A Specialized Therapeutic Approach to Chronic Urticaria Patient’s Refractory to H1-Antihistamines Improves the Burden of the Disease. The Spanish AWARE Experience

Short Title: CU refractory to H1-AH in Spain


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ABSTRACT

Objective: AWARE study assesses disease activity, patient’s quality of life (QoL) and treatment patterns in chronic urticaria (CU) patient’s refractory to H1-antihistamines (H1-AH) in clinical practice during the first year of the study.

Methods: Observational, prospective (24 months), international, multicenter study. Patients ≥18 years with H1-AH-refractory CU diagnosis (>2 months). At each visit, patients completed questionnaires to assess disease burden (Urticaria Control Test [UCT]), disease activity (7 day-Urticaria Activity Score [UAS7]), QoL (Dermatology Life Quality index [DLQI]), Chronic Urticaria Quality of Life Questionnaire [CU-QoL], Angioedema Quality of Life [AE-QoL]). We present Spanish data.

Results: 270 evaluable patients included (73.3% female, mean age [SD] 48.9 [14.7] years). At baseline, 89.3% were prescribed a CU treatment. After 1-year, first/second line treatments tended to decrease and third line to increase. 47.0% patients experienced angioedema at baseline, being 11.8% at 1-year. Mean (SD) AE-QoL went from 45.2 (28.7) to 24.0 (25.8). Mean (SD) UCT went from 7.0 (4.5) to 12.1 (4.1). According to UAS7, 38.2% patients reported absence of wheals and itch in the last 7 days at 1-year versus 8.3% at baseline. Mean (SD) DLQI went from 8.0 (7.4) to 2.8 (4.6). At 1-year visit, the percentage of patients reporting high/very high QoL impact went from 29.9% to 9.6%.

Conclusions: Spanish H1-AH-refractory CU patients present a lack of symptomatology control with an important impact in their QoL. Continuous follow-up of chronic spontaneous urticaria patients and third line therapies have shown a tendency to reduce the burden of the disease and to improve patients’ QoL.

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, 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 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.

INTRODUCTION

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

The estimated CU prevalence in 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 among non-acute types (about 70%) [6] occurring without a specific trigger. CINDU appears as a response to certain stimuli (exposure to cold, heat or sun light, among others) [2,7]. Clinical CU patterns are broad, and patients often exhibit both subtypes concomitantly [8].

CU duration (from months to years) has a negative impact on patients’ health-related quality of life (HR-QoL) and their productivity [2]. Current quality of life (QoL) and disease activity questionnaires are useful tools in usual clinical practice to help physicians to determine CU prognosis and severity [9-12].

International clinical practice guidelines recommend an individualized management to achieve a rapid and complete CU symptom control, selecting the most effective and safest medication [1,2]. Current first line (1L) treatment is non-sedating H1-antihistamines (NS-H1-AH) at licensed doses. If symptoms persist, NS-H1-AH licensed doses may be increased up to four times as second line (2L) treatment [1,2,4,13]. Omalizumab is recommended as third line (3L) [1]. Despite cyclosporine A was recommended as 3L as well, new guidelines place it as fourth line treatment [1]. Similarly, montelukast was recommended as 3L, although not in the updated guidelines due to lack of clinical evidence [1]. In addition, systemic corticosteroids can be used for a maximum of 7-10 days in case of exacerbation [1,13]. It is worth noting that 77.7% of CSU patients were symptomatic despite the use of licensed doses of second-
generation H1-antihistamines (H1-AH), although 63.2% of non-respondent patients to the labelled dose could benefit from increased doses [14].

The main objective of the AWARE study was to assess disease activity and HR-QoL of CU patients’ refractory to at least one course of treatment with H1-AH in routine clinical practice. Likewise, it aims to evaluate the relationship between the patient-reported outcomes (PROs) and the therapeutic regimen received. Herein, we report the results for the Spanish AWARE patients in the first year of study.

Materials and methods

Study design

AWARE (A Worldwide Antihistamine-Refractory Chronic Urticaria Patient Evaluation) is a 24-month, prospective, multi-country (14 countries), non-interventional study. We present data retrieved at baseline and at the 1-year visit (up to January 18th, 2017) in Spain, from 40 Spanish dermatology and allergology hospital services.

The study was performed according to guidelines on observational post-authorization 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 favorable opinion by the accredited Clinical Research Ethics Committees of Basque Country’s Health Department, with the ethics approval number EPA2014034. The study was conducted according to Good Clinical Practice (International Conference of Harmonization) guidelines, the Declaration of Helsinki and following the local regulation, including privacy laws, at the time of the initiation of the study.

Sample size estimation was based on disease incidence, prevalence, sample size related to total population and anticipated recruitment within the study period. In Spain, 250 patients were planned to be enrolled.

Inclusion criteria comprised adult patients (≥18 years) with confirmed CU diagnosis for ≥2 months, resistant to H1-AH treatment according to clinical criteria who provided informed
consent. Patients participating in any other urticaria clinical study or who were unlikely to complete the 2-year follow-up according to physician criteria were excluded.

The study included nine visits along 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 validated questionnaires (Urticaria Control Test [UCT], 7 day-Urticaria Activity Score [UAS7], Dermatology Life Quality index [DLQI], Chronic Urticaria Quality of Life Questionnaire [CU-QoL], Angioedema Quality of Life [AE-QoL] and Work Productivity and Activity Impairment–Chronic Urticaria [WPAI-CU]) [15-21] (Figure 1).

**Statistical methods**

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

Statistical analysis was conducted in evaluable patients stratified in five treatment groups according to the 2014 international clinical practice urticaria guidelines treatment steps in each visit [22]: 1L (NS-H1-AH at approved doses); 2L (NS-H1-AH at high dose [up to x4 the approved dose]); 3L (2L treatment administered together with omalizumab or cyclosporine A or montelukast); other combinations (it is a heterogeneous group which includes any other treatment combinations not mentioned in 1L, 2L or 3L groups and not included in the therapeutic algorithm); without medication. 1L and 2L groups results are reported together (1L/2L).

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

Results

**Demographic characteristics**

278 patients were included in Spain and 270 (97.1%) were analyzed. Mean (SD) age of patients was 48.9 (14.7) years, the majority being female (73.3%) (Table 1). 207 (76.7%) patients presented comorbidities, 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 CU treatment. 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 in treated patients before and during the study. Still, NS-H1-AH use tended to decrease during this first year (from 88.8% to 72.8%). Omalizumab patients (in 3L or other combinations) tended to increase during the study (18.2% of treated patients before baseline, 37.3% at baseline and 46.7% after one year). Despite sedative H1-antihistamines (S-H1-AH) are not recommended in the current CU therapeutic guidelines, their use among treated patients ranged from 23.2% at baseline to 12.0% at one year. Corticosteroids were the fourth most used drug (from 20.7% at baseline to 12.5% at one 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, 939 visits were recorded. Similar retention rates were observed across different treatment groups during the study (84.0%, 88.0%, 77.4%, 73.3% for 1L/2L, 3L, other
combinations and without medication groups, respectively). Treatment group switches were observed in 161 (17.1%) of the total visits. Switching patterns show how most of the 1L/2L patient switches (61.0%) were towards the 3L group, as expected according to treatment guidelines. There were patients in 3L (38.9%) and other combinations (20.0%) groups taking steps backwards in CU therapeutic algorithm to 1L/2L group. 50 (31.1%) of the switching visits were from patients in any active treatment group being withdrawn from their medication (Figure 2b).

At one year, 184 (83.6%) patients were in any of the active treatment groups. There was a tendency to increase in 3L group versus baseline, mostly due to the 1L/2L treatments reduction (Figure 2a). Patients without medication tended to increase throughout the first year (36 [16.4%]). 43 patients (15.9%) out of the 270 initial ones discontinued (29 [67.4%] due to lost to follow-up, 11 [25.6%] for remission and 3 [7.0%] for relocation).

Treatment satisfaction assessment revealed an improvement trend throughout the study. At baseline, 268 patients scored a mean (SD) of 5.6 (3.0) in a scale 0-10. At the 1-year visit this score raised to 8.4 (2.1) with 184 patients rating their treatment satisfaction.

**Disease control**

UCT is a PRO that allows classifying patient’s control status with a score from 0-16. For UCT≥12, we consider that the patient has a good control of urticaria, whereas if UCT<12, patient is in a poor control. At baseline, 219 patients (82.0%) out of 267 with available results scored poor disease control with a mean (SD) of 7.0 (4.5). It was observed a tendency to increase this mean (SD), being 10.4 (4.2) at the 3-months visit and 12.1 (4.1) at 1-year. At the 1-year visit, 70 patients out of 198 (35.4%) still reported a poor disease control. Patients with higher CU control rates at baseline were those in the 3L group with a mean (SD) of 8.6 (5.3) and 31.8% in good control. At the 1-year visit, mean (SD) for 3L patients was 12.5 (3.9) and good control rates doubled baseline’s (66.2%). Patients without medication achieved the
highest control rates at one year, with a mean (SD) 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 86.3% scoring a poor disease control at baseline and 41.3% at 1-year visit (Figure 3a, Figure 3c).

**Disease activity**

UAS7 questionnaire expresses the disease activity of CSU patients throughout the last 7 days before each visit. UAS7 score ranges from 0 to 42 with higher scores indicating more severe disease. Total UAS7 mean (SD) at baseline was 20.0 (12.4), tending to decrease to 12.9 (11.2) at 3-months visit and reaching 8.4 (10.1) at 1-year visit. At baseline, mean UAS7 ranged from 19.5 to 22.8 on treatment groups, indicating a moderate CU activity, and dropping to 8.3 to 9.5 after one year. For patients without medication, a mean (SD) UAS7 score of 17.7 (16.6) was reported at baseline, being of 4.9 (6.7) at the 1-year visit (Figure 3b).

In the treatment subgroup analysis we differentiate severe, moderate and mild CSU patients (UAS7≥6) from those with low disease activity or without itching and hives (UAS7≤6) [23]. Across all groups, there was an overall tendency to increase in the proportion of patients with UAS7≤6 throughout the study. Higher UAS7≤6 rates were found at the 1-year visit in 3L (55.4%) and without medication (66.7%) groups. In contrast, 1L/2L patients had the lowest UAS7≤6 at the 1-year visit (45.5%), indicating that despite the NS-H1-AH treatment, most patients still displayed mild-to-severe CSU (Figure 3d).

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

**Angioedema control and HR-QoL**

Presence of angioedema tended to decrease during the study, going 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 a medication. There were no cases of hereditary angioedema or acquired C1-esterase-inhibitor deficiency. At baseline, 52.0% of the reported angioedema was mild, 34.7% moderate and 8.7% severe (intensity was unknown in 1.6% patients).

Angioedema impact in QoL was evaluated through AE-QoL, a validated test that ranges 0-100 with higher scores indicating greater impact on QoL [24]. At baseline, angioedema had a mild impact on patients’ QoL, with an AE-QoL mean (SD) of 45.2 (28.7), being 24.0 (25.8) after one year. At baseline, other combinations and 1L/2L groups had the worst HR-QoL (50.4 [30.5] and 49.5 [29.4], respectively). After one year, all groups tended to reduce AE-QoL scores, ranging between 23.0 and 29.8, except for the non-medicated group, with a mean (SD) of 7.6 (7.2) (Figure 5b).

**QoL**

CSU impact in patients’ QoL was measured by DLQI and CU-QoL questionnaires. DLQI ranges from 0-30 and CU-QoL from 0-100, with higher values indicating greater impact on QoL in both questionnaires [17,25]. DLQI total mean (SD) score at baseline was 8.0 (7.4) (Figure 6a), with 80 patients (29.6%) reporting a very large or extremely large impact on HR-QoL, whereas the rest referred a small-to-moderate impact (131 patients, 48.5%) or no impact (57 patients, 21.1%). After one year, mean (SD) was 2.8 (4.6), with 19 (8.6%) patients reporting very large or extremely large impact, 56 (25.5%) small/moderate impact and 122 (55.5%) no impact (Figure 6a). DLQI baseline scores ranged from 7.2 to 8.8 for all active treatment groups, indicating a
moderate impact on most CU patients. After one year, mean DLQI of all active treatment groups ranged between 2.5 and 3.5, indicating an improvement trend in patients’ QoL. The non-medicated group DLQI mean (SD) was 7.1 (6.0) at baseline, dropping to 0.7 (1.2) after one year, showing that CU had no further effect on the HR-QoL of these patients (Figure 6a).

CU-QoL score showed a mild-to-moderate impact on patients’ HR-QoL at baseline, with a mean (SD) of 31.4 (21.7), dropping to 12.5 (15.4) after one year (Figure 6b). This improvement trend was observed in each domain of the questionnaire. After one year, all groups achieved a lower HR-QoL impact with means between 12.9 and 15.2, except for the non-medicated group (5.3 [5.8]) (Figure 6b).

Discussion

This sub-analysis of the AWARE study presents real-world results about burden of disease and disease activity and its impact on patients’ HR-QoL in CU patients refractory to H1-AH treatment in Spain. Most patients were women (73.3%) with a mean age of 48.9 years, consistent with previous studies [26-31].

Prior to the study, most treated patients were taking NS-H1-AH (81.8%), followed by omalizumab (18.2%). After one 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 a considerable use of S-H1-AH. 20.3% of patients received S-H1-AH prior to study and, although their use tended to decrease, it was still 12.0% at one year. Treatment distribution of AWARE study in Spanish patients was similar to other countries [31,32]. A retrospective study with CU patients in Ecuador reported that the most prescribed was NS-H1-AH alone (44.6%) followed by the combination of any H1-AH plus another treatment (corticosteroids, anti-leukotriene agents, hydroxychloroquine or omalizumab) (42.0%) [32]. Curto-Barredo et al showed that more than 75% of CSU patients were refractory to 1L treatment with licensed doses [6]. 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, among non-responders, 60% would respond to up-dosing H1-AH [14]. Although corticosteroids were the fourth most used drug (20.7% at baseline), its use tended to decrease after one year of study (12.5%). In this sense, international guidelines recommend avoiding the long-term use of corticosteroids outside specialist clinics [1].

We think that PROs can be a useful tool for diagnosis and monitoring disease activity and symptomatic control, impact on HR-QoL and productivity. After one year of study, all questionnaire scores showed a tendency to improve. However, almost 50% of patients still presented a mild-to-severe CU activity (UAS7>6). At that time, the 1L/2L group showed the highest disease activity and the highest uncontrolled patients’ rate (54.5% had UAS7>6 and 43.1% poor control according to UCT). Hence, an important number of CU patients might be refractory to H1-AH, which reinforces the importance to escalate to 3L biologic treatment to control CU. In addition, high retention rates were observed in 1L/2L group (84.0%), highlighting the need of revising treatment response every 2 to 4 weeks using UAS7 or UCT irrespectively as per EAACI/GA(2)LEN/EDF/WAO guideline [1]. This is aligned with the results of other countries like Germany, where escalation to 3L treatment of AWARE patients was not as high as expected (from 8.5% at baseline to 21.4% at 1-year visit) [30]. In other groups (3L and other combinations), high retention rates were also observed. Despite UAS7≤6 and good control UCT rates are slightly better than in 1L/2L, there is still room for improvement. Overall, this might explain the lower rates of patients in good control according to UCT, also observed in Germany (35.4% and 42.2%, respectively) [30]. The proportion of patients without treatment with UCT good control (UAS7≤6), lower rates of angioedema and impact in QoL after the first year of the study was higher than in treated groups. This could possibly be due to a spontaneous CU remission or a complete treatment response and a consequent withdrawn of their treatment. In this regard, there is a need to better define what CSU remission is and when and how a treatment could be safely withdrawn.
At baseline, >80% of patients presented poor disease control according to UCT and >50% of patients who responded UAS7 questionnaire experienced moderate-to-severe activity. Reported lack of disease control is associated with an impact on patients’ daily live [33], consistent with the HR-QoL outcomes observed in our pool of patients. At baseline, 48.5% of patients presented a mild/moderate impact on HR-QoL, and 29.6% severe/very severe impact according to DLQI questionnaire. In a prospective study conducted in Brazil, CU patients reported a moderate impact on HR-QoL according to DLQI questionnaire [34]. Similarly, mean DLQI scores of 12 CU studies summarized by O’Donnell et al. ranged between 7.2 and 13.4, indicating a moderate-to-severe impact [35]. The ASSURE-CSU study reported a mean (SD) of 9.1 (6.6) and 33.6 (21.0) on DLQI and CU-QoL, respectively, and revealed that CSU interfered with sleep and daily activities [36]. In a cross-sectional study conducted in Portuguese and Brazilian patients, a CU-QoL mean of 36 was reported [37], consistent with the baseline CU-QoL of our study (31.4). Overall, these results reveal the negative impact that urticaria has on patients’ QoL and the difficulties to achieve symptomatic control, even in treated patients.

The Spanish cohort registered a low baseline rate of non-treated patients versus the rest of Europe or in Central and South America (10.7% versus 31.9% and 45.1%, respectively) [30]. Even so, Spanish patients reported high rates of uncontrolled disease with mean UCT scores at baseline comparable with those described in other countries (7.0 [4.5] versus 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, these data suggest that most CU patients worldwide do not achieve this goal.

In this study, 47.0% CSU patients exhibited angioedema from the last 6 months to baseline, which is consistent with former studies [29,36,38]. After one year, this percentage dropped to 11.8%. Angioedema implies a great burden for CU patients, affecting severely their HR-QoL. After one year, we observed a tendency to improve of the HR-QoL according to DLQI and CU-QoL questionnaire (mean [SD] for all groups went 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-QoL). This is consistent with the tendency to improve in both disease control and activity according to UCT and UAS7, but also with the tendency to reduction of angioedema throughout the study. The overall tendency to improvement across the study might be due to the spontaneous CU remission but also to the introduction of new therapies as omalizumab. According to the clinical trials [28,29,39], omalizumab treated patients experienced an improvement in the number of hives and the itch severity versus placebo. In another study, a greater mean of angioedema-free days versus placebo group was observed in patients suffering from CSU plus angioedema. Such studies report a clinical benefit of omalizumab in refractory to H1-AH treatment in controlling CSU signs, symptoms and QoL [28,29,39,40].

Although our results are consistent with those reported in previous studies, the AWARE study entails limitations due to its design. Each participating physician included patients with recent or established CU diagnosis who consecutively attend to the physician’s office. This might have caused a recruitment selection bias because included patients might be those attending physician’s office more often. Since these patients might have a higher prevalence of comorbidities and symptomatology, and patients with a non-severe disease could be followed up only by the primary care doctor and not by the specialist, they might not be completely representative of the overall CU population. In this regard, results related to burden of disease may be overestimated. In addition, at baseline, 198 out of 270 patients did not complete the UAS7 questionnaire. This high level of missing data may hamper the validity of our results. To minimize the impact of missing data in the study, the calculation of percentages was based on the valid data per parameter, excluding patients with missing values.

Overall, this observational study provides high valuable data about the clinical CU scenario in Spain, including disease control and activity status, HR-QoL impact and treatment patterns of Spanish CU patient’s refractory to H1-AH in clinical practice, providing new insights on how variations in treatment patterns might have an impact on these patients.
Conclusions

Burden of disease (disease control, activity status and HR-QoL impact) and treatment patterns of CU patients in Spain are presented in this manuscript, highlighting the difficulties to achieve a well-controlled CU and how that affects patients’ HR-QoL. Despite an overall questionnaire score tended to improve after one year of study, almost 50% of patients still presented a mild-to-severe CU activity (UAS7>6). The high number of CU patient’s refractory to NS-H1-AH (>40%), could benefit from the introduction of 3L novel therapies, like omalizumab, to improve their disease activity and QoL. The results obtained in this study indicate that the current clinical practice should be reviewed, and treatment guidelines should be adapted to improve both the control and QoL of CU patients.

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Previous presentations

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

Conflict 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 industries. Pau Terradas is a Novartis employee.

Authors’ contribution

All the authors participated actively both in the conception and design of the work. All the authors have equally contributed to the development of the current manuscript, have performed an exhaustive review of its content and have approved the final version.

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References


### TABLES

**Table 1.** Baseline demographic and clinical characteristics of the Spanish population of the study

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<td><strong>Time from diagnosis to baseline visit, years, mean (SD)</strong></td>
<td>5.0 (7.1)</td>
</tr>
<tr>
<td><strong>Time for diagnosis to baseline visit, years, median (range)</strong></td>
<td>2.2 (0 – 47)</td>
</tr>
<tr>
<td><strong>Patients with angioedema from the last 6 months to baseline, n (%)</strong></td>
<td>127 (47.0)</td>
</tr>
<tr>
<td><strong>Patients with CINDU, n (%)</strong></td>
<td>71 (26.3)</td>
</tr>
<tr>
<td><strong>Working patients, n (%)</strong></td>
<td>144 (53.3)</td>
</tr>
</tbody>
</table>

CINDU: chronic inducible urticaria; cm: centimeters; kg: kilograms; m: meters; mmHg: millimeters of mercury; SD: standard deviation.
FIGURES

Figure 1. Study design

AE-QoL: angioedema quality of life questionnaire; CU-QoL: 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.
**Figure 2.** Patient’s treatment distribution and switching patterns

*Treated patients: total evaluable patients in 1L/2L, 3L and other combination treatment groups: pre-baseline (n=231), baseline (n=241), 3 months (n=219), 6 months (n=204), 9 months (n=197), 1 year (n=184).

1L: first line; 2L: second line; 3L: third line; NS-H1-AH: non-sedating H1-antihistamines; S-H1-AH: sedative H1-antihistamines.
**Figure 3.** UCT disease control status and UAS7 activity status in different treatment groups

*Number of evaluable patients with available data at baseline and one 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 one 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: first line; 2L: second line; 3L: third line; SD: standard deviation; UAS7: urticaria activity score over 7 days; UCT: urticaria control test.
**Figure 4.** Evolution of CSU activity throughout the study*

*Missing data: 198, 31, 39, 37 and 47 patients at visits 1 to 5, respectively.

CSU: chronic spontaneous urticaria; UAS7: urticaria activity score over 7 days.
**Figure 5.** Presence of Angioedema and AE-QoL

*Presence of angioedema by visit in evaluable population. Baseline reports data from 6 months before visit 1. Other study visits report data from previous study visit to each visit.

**Number of evaluable patients with available data at baseline and one year: 1L/2L: 63 and 22; 3L: 48 and 41; other combinations: 34 and 11; without medication: 14 and 5; total: 159 and 79.

1L: first line; 2L: second line; 3L: third line; AE-QoL: angioedema quality of life questionnaire; SD: standard deviation.
Figure 6. CU HR-QoL assessments

*Number of evaluable patients with available data at baseline and one 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 one year: 1L/2L: 127 and 73; 3L: 66 and 77; other combinations: 48 and 28; without medication: 29 and 21; total: 270 and 199.

1L: first line; 2L: second line; 3L: third line; CU-QoL: chronic urticaria quality of life questionnaire; DLQI: dermatology life quality index; SD: standard deviation.