# Chronic Urticaria in the Real-life Clinical Practice Setting in Portugal: Two-Year Results from the Non-Interventional Multicenter AWARE Study

# Urticária Crónica na Prática Clínica de Vida Real em Portugal: Resultados de Dois Anos do Estudo Não Intervencional de Vida-Real AWARE

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**Acta Med Port 2022 Jan;35(1):12-19 ▪ https://doi.org/10.20344/amp.14477**

## ABSTRACT

**Introduction:** Information regarding chronic urticaria patients in the real-world setting is scarce. This analysis reports the two-year results of Portuguese patients included in the AWARE study.

**Material and Methods:** Non-interventional cohort study. Adult patients with a diagnosis of chronic urticaria with symptoms for at least two months, refractory to H1-antihistamines, consulting one of the 10 participating urticaria centers throughout Portugal, from the 31st October 2014 to 31st July 2015, have been included in the study. Clinical parameters, medicines taken for urticaria symptom relief, weekly urticaria activity score, and dermatology quality of life index have been collected throughout the two years of the study.

**Results:** Seventy-six patients were enrolled in the study. Results showed that the proportion of patients with omalizumab therapy almost duplicated after two years of the AWARE study, which was accompanied by the decrease of medical resources use and absenteeism. Moreover, urticaria severity and impact on quality of life both decreased after one year and continued to decrease at two years, although decreased severity was significant at both time points and quality of life was only significant at two years. At the end of two years, 79.0% of patients had their disease controlled compared to 29.3% at baseline ($p < 0.001$).

**Conclusion:** Chronic urticaria still has a significant impact on quality of life and therefore there is opportunity for further therapy optimization.

**Keywords:** Urticaria/classification; Urticaria/diagnosis; Urticaria/therapy

## RESUMO

**Introdução:** A informação disponível sobre doentes com urticária crónica em contexto da prática clínica real é escassa. Esta análise reporta os resultados a dois anos dos doentes portugueses incluídos no estudo AWARE.

**Material e Métodos:** Estudo de coorte, observacional, prospetivo, de doentes adultos com diagnóstico de urticária crónica, com sintomas há pelo menos dois meses, refratários a antihístamínicos-H1 na dose aprovada, seguidos em 10 centros de urticária em Portugal, incluídos entre 31 de outubro de 2014 e 31 de julho de 2015. Ao longo dos dois anos do estudo AWARE foram avaliados parâmetros clínicos, medicação utilizada para alívio dos sintomas de urticária, o *Weekly Urticaria Activity Score* e o índice de qualidade de vida dermatológico.

**Resultados:** Foram incluídos setenta e seis doentes. Após dois anos do estudo AWARE, a percentagem de doentes sob terapia com omalizumab quase duplicou, sendo acompanhada por uma diminuição da utilização de recursos médicos e absenteísmo. A gravidade da urticária e o impacto na qualidade de vida diminuíram após um ano e continuaram a diminuir aos dois anos, embora o aumento da qualidade de vida apenas tenha atingido significado estatístico no segundo ano. A percentagem de doentes com patologia controlada aumentou de 29,3% no início do estudo para 79,0% ($p < 0,001$).

**Conclusão:** A urticária crónica tem impacto na qualidade de vida da população, mostrando que a terapêutica ainda poderá ser otimizada.

**Palavras-chave:** Urticaria/classificação; Urticaria/diagnóstico; Urticaria/tratamento

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**Recebido:** 07 de julho de 2020 - **Aceite:** 19 de fevereiro de 2021 - ***First published*:** 09 de junho de 2021 - ***Online issue published*:** 03 de janeiro de 2022

## INTRODUCTION

Chronic urticaria (CU) is a group of skin diseases characterized by itchy wheals and/or angioedema for more than six weeks. CU is divided into spontaneous (CSU) or inducible (CIndU), the latter being triggered by specific stimuli such as heat, cold, sun exposure or pressure.[1] It is known that two or more different subtypes of urticaria can coexist in any given patient.[1] An urticaria wheal has a fleeting nature and the skin returns to its normal appearance usually within 30 minutes to 24 hours.[1]

The diagnosis of urticaria is clinical and established by the evaluation of the typical features of symptomatic wheals.[2] The recommendations for Portugal on the diagnosis and management of CSU have been published in 2016.[3] In these recommendations, omalizumab was proposed as third line therapy, and cyclosporine should only be used as off-label therapy in case of inadequate control with omalizumab.[3] The same approach was proposed later, in 2017, by the EAACI/GA²LEN/EDF/WAO guidelines, in the chronic urticaria treatment algorithm.[1]

At the time of the AWARE study, the current guidelines were the 2014 EAACI/GA²LEN which recommended daily use of approved doses of non-sedative H1-antihistamines (H1-AH) as standard of care for CU.[1,2,4-9] Moreover, the dosage of these drugs could be increased up to fourfold, as second line therapy, in case of lack of response,[1,2,4-7,10-12] followed by add-on therapy with omalizumab, cyclosporine or montelukast as third-line therapy, the latter two being off-label for urticaria.[2] The 2017 revision of the guidelines have changed the recommendation of third line therapy to include only omalizumab. Cyclosporine was moved to forth line therapy, and montelukast has been moved to 'others', due to insufficient scientific evidence.[1]

This change was a result of the effectiveness that omalizumab showed in the control of H1-AH refractory CU patients.[13-16] Symptom control is the consensual therapeutic goal[1,2,4,6,9,11] and the weekly urticaria activity score (UAS7) questionnaire is the preferred tool for evaluating disease activity.[1,2,4,5,10-12] Given its strong impact on patients' quality of life (QoL), it is highly recommended that CU is assessed using a QoL tool such as the dermatology quality of life index (DLQI).[9,10,17] Moreover, the impact of symptoms and QoL on direct and indirect costs involving medication, physician appointments, visits to the emergency room (ER), hospitalizations and absenteeism,[4] although acknowledged, remain largely unknown in the real-word setting.[18-23] The non-interventional AWARE study was designed in order to overcome this gap. AWARE was a global (36 countries), prospective study of CU patients refractory to standard doses of H1-AH therapy in the real-world setting, conducted in specialized urticaria centers, designed to evaluate the CU disease burden and impact on QoL in these patients, as well as which therapies and medical resources are used.[24]

In this paper, we report the final 2-year data from patients with CU included in the AWARE study in Portugal. Baseline characteristics of the Portuguese patients enrolled in this study have been previously reported.[24]

## MATERIAL AND METHODS

### Study design

The AWARE (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) study was designed to evaluate the real-world disease burden of adult patients with a diagnosis of CU for at least two months who were refractory to the approved dose of at least one H1-AH. Patients were enrolled at specialist urticaria centers, and the used therapies, impact on QoL and work productivity of individual patients were also evaluated. The study was approved by the Ethics Committee of each participating center and conducted according to the tenets of the Declaration of Helsinki, as revised in 2013.

### Setting and participants

The AWARE study was a worldwide non-interventional international multicenter study conducted in 36 countries. This paper pertains only to patients recruited from the 10 participating centers throughout Portugal, from 31st October 2014 to 31st July 2015. In this cohort study, all study variables were collected at baseline, one year and two years, during a follow-up period of two years. Diagnosis of urticaria was confirmed at enrollment according to the European Guidelines.[2]

Inclusion criteria included written informed consent of the patient to participate in the study; age 18 years and over; medically confirmed diagnosis of CU present for more than two months; refractoriness to treatment with standard doses of H1-AH. Anticipated difficulties of follow-up during at least two years and participation in any other clinical urticaria study were defined as exclusion criteria.[24]

### Methods of assessment

All variables were collected on an electronic case report form (eCRF) specifically designed for the study. Patient reported outcomes (PROs) evaluated included UAS7 from the week before the consultation[2,4,5,10-12] and DLQI[9,10,17] filled during the consultation, and scores were introduced on the eCRF. The UAS7 is a questionnaire that measures disease activity during seven days: UAS7 = 0 means urticaria-free, UAS7 = 1 - 6 means well controlled urticaria, UAS7 = 7 - 15 reflects mild urticaria, UAS7 = 16 - 27 reflects moderate urticaria and UAS7 = 28 - 42 corresponds to severe urticaria.[24] DLQI measures QoL in patients with chronic dermatologic diseases, including CU: DLQI between 0 - 1 indicates that the urticaria has no effect on patients' life; DLQI between 2 - 5 that it has a small effect on patients' life; DLQI between 6 - 10 that it has a moderate effect; DLQI between 11 - 20 that it has a very large effect; and DLQI between 21 - 30 indicates that urticaria has an extremely large effect on patients' life.[25,26] Neither UCT (urticaria control test) nor CuQ2oL were used because, at the time of the study, they were not validated for the Portuguese population.[3,27]

### Quantitative variables

In addition to descriptive statistics, inference statistics

were performed for UAS7 and DLQI as continuous variables, in order to address their change from baseline to one and two years of the AWARE study. Inference statistics were also performed to evaluate the impact of CU on sick leave and in the use of medical resources at baseline, one year and two years.

### Statistical methods

Continuous variables are presented as mean (95% confidence interval [95% CI]) and categorical variables as number (percentage). Between group analyses were performed using the Mann-Whitney U test when comparing two groups or the Kruskal-Wallis test with correction for multiplicity when comparing more than two groups. Within-group analyses were performed using the Friedman test or the Cochran's Q, both corrected for multiplicity, as appropriate. Correlations were assessed with the Spearman r test. Tests were considered significant at $\alpha = 0.05$ significance level (two-sided). The software used was SPSSv20.

## RESULTS

### Participants

Of the 5237 patients included worldwide in the AWARE study, the 76 patients enrolled and included in the Portuguese cohort were analyzed. Sixteen patients were lost to follow-up and thirty patients had all the data available. All tables and figures state the number of patients with data available for each analyzed variable. Missing data were considered to be missing completely at random (MCAR).

### Demographic and clinical baseline characteristics

The demographic and clinical baseline characteristics of the AWARE study, reflecting the Portuguese population sample, have already been published.[24] Most patients had only CSU (63.2%), 13.2% had only some form of CIndU, and the remaining 23.6% showed both CSU + CIndU. The median age of the study cohort was 46.5 years and 76.3% of the patients were women. Only 29.3% of patients had well-controlled urticaria at enrollment, measured by UAS7.

### Angioedema

Angioedema, present in 39.5%[24] of patients at baseline, was significantly decreased after one and two years to 10.7% and 12.2% ($p < 0.001$), respectively, with no difference between year one and year two.

### Proportion of patients with omalizumab therapy

Non-sedative H1-AH were used by 85.5% of patients at baseline and 76.8% and 73.5% at one and two years, respectively. The proportion of patients under cyclosporin was 4.6% at baseline[24] and at year one and two no patients were under this therapy. Corticosteroid therapy was used by

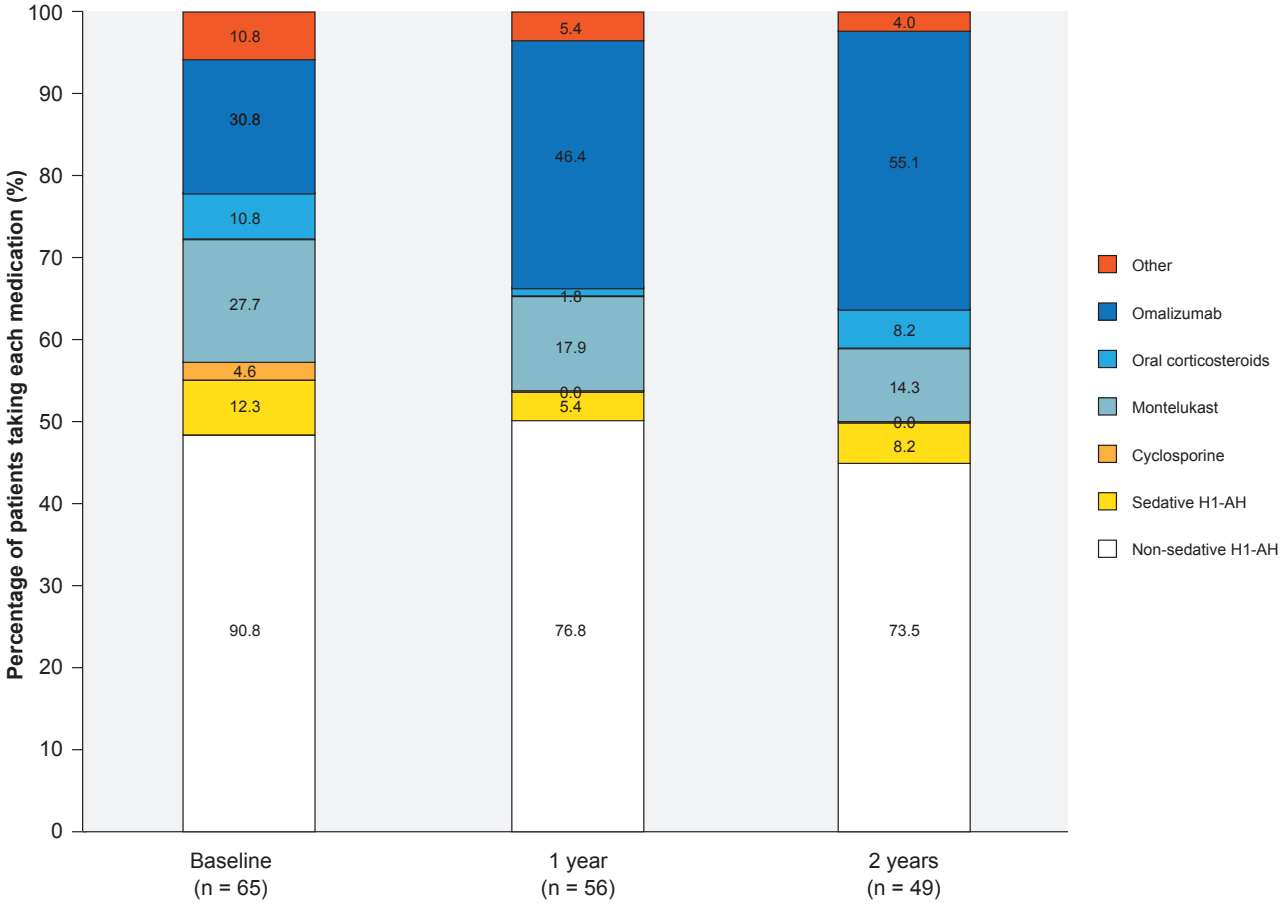


Figure 1 – Medication at baseline, one year and two years
H1-AH = H1: antihistamines

approximately 11% of patients at baseline and 1.8% and 8.2% at one and two years, respectively. Around 24% of patients were treated with montelukast at baseline, and 17.9% and 14.3% at year one and two, respectively. Throughout the study the proportion of patients under omalizumab almost duplicated from baseline (30.8%) to year two (55.1%) – Fig. 1.

### Medical resources use and absenteeism

Medical resources and absenteeism are indirect measures of urticaria control. At the beginning of the AWARE study, 25% of patients had experienced at least one episode of sick leave due to urticaria, and around 70% had used medical resources, such as visits to the ER, primary care, other specialized care including dermatology and allergology medical appointments and, in more severe cases, hospitalization – Table 1. Over the two years of this study, there was a significant decrease of all used resources from baseline to years one and two ($p < 0.001$), except hospitalizations. Although not reaching statistical significance, the proportion of hospitalizations changed from 5.3% at baseline to 0.0% at years one and two. The proportion of patients with no sick leaves and that used no medical resources reached 100% at year one and two, respectively ($p < 0.001$). There were no significant changes between year one to year two.

### Urticaria disease activity

Urticaria disease activity and the impact in QoL were measured through two patient reported outcomes (PROs): UAS7 and DLQI, respectively. Fig. 2 shows that UAS7 decreased after year one and further decreased at year two. Of notice, the decrease in year two is statistically significant when compared to baseline and to year one. UAS7 did not correlate with the number of years of urticaria diagnosis nor was it associated with the presence of angioedema.

Concerning DLQI, and although there was a decrease from baseline to year one, this was not statistically significant, only reaching significance at year two when compared to baseline (Fig. 3). At the end of the second year, 79.0% of patients had well controlled urticaria, which represented a significant improvement when compared to baseline ($p < 0.001$).

## DISCUSSION

Although CU is a relatively common condition, there is a lack of studies evaluating patient care of urticaria patients in a real-world setting. This study presents the two-year results from the 76 patients of the AWARE Portuguese cohort, in a real-world context, and reflects the resources allocated during follow-up and treatment of CU patients.

Current urticaria guidelines recommend that complete symptom control should be the aim of CU treatment.[1] In this study, the main therapies used were non-sedative H1-AH, with a variation from 85.5% at baseline to 76.8% and 73.5% at year one and two, respectively. Omalizumab is recommended for the treatment of CSU in patients who remain symptomatic despite H1-AH therapy.[1] In the Portuguese cohort, the proportion of patients treated with omalizumab at baseline was 28.9% and almost duplicated at year two to 55.1%. The proportion of patients under omalizumab at baseline was similar to the proportion reported in the AWARE German cohort (21.4%).[28] However, it seems to be higher in our cohort at year two: 55.1% *vs* 31.4%.[29] This could reflect the fact that the AWARE study in Portugal recruited CU patients referred to specialized urticaria centers, who probably had more severe forms of CU.

Regarding corticosteroid therapy, and according to current recommendations, a short course of corticosteroids can be prescribed as relief therapy, regardless of the line of therapy the patient is receiving. Since urticaria is not a stable condition, oscillating between exacerbations and remissions, often without apparent triggering factors, the proportion of patients on this therapy at baseline, one year and two years may reflect the different exacerbation or remission phase the patient was experiencing when the visit occurred.

Although the current standard therapy with standard doses of H1-AH is still the mainstay of treatment for CSU, it only leads to an absence of symptoms in less than 50% of patients, and even increasing the dose still leaves approximately 30% of patients symptomatic. Omalizumab has been a major breakthrough in the care of these patients.[30]

The most important factors contributing to the impact of CU in QoL and psychological distress are the severe pruritus and the unpredictability of the disease episodes,[31] as well as the presence of angioedema and concomitant

Table 1 – Use of medical resources and sick leave at baseline, one year and two years

| Variable | Baseline (n = 76) | 1 year (n = 56) | 2 years (n = 49) | *p*-value |
|---|---|---|---|---|
| Sick leave | 19 (25.0) | 0 (0.0) | 0 (0.0) | **< 0.001** |
| **Utilization of medical resources** | | | | |
| None | 29 (38.2) | 52 (92.9) | 49 (100.0) | **< 0.001** |
| ER | 40 (52.6) | 2 (3.6) | 0 (0.0) | **< 0.001** |
| Primary care | 38 (50.0) | 1 (1.8) | 0 (0.0) | **< 0.001** |
| Hospitalization | 4 (5.3) | 0 (0.0) | 0 (0.0) | 0.102 |
| Other specialized care | 34 (44.7) | 1 (1.8) | 0 (0.0) | **< 0.001** |

All values presented as n (%). *p* values refer to the difference from one year or two years *versus* baseline using the Cochran's Q test. There were no significant differences from year one to year two.
ER: emergency room

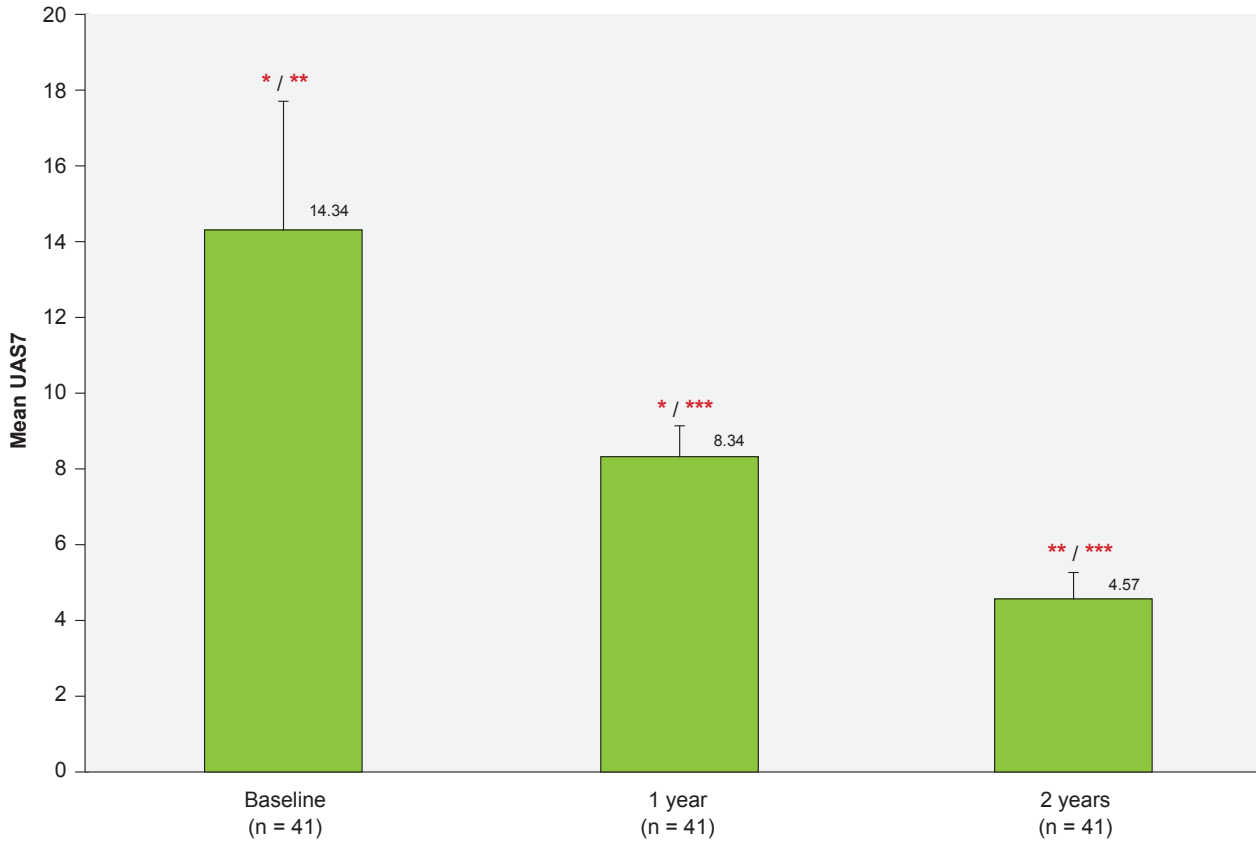


Figure 2 – UAS7 score at baseline, one year and two years

Bars represent means, error bars represent 95% CI. **p* = 0.001 baseline *versus* one year; ***p* < 0.001 baseline *versus* two years; ****p* < 0.001, one year *versus* two years. *P*-values obtained from the Friedman test with correction for multiplicity.

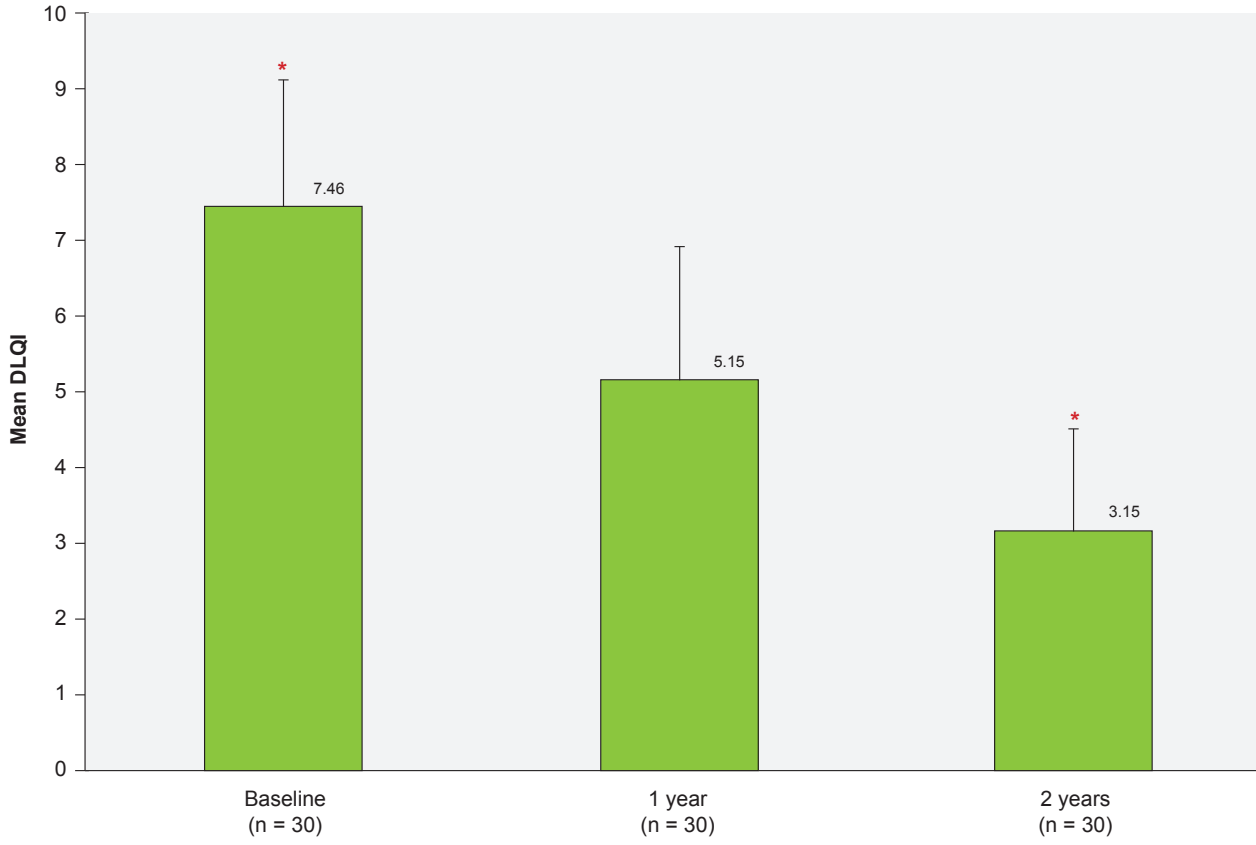


Figure 3 – DLQI total score at baseline, one year and two years.

Bars represent means, error bars represent 95% CI. **p* = 0.001, baseline *versus* two years

*P*-values obtained from the Friedman test with correction for multiplicity.

CIndU. Therefore, the impact of CU in the life of patients goes beyond the effects on the skin. The baseline results from the AWARE study in Portugal showed that CU had a very large impact in work activities, since 25% of patients experienced at least one episode of sick leave due to CU.[24] This proportion was similar to the one reported in the AWARE study in other countries such as Sweden, Norway, Denmark[32] and Germany.[33] The severity of the disease has been associated with sick leave, which has personal, social and economic implications.[19] Moreover, these studies also showed that CU patients were frequent users of medical resources,[24,32,33] an important aspect in CU, given it reflects direct and indirect costs associated with the condition.[34]

Our results show that the number of patients that have not used medical resources, including ER visits, primary care, and other specialized care, decreased from baseline to year one and reached 100% at year two ($p < 0.001$ compared to baseline at both time points). This decrease in medical resources use may reflect the control of CU and has an impact in both direct and indirect costs associated with the disease. Indirect costs, including wage loss due to medical appointments and to sick leave, and lack of productivity due to sick leave, are the second component of the total costs of CU, second to direct costs with medication.[35] Our results revealed that over the study period, no patients lost work-days due to CU at years one and two, except to attend medical consultations or for administrations of omalizumab, but not due to disease severity. This fact highlights the importance of disease control since year one, not only regarding symptoms but also in terms of the impact on personal and professional life.

The severity of CU was assessed by UAS7. UAS7 is based on the objective assessment of disease activity self-reported by the patient, which makes this score particularly valuable.[3] Moreover, as the urticaria activity can change in a short period of time, this score allows for the patient to quantify it every day during seven days.[14] The mean UAS7 at baseline was 14.34, corresponding to 'mild disease'; however, it is in the upper limit. The decrease to 8.34 at year one was significant ($p = 0.001$), although it remained in the 'mild disease' category. At year two the mean UAS7 further decreased to the level of 'well controlled disease', statistically different from baseline and year one ($p < 0.001$). These results are in line with other AWARE reports that have shown a decrease in total mean UAS7 score in CSU patients from baseline to year two, suggesting an improvement in disease control,[29,36,37] and reaching the level of 'well controlled disease' at year two.[29,37]

DLQI measures the impact of skin disease in the patients' QoL, ranging from no impact to most severe impact with a recall period of seven days.[3] In this study, the impact of CU on QoL was 'moderate' at baseline (mean DLQI 7.46) and changed to 'small effect' at year one (5.15) and year two (3.15). Although the decrease was significant only at year two ($p = 0.001$ *vs* baseline), it never reached 'no effect'. Our results at baseline and year one are in accordance with the AWARE study in Germany, with a median of DLQI of 8.3 at baseline and 4.1 at year one.[28]

The analysis of the variations in UAS7 and DLQI may lead us to speculate that since the decrease in symptoms occurred at year one and the significant differences in QoL were only apparent at year two, the perception of the effect on QoL occurs later than the perception of symptom improvement. Only when patients have the 'disease controlled', they recognize that CU has a 'small effect' on their QoL. Once more, this strengthens how much CU impacts the patients' QoL.

It is known that spontaneous remission of CU occurs in some patients and severity has been associated with the duration of the disease.[38] A study showed that symptoms disappeared spontaneously after one year, in 47.4% of patients in whom the cause of urticaria had not been identified.[39] In our study, there was no correlation between the duration of the disease and UAS7, probably reflecting the fact that patients with long-term CU refractory to H1-AH are not able to achieve spontaneous remission. Moreover, and although the burden of disease has been reported to be particularly high in patients with CSU and associated angioedema,[23] in our study, disease severity was not associated with the presence of angioedema ($p = 0.390$) or with the presence of CIndU ($p = 0.128$). Also, duration of CSU was not associated with the presence of angioedema ($p = 0.335$). However, the proportion of patients with angioedema significantly decreased from baseline to years one and two.

Taken together, all results showed a better disease control, evident at year one and confirmed at year two, through the improvement of the different analyzed variables. Based on these results, we could hypothesize that 1) referral to a specialist center for urticaria treatment is important and 2) the type of therapy is relevant. All our patients were followed-up in specialist urticaria centers and a high proportion had their urticaria signs and symptoms better controlled with an impact on QoL. We may speculate that one of the reasons for this is the number of patients under omalizumab therapy. Indeed, recent studies[14,15] have shown that omalizumab is a highly effective therapy in patients refractory to H1-AH therapy.

Three important key factors for this success are careful analysis of patient history,[31] reliability on therapy escalation, namely up-dosing of H1-AH, and omalizumab prescribing.[28] The impact on QoL should be emphasized in the choice of treatment in patients with CU refractory to H1-AH.[1]

An important message to highlight based on these results is the fact that if the patient is controlled in specialist centers, it is of paramount importance to alert primary care physicians regarding the referral of uncontrolled patients to specialist care.[40]

One limitation of the AWARE study is that it recruited CU patients referred to specialist urticaria centers from public primary care services, due to being refractory to at least the approved H1-antihistamine dose. If patients were not previously diagnosed with CU in the primary care setting, they would not be included. The non-interventional, observational

study design, depending on the information provided by the physician, is another limitation of this study.

## CONCLUSION

The AWARE study was a real-world study that evaluated the impact of CU in patients refractory to H1-AH therapy. At the beginning of the study, a significant proportion of patients did not have the disease controlled with impact on quality of life and work productivity. At the end of two years, a significant proportion of patients had their disease controlled, an improvement on QoL, evaluated through DLQI, and a decrease of the use of medical resources. Therefore, the AWARE study allowed Portuguese physicians to recognize the importance of symptom control in CU, minimizing the resources involved in the management of this condition. Nevertheless, the mean DLQI at year two demonstrated that CU still has an effect in the QoL of Portuguese patients and therefore optimization of therapy can be further improved.

## AUTHORS CONTRIBUTION

Both authors had equal contributions for the conception, design, draft, critical review and final approval of the paper.

## ACKNOWLEDGEMENTS

The authors would like to thank all study personnel who participated in the collection of these data.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publications

## COMPETING INTERESTS

Célia Costa declares having received honoraria as a speaker and/or medical advisor from Novartis, Menarini, AstraZeneca, Sanofi and LETIPharma outside the scope of this paper. João Gaspar Marques declares having received honoraria (lecture fees or medical consulting) from Astrazeneca, Bial, Laboratórios Vitória, Menarini, Mundipharma, Novartis, Procter&Gamble, Sanofi, Tecnifar and Teva, as well as research grants from Astrazeneca and Laboratórios Vitória. José Ferreira declares having received honoraria (lecture fees, medical consulting fees or research grants) from Astrazeneca, Bial, Laboratórios Vitória, Menarini, Novartis, Sanofi, Tecnifar, GSK, LETIPharma and Roxall. Gabriela Marques Pinto declares having received honoraria (lecture fees, medical consulting fees or advisory boards fees) from Leo Farmacêutica Portugal, Pfizer, Novartis, Lilly, Janssen and Abbvie. Sara Prates and Virgínia Sousa declare they have no conflicts of interests. Remaining authors are missing conflicts of interests disclosure.

## FUNDING SOURCES

Funding for the AWARE study was provided by Novartis. Funding for this paper was provided by Novartis Portugal. Funding was used to access all necessary scientific bibliography and cover editorial assistance services. Novartis Portugal had no role in the collection, analysis and interpretation of data, in the writing of the paper or in the decision to submit the paper for publication.

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