain. It also aimed to evaluate the relationship between patient-reported outcomes (PROs) and the therapeutic regimen received. Herein, we report results from the first year of the Spanish AWARE study.

Material and Methods

Study Design

AWARE is a 24-month, prospective, multinational (14 countries), noninterventional study. We present data recorded at baseline and at the 1-year visit (up to January 18th, 2017) from 40 Spanish hospital dermatology and allergology departments in Spain.

The study was performed according to guidelines on observational postauthorization studies for medicinal products for human use specified in Order SAS/3470/2009 of the Spanish Agency of Medicines and Medical Devices (AEMPS) and obtained a favorable opinion by the accredited Clinical Research Ethics Committees of the Health Department of the Basque Country, with approval number EPA2014034. The study was conducted according to the principles of Good Clinical Practice (International Conference of Harmonization), the Declaration of Helsinki, and local regulations, including privacy laws in force at initiation.

The sample size was estimated based on incidence, prevalence, sample size related to total population, and anticipated recruitment during the study period. The population to be enrolled in Spain was 250 patients.

The inclusion criteria comprised age ≥18 years with a confirmed diagnosis of CU (≥2 months), resistance to treatment with H1-AH according to clinical criteria, and informed consent. Patients participating in any other clinical study on urticaria or who were unlikely to complete the 2-year follow-up according to the physician's criteria were excluded.

The study comprised 9 visits over the 24-month follow-up period (quarterly and annually, according to routine clinical practice).

Patient demographics, CU-related medical history, comorbidities, and previous treatments were collected at baseline. At all visits, patients completed a series of validated questionnaires, namely, the Urticaria Control Test (UCT), 7 day-Urticaria Activity Score (UAS7), Dermatology Life

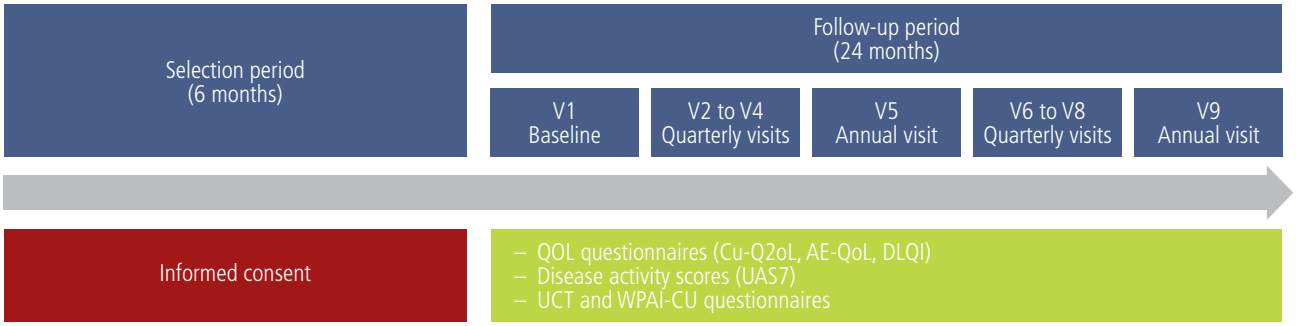

Figure 1. Study design. AE-QoL indicates Angioedema Quality of Life Questionnaire; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; DLQI, Dermatology Life Quality Index; QOL, quality of life; UAS7, Urticaria Activity Score Over 7 Days; UCT, Urticaria Control Test; V, visit; WPAI-CU, Work Productivity and Activity Impairment - Chronic Urticaria.

Quality index (DLQI), Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), Angioedema Quality of Life (AE-QoL), and Work Productivity and Activity Impairment–Chronic Urticaria (WPAI-CU) [15-21] (Figure 1).

Statistical Analysis

Although considerations of sample size were based on formal statistical principles, determination of the α error and statistical power were not anticipated.

The statistical analysis was based on evaluable patients stratified into 5 treatment groups at each visit according to the treatment steps of the 2014 international clinical practice guidelines for urticaria [22]: 1L (NS-H1-AH at approved doses); 2L (NS-H1-AH at high doses [up to 4 times the approved dose]); 3L (2L treatment administered together with omalizumab or cyclosporine A or montelukast); other combinations (a heterogeneous group including any other treatment combinations not mentioned in the 1L, 2L, or 3L groups and not included in the therapeutic algorithm); and no medication. Data for the 1L and 2L groups are reported together (1L/2L).

A descriptive analysis was performed individually for all variables based on continuous variables (number of observations, missing data, mean [SD]), qualitative variables (means of frequency distributions [absolute and relative]), quantitative variables (valid N, missing N, mean [SD], minimum and maximum, median [IQR]), and discrete variables. Percentages were calculated based on the valid data per parameter, excluding patients with missing values, at every visit. The results are provided for the group, not per patient (baseline to 1 year). Data were analyzed using SAS version 9.4 for Windows.

Table. Baseline Demographic and Clinical Characteristics of the Spanish Study Cohort

	(N=270)
Female sex, No. (%)	198 (73.3)
Mean (SD) age, y	48.9 (14.7)
Mean (SD) height, cm	163.8 (8.6)
Mean (SD) weight, kg	71.9 (15.1)
Mean (SD) body mass index, kg/m^2	26.8 (5.0)
Mean (SD) systolic blood pressure, mmHg	125.3 (16.3)
Mean (SD) diastolic blood pressure, mmHg	75.4 (10.7)
Mean (SD) time from diagnosis to baseline visit, y	5.0 (7.1)
Median (range) time for diagnosis to baseline visit, y	2.2 (0-47)
Patients with angioedema from the last 6 months to baseline, No. (%)	127 (47.0)
Patients with CINDU, No. (%)	71 (26.3)
Working patients, No. (%)	144 (53.3)

Abbreviations: CINDU, chronic inducible urticaria.

Results

Demographic Characteristics

The study population comprised 278 patients, of whom 270 (97.1%) were eventually analyzed. Mean (SD) age was 48.9 (14.7) years, and most were women (73.3%) (Table). Comorbidities were recorded in 207 patients (76.7%), mainly hypertension (27.1%), hypercholesterolemia (20.3%), and allergic rhinitis (17.9%).

Treatment Approach to CU

At baseline, 241 (89.3%) patients were prescribed a treatment for CU. Of these, 127 (47.0%), 66 (24.4%), and 48 (17.8%) were prescribed a 1L/2L, 3L treatment, or other combinations, respectively (Figure 2A).

NS-H1-AH were the most common drugs before and during the study. Still, NS-H1-AH use decreased during the first year (from 88.8% to 72.8%). The number of patients taking omalizumab (in 3L or other combinations) increased during the study (18.2% of treated patients before baseline, 37.3% at baseline, and 46.7% after 1 year). Although sedative H1-antihistamines (S-H1-AH) are not recommended in current CU therapeutic guidelines, their frequency of use ranged from 23.2% at baseline to 12.0% at 1 year. Corticosteroids were the fourth most used drug (from 20.7% at baseline to 12.5%

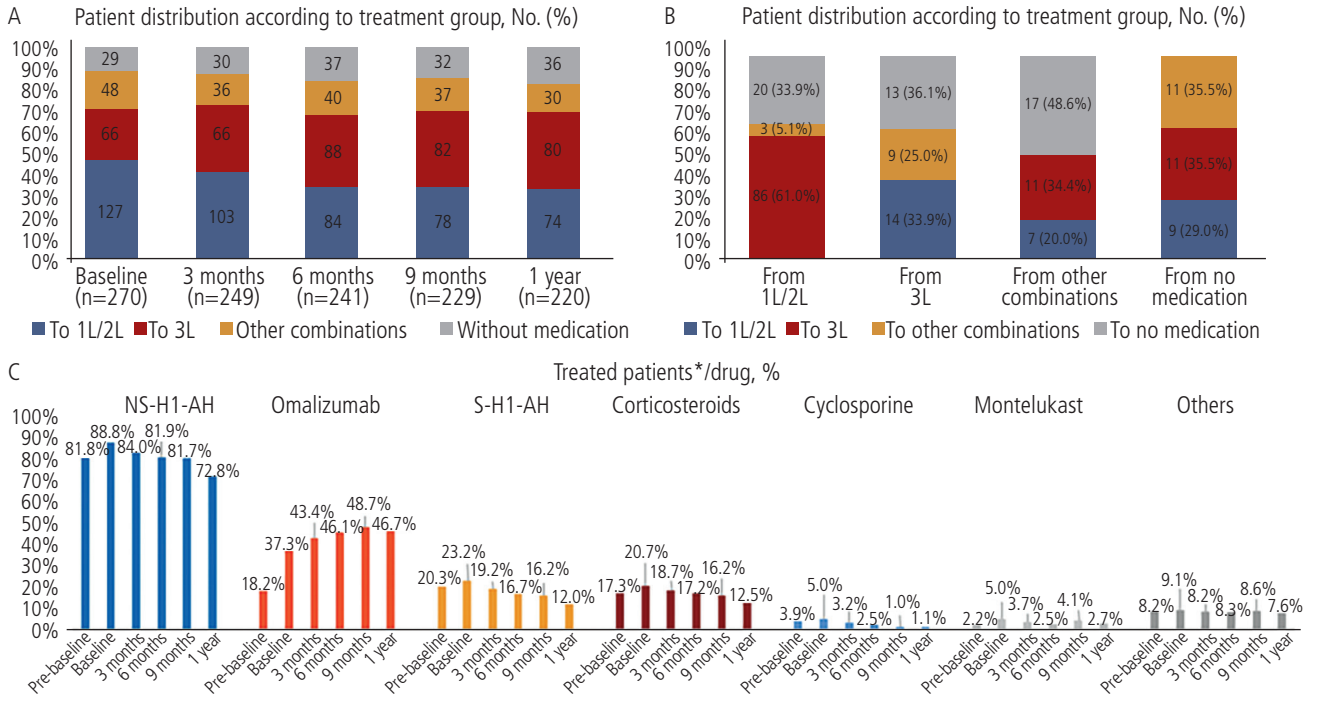

Figure 2. Distribution of treatment and switching patterns. *Treated patients: total evaluable patients in 1L/2L, 3L and other combination treatment groups before baseline (n=231) and at baseline (n=241), 3 months (n=219), 6 months (n=204), 9 months (n=197), and 1 year (n=184). 1L indicates first line; 2L, second line; 3L, third line; NS-H1-AH, nonsedating H1-antihistamines; S-H1-AH, sedative H1-antihistamines.

at 1 year). A lower number of patients were treated with cyclosporine and montelukast (from 1.0% to 5.0% and 2.2% to 5.0%, respectively) (Figure 2C).

During the first year, a total of 939 visits were recorded. Similar retention rates were observed across the treatment groups during the study (84.0%, 88.0%, 77.4%, and 73.3% for the 1L/2L, 3L, other combinations, and no medication groups, respectively). Treatment was switched at 161 visits (17.1%). Most of the 1L/2L patient switches (61.0%) were towards the 3L group, as expected according to treatment guidelines. Some patients in 3L (38.9%) and other combinations (20.0%) took steps backwards to 1L/2L in the CU therapeutic algorithm. Fifty visits (31.1%) were for patients in any active treatment group whose medication was withdrawn (Figure 2B).

At 1 year, 184 patients (83.6%) were in an active treatment group. More patients were receiving 3L treatment compared with baseline, mostly due to the decrease in 1L/2L treatments (Figure 2B). The number of patients not taking medication increased throughout the first year (36 [16.4%]). Of the initial 270 patients, 43 (15.9%) discontinued (29 [67.4%] were lost to follow-up, 11 [25.6%] because of remission, and 3 [7.0%] because of relocation).

Satisfaction with treatment improved throughout the study. At baseline, 268 patients scored a mean (SD) of 5.6 (3.0) on a scale of 0 to 10. At the 1-year visit, this score increased to 8.4 (2.1), with 184 patients rating their treatment satisfaction.

Disease Control

The UCT result is a PRO that makes it possible to assess patients' control of their disease (score ranging from 0 to 16). In the present study, UCT≥12 was considered good control, whereas UCT<12 was considered poor control. At baseline, 219 of 267 patients with available results (82.0%) had poor disease control, with a mean (SD) score of 7.0 (4.5). This value increased to 10.4 (4.2) at the 3-month visit and to 12.1 (4.1) at 1 year. At the 1-year visit, 70 of 198 patients (35.4%) still reported poor disease control. The highest CU control rates at baseline were for patients in the 3L group, with a mean of 8.6 (5.3) and 31.8% in good control. At the 1-year visit, the mean score for 3L patients was 12.5 (3.9), with good control rates that were twice the baseline value (66.2%). Patients not taking medication achieved the highest control rates at 1 year, with a mean of 14.3 (2.2) and 85.7% reporting good control. Patients in 1L/2L exhibited the lowest rates of disease control across all the study visits, with poor disease control recorded in 86.3% of patients at baseline and 41.3% at the 1-year visit (Figure 3A, Figure 3C).

Disease Activity

The UAS7 questionnaire assesses the activity of CSU during the 7 days before each visit. The UAS7 score ranges from 0 to 42, with higher scores indicating more severe disease. The mean total UAS7 at baseline was 20.0 (12.4), decreasing to 12.9 (11.2) at the 3-month visit and reaching 8.4 (10.1) at the 1-year visit. At baseline, the mean UAS7 ranged from 19.5 to 22.8 in the treatment groups, indicating moderate CU activity, and dropped to 8.3 to 9.5 after 1 year. For patients without medication, a mean UAS7 score of 17.7 (16.6) was reported at baseline, falling to 4.9 (6.7) at the 1-year visit (Figure 3B).

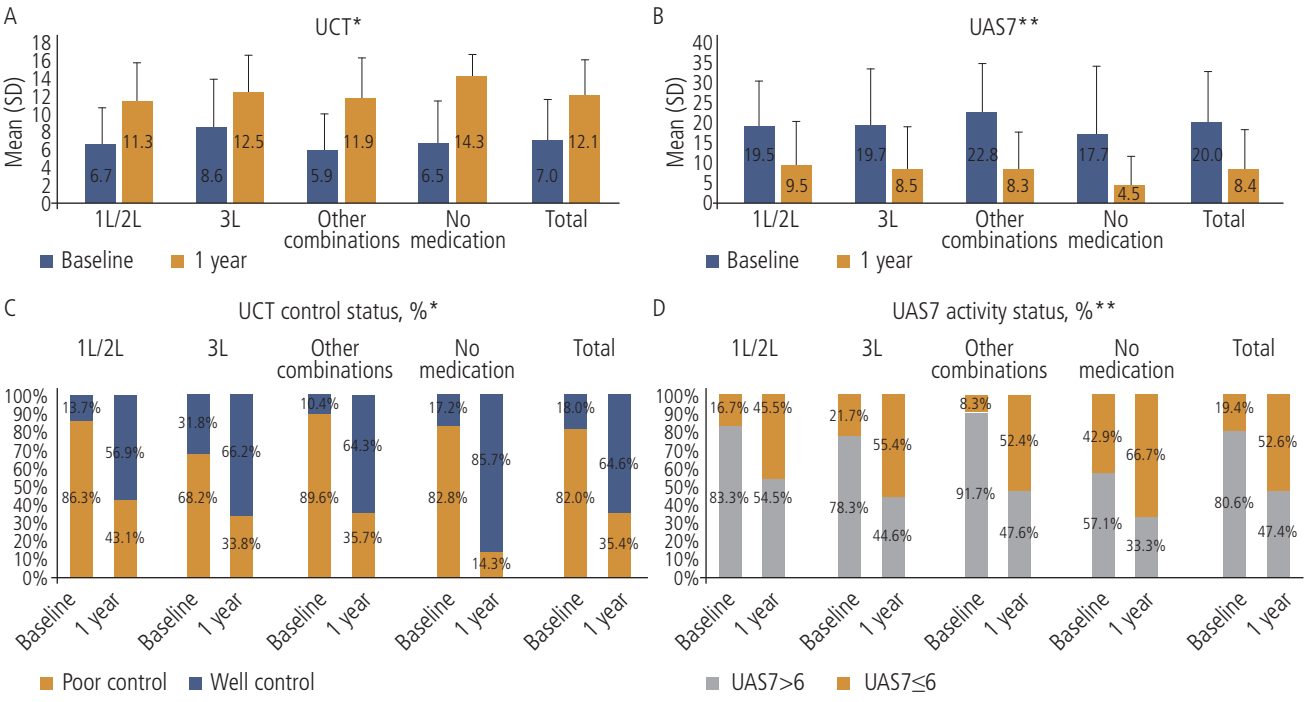

Figure 3. UCT disease control status and UAS7 activity status in the treatment groups. *Number of evaluable patients with available data at baseline and 1 year: 1L/2L, 124 and 72; 3L, 66 and 77; other combinations, 48 and 28; without medication, 29 and 21; total, 267 and 198. **Number of evaluable patients with available data at baseline and 1 year: 1L/2L, 30 and 66; 3L, 23 and 65; other combinations, 12 and 21; without medication, 7 and 21; total, 72 and 173. 1L indicates first line; 2L, second line; 3L, third line; UAS7, Urticaria Activity Score over 7 days; UCT, Urticaria Control Test.

In the treatment subgroup analysis, we differentiated between severe, moderate, and mild CSU patients (UAS7 >6) and those with low disease activity or without itching and hives (UAS7 ≤6) [23]. The tendency across the groups throughout the study was toward an increase in the proportion of patients with UAS7 ≤6. Higher UAS7 ≤6 rates were found at the 1-year visit in 3L (55.4%) and in patients not taking medication (66.7%). In contrast, 1L/2L patients had the lowest UAS7 ≤6 at the 1-year visit (45.5%), indicating that despite treatment with NS-H1-AH, most patients still displayed mild-to-severe CSU (Figure 3D).

Overall, disease activity according to UAS7 improved throughout the study. The percentage of patients without itch and hives for 7 days (UAS7=0) was 8.3% at baseline and 38.2% at 1 year, whereas for patients with severe CSU (UAS7 ≥28) and moderate CSU (UAS7, 16-27), this percentage was 30.6% and 27.8% at baseline and 6.9% and 12.7% at 1 year, respectively. The percentage of patients with mild CSU (UAS7, 7-15) and low disease activity (UAS7 1-6) remained stable throughout the study (22.2% and 11.1% and 27.7% and 14.5%, respectively) [23] (Figure 4).

Control of Angioedema and Impact on HRQOL

The frequency of angioedema decreased during the study, from 127 patients (47.0%) at baseline to 26 (11.8%) at the 1-year visit (Figure 5A). At baseline, 7 patients (5.5%) reported angioedema related to medication. There were no cases of hereditary angioedema or acquired C1-esterase-inhibitor deficiency. At baseline, angioedema was mild in 52.0%, moderate in 34.7%, and severe in 8.7% (intensity was unknown in 1.6% patients).

The impact of angioedema on HRQOL was evaluated through the AE-QoL, a validated test on which the score ranges from 0 to 100, with higher scores indicating greater impact on HRQOL [24]. Angioedema had a mild impact on patients' HRQOL, with a mean AE-QoL score of 45.2 (28.7) at baseline, falling to 24.0 (25.8) after 1 year. At baseline, the poorest HRQOL was recorded for other combinations and 1L/2L (50.4 [30.5] and 49.5 [29.4], respectively). After 1 year, the AE-QoL scores fell in all groups, ranging between 23.0 and 29.8, except for the nonmedicated group, where the mean score was 7.6 (7.2) (Figure 5B).

HRQOL

The impact of CSU on HRQOL was measured using the DLQI and CU-Q2oL questionnaires. The DLQI score ranges from 0 to 30 and that of the CU-Q2oL from 0 to 100, with higher values indicating greater impact on HRQOL in both questionnaires [17,25]. The mean total DLQI score at baseline was 8.0 (7.4) (Figure 6A), with 80 patients (29.6%) reporting a very large or extremely large impact on HRQOL; the remaining patients reported a small-to-moderate impact (131 patients, 48.5%) or no impact (57 patients, 21.1%). After 1 year, the mean score was 2.8 (4.6), with 19 (8.6%) patients reporting a very large or extremely large impact, 56 (25.5%) a small/moderate impact, and 122 (55.5%) no impact (Figure 6A). Baseline DLQI scores ranged from 7.2 to 8.8 for all active treatment groups, indicating a moderate impact on

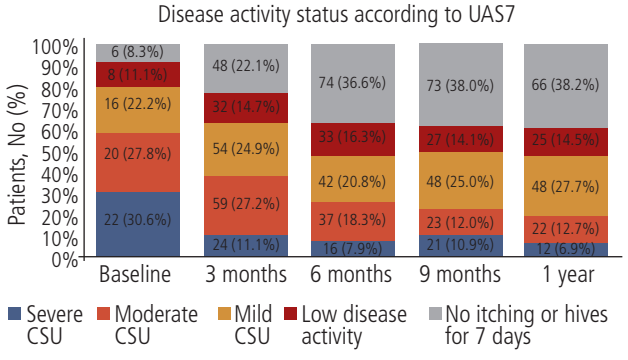

Figure 4. Activity of CSU throughout the study. *Missing data: 198, 31, 39, 37, and 47 patients at visits 1 to 5, respectively. CSU indicates chronic spontaneous urticaria; UAS7, urticaria activity score over 7 days.

most CU patients. After 1 year, the mean DLQI score of all active treatment groups ranged between 2.5 and 3.5, indicating an improvement in HRQOL. The mean DLQI score in the nonmedicated group was 7.1 (6.0) at baseline, dropping to 0.7 (1.2) after 1 year, thus indicating that CU had no further effect on HRQOL (Figure 6A).

The CU-Q2oL score indicated a mild-to-moderate impact on HRQOL at baseline, with a mean score of 31.4 (21.7), dropping to 12.5 (15.4) after 1 year (Figure 6B). This improvement was observed in each domain of the questionnaire. After 1 year, all groups achieved a lower HRQOL, with means between 12.9 and 15.2, except for the nonmedicated group (5.3 [5.8]) (Figure 6B).

Discussion

This subanalysis of the AWARE study presents real-world data on disease burden and activity and impact on HRQOL in CU patients refractory to H1-AH treatment in Spain. Consistent with previous studies, most patients were women (73.3%), with a mean age of 48.9 years [26-31].

Prior to the study, most treated patients were taking NS-H1-AH (81.8%), followed by omalizumab (18.2%). After 1 year, 72.8% of patients were taking NS-H1-AH, whereas 46.7% of patients were treated with omalizumab. Despite the indications of CU guidelines for 1L/2L [1], there was considerable use of sedating H1-AH, with 20.3% of patients receiving sedating H1-AH before the study. Although this frequency of use decreased, it was still 12.0% at 1 year. The distribution of treatment in the Spanish AWARE study was similar to that reported in other countries [31,32]. A retrospective study of CU patients in Ecuador reported that the most prescribed drug was NS-H1-AH alone (44.6%), followed by the combination of any H1-AH plus another treatment (corticosteroids, antileukotriene agents, hydroxychloroquine, or omalizumab) (42.0%) [32]. Curto-Barredo et al [6] showed that more than 75% of CSU patients were refractory to 1L treatment at licensed doses. Similarly, a meta-analysis of 15 studies revealed that the rate of response to standard doses of H1-AH in CU patients was 38.6% and that, among nonresponders, around 60% responded to up-dosing of H1-AH [14]. Although corticosteroids were the fourth most used drug (20.7% at baseline), administration tended to decrease after 1 year of study (12.5%). In this sense, international guidelines recommend avoiding long-term use of corticosteroids outside specialist clinics [1].

We think that PROs can be a useful tool for diagnosis, monitoring of disease activity, control of symptoms, impact on HRQOL, and productivity. After 1 year of study, all questionnaire scores had improved. However, almost 50% of patients still presented mild-to-severe CU (UAS7 >6). At that time, disease activity and the frequency of uncontrolled disease was highest in the 1L/2L group (54.5% had UAS7 >6 and 43.1% poor control according to the UCT). Hence, many CU patients might be refractory to H1-AH, thus reinforcing the importance of escalating to 3L biologic treatment to control CU. In addition, high retention rates were observed in the 1L/2L group (84.0%), underscoring the need to review the response to treatment every 2 to 4 weeks using the UAS7 or the UCT as per the EAACI/GA(2)LEN/EDF/WAO guideline [1]. This observation is consistent with results from other countries, such as Germany, where escalation to 3L treatment in AWARE patients was not as frequent as expected (from 8.5% at baseline to 21.4% at the 1-year visit) [30]. High retention rates were also observed in other groups (3L and other combinations). Despite

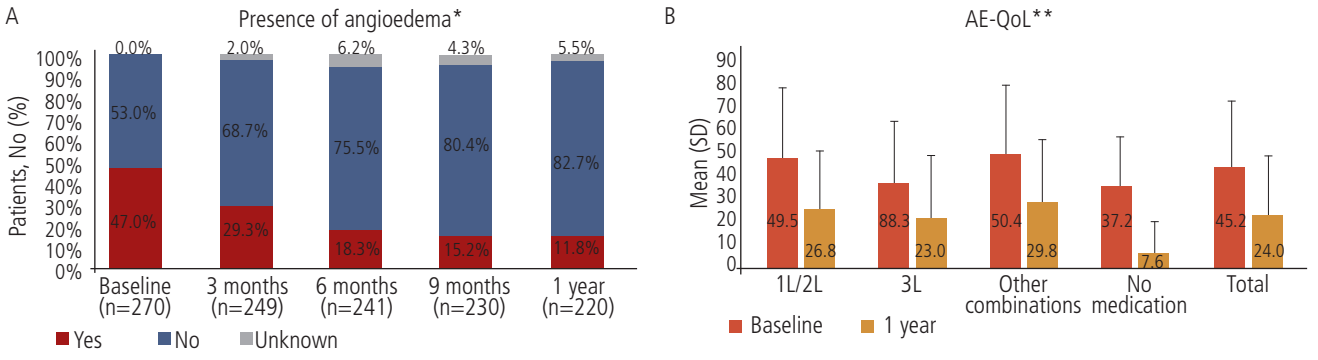

Figure 5. Presence of angioedema and AE-QOL. *Presence of angioedema by visit in the evaluable population. Baseline includes data from 6 months before visit 1. Other study visits report data from the previous study visit to each visit. **Number of evaluable patients with available data at baseline and 1 year: 1L/2L, 63 and 22; 3L, 48 and 41; other combinations, 34 and 11; no medication, 14 and 5; total, 159 and 79. 1L indicates first line; 2L, second line; 3L, third line; AE-QoL, Angioedema Quality of Life Questionnaire.

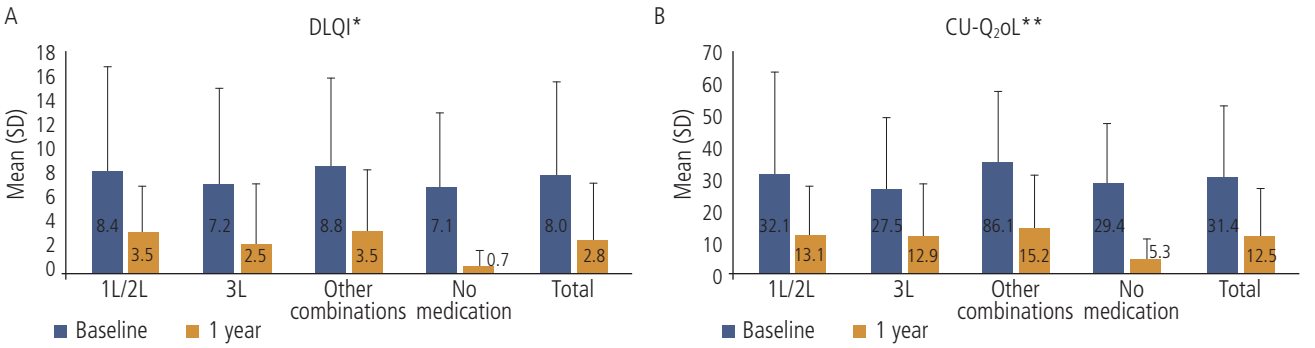

Figure 6. CU HR-QoL assessments. *Number of evaluable patients with available data at baseline and 1 year: 1L/2L, 125 and 71; 3L, 66 and 77; other combinations, 48 and 28; without medication, 29 and 21; total, 268 and 197. **Number of evaluable patients with available data at baseline and 1 year: 1L/2L, 127 and 73; 3L, 66 and 77; other combinations, 48 and 28; no medication, 29 and 21; total, 270 and 199. 1L indicates first line; 2L, second line; 3L, third line; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; DLQI, Dermatology Life Quality Index.

a UAS7 score ≤6 and good control, UCT rates were only slightly better than in the 1L/2L group. Consequently, there is still room for improvement. These findings might explain the lower rates among patients with well-controlled disease according to UCT, as also observed in Germany (35.4% and 42.2%, respectively) [30]. The percentage of patients who did not receive treatment and who had a UCT score indicating good control (UAS7≤6), lower rates of angioedema, and an impact on HRQOL after the first year of the study was higher than in the treated groups. This may be due to spontaneous remission of CU or complete response to treatment and consequent withdrawal of treatment. In this regard, there is a need to better define remission of CSU and when and how treatment can be safely withdrawn.

At baseline, >80% of patients had poor disease control according to the UCT and >50% of patients who responded to the UAS7 questionnaire experienced moderate-to-severe activity. Reported lack of disease control is associated with an impact on patients' daily activities [33], consistent with the HRQOL outcomes observed in our cohort. According to the DLQI, at baseline, the impact on HRQOL was mild to moderate in 48.5% of patients and severe to very severe in 29.6%. In a prospective study conducted in Brazil, CU patients reported a moderate impact on HRQOL according to the DLQI questionnaire [34]. Similarly, the mean DLQI scores of 12 CU studies summarized by O'Donnell et al [35] ranged between 7.2 and 13.4, indicating a moderate-to-severe impact. The ASSURE-CSU study reported a mean score of 9.1 (6.6) and 33.6 (21.0) on the DLQI and CU-Q2oL, respectively, and revealed that CSU interfered with sleep and daily activities [36]. A cross-sectional study conducted in Portuguese and Brazilian patients reported a mean CU-Q2oL score of 36 [37], which was consistent with the baseline CU-Q2oL in our study (31.4). Overall, these results reveal the negative impact of urticaria on HRQOL and the difficulties in achieving control of symptoms, even in treated patients.

The baseline rate of nontreated patients was lower for the Spanish cohort than for the rest of Europe or Central and South America (10.7% vs 31.9% and 45.1%, respectively) [30]. Even so, rates of uncontrolled disease among Spanish patients were high, with mean UCT scores at baseline similar to those described in other countries (7.0 [4.5] vs 7.2 [4.1] in Europe and 7.7 [4.3] in Central and South America) [30,31]. Although current urticaria guidelines state that CU treatment should aim to completely control disease symptoms, data suggest that most CU patients worldwide do not achieve this goal.

In our study, 47.0% of CSU patients experienced angioedema during the 6 months before baseline, consistent with data reported elsewhere [29,36,38]. After 1 year, this percentage dropped to 11.8%. Angioedema implies a considerable burden for CU patients, severely affecting their HRQOL. After 1 year, we observed an improvement in HRQOL according to the DLQI and CU-Q2oL questionnaires (the mean for all groups fell from 8.0 [7.4] to 2.8 [4.6] in DLQI and from 31.4 [21.7] to 12.5 [15.4] in CU-Q2oL). These findings are consistent not only with the improvement in both disease control and activity according to the UCT and UAS7, but also with the reduced frequency of angioedema observed throughout the study. The overall improvement across the study might be due not only to the spontaneous remission of CU, but also to the introduction of new therapies such as omalizumab. According to the clinical trials [28,29,39], omalizumab-treated patients experienced an improvement in the number of hives and severity of itch compared with placebo. Another study reported a greater mean number of angioedema-free days than with placebo in patients with CSU plus angioedema. Such studies report a clinical benefit of omalizumab in disease refractory to H1-AH treatment in the form of control of the signs, symptoms, and HRQOL associated with CSU [28,29,39,40].

Although our results are consistent with those reported in previous studies, the AWARE study is subject to limitations associated with its design. Each participating physician included patients with a recent or established diagnosis of CU who consecutively visited the office. This may have led to a recruitment selection bias, because the patients included might have been those attending the office more often. Since these patients might have a higher prevalence of comorbidities and symptoms and patients with nonsevere disease could be followed up only by the primary care physician and not by the specialist, they might not be completely representative of the overall CU population. In this regard, results for disease

burden may be overestimated. In addition, at baseline, 198 of 270 patients did not complete the UAS7 questionnaire, and the considerable amount of missing data may undermine the validity of our results. To minimize the impact of missing data in the study, percentages were based on the valid data per parameter, excluding patients with missing values.

In any case, our observational study provides highly valuable data about the clinical scenario of CU in Spain, including disease control and activity status, impact on HRQOL, and patterns of treatment of patients whose CU is refractory to H1-AH in clinical practice. Our findings provide new insights into how variations in treatment patterns might have an impact on affected patients.

Conclusions

We present our findings on disease burden (disease control, activity status, and impact on HRQOL) and treatment patterns in CU patients in Spain, highlighting the difficulties involved in controlling CU and the ways in which the disease affects patients' HRQOL. While questionnaire scores tended to improve after 1 year of study, almost 50% of patients still presented mild-to-severe disease activity (UAS7>6). The high percentage of CU refractory to NS-H1-AH (>40%) could be improved with the introduction of novel 3L therapies, such as omalizumab, to improve disease activity and HRQOL. The results obtained in this study indicate that current clinical practice should be reviewed and that treatment guidelines should be adapted to improve both the control and HRQOL of CU patients.

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Conflicts of Interest

Anna Gimenez-Arnau, Joan Bartra, Marta Ferrer, Ignacio Jauregui, Jesús Borbujo, Ignasi Figueras, Francisco Javier Muñoz, Javier Pedraz, Esther Serra, Miguel A. Tejedor-Alonso, Manuel Velasco, and Moisés Labrador have collaborated with Novartis and other pharmaceutical companies. Pau Terradas is an employee of Novartis.

Previous Presentation

Data included in this manuscript were presented at the following meetings: 26th European Academy of Dermatology and Venereology Congress, 2017; Simposio Internacional de Aerobiología, Contaminación y Cambio Climático, 2017; and the 45º Congreso Nacional de la Academia Española de Dermatología y Venereología, 2017.

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