



ORIGINAL ARTICLE

Improvement in the quality of life of patients with chronic spontaneous urticaria treated with omalizumab in real life[☆]



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KEYWORDS

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Abstract

Objective: Evaluation of the impact on the quality of life (QOL) relating to health in patients with chronic urticaria (CSU) treated with omalizumab.

Method: Longitudinal descriptive observational study of quality of life based on 18 patients with chronic urticaria ≥ 12 years treated with omalizumab. Changes in QOL examined at 1 month (T1), at 6 months (T6) and 12 months (T12), by: Visual Analogical Scale (UAS), specific urticaria QOL questionnaire (CU-Q2oL), general health questionnaire (SF-36) and activity of urticaria questionnaire (Score UAS7).

Results: The most disabling symptoms for patients were: pruritus (61.1%); decrease in health and physical activity (55.5%), wheals, swelling and nervousness (50%); depression and shame of marks (38.89%); side effects to drugs (33.33%); sleepiness and tiredness (27.78%); work (22.22%); "choosing clothes and pain" 16.67% and social relations (11.11%). Statistically significant differences were observed in T1, T6 and T12. In T1, UAS -4.72 ($p=0.001$); CU-Q2oL -16.38 ($p<0.001$); SF-36 15.44 ($p=0.006$); UAS7 wheals -7.27 ($p=0.001$), UAS7 pruritus -8.72 ($p=0.003$). In T6, UAS -4.26 ($p=0.001$); CU-Q2oL -18.94 ($p<0.001$); SF-36 15.41 ($p<0.001$); UAS7 wheals -7.41 ($p=0.001$), UAS7 pruritus -7.11 ($p=0.001$). In T12 UAS -9.61 ($p=0.004$); CU-Q2oL -21.38 ($p=0.01$); SF-36 17.53 ($p=0.04$); UAS7 wheals -8.23 ($p=0.004$), UAS7 pruritus -10.69 ($p=0.004$).

Conclusions: There was a very good response in T1, which was maintained in T6 and T12. Patients with chronic urticaria treated with omalizumab presented good results with a reduction of CUE activity and improvement of their QOL.

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PALABRAS CLAVE

Calidad de vida;
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Omalizumab;
Cuestionario calidad
de vida

Mejora de la calidad de vida de los pacientes con urticaria crónica espontánea tratados con omalizumab en vida real

Resumen

Objetivo: Evaluación del impacto en la calidad de vida (CdV) relacionada con la salud en los pacientes con urticaria crónica espontánea en tratamiento con omalizumab.

Método: Estudio observacional descriptivo longitudinal de calidad de vida partiendo de 18 pacientes con urticaria crónica espontánea ≥ 12 años tratados con omalizumab. Se analizaron los cambios en la CdV al mes (T1), a los 6 (T6) y a los 12 meses (T12), mediante: escala analógica visual (EVA), cuestionario de CdV específico de urticaria (CU-Q2oL), cuestionario de salud general (SF-36) y cuestionario de actividad de urticaria (Score UAS7).

Resultados: Los síntomas más condicionantes para los pacientes fueron: prurito (61,1%); disminución de la salud y actividad física (55,5%); ronchas, hinchazón y nerviosismo (50%); depresión y vergüenza de marcas (38,89%); efectos secundarios a fármacos (33,33%); sueño y cansancio (27,78%); trabajo (22,22%); «elección de ropa y dolor» 16,67% y relaciones sociales (11,11%). Se observaron diferencias estadísticamente significativas en T1, T6 y T12. En T1, EVA -4,72 ($p=0,001$); CU-Q2oL -16,38 ($p<0,001$); SF-36 15,44 ($p=0,006$); UAS7 ronchas -7,27 ($p=0,001$), UAS7 prurito -8,72 ($p=0,003$). En T6, EVA -4,26 ($p=0,001$); CU-Q2oL -18,94 ($p<0,001$); SF-36 15,41 ($p<0,001$); UAS7 ronchas -7,41 ($p=0,001$), UAS7 prurito -7,11 ($p=0,001$). En T12 EVA -9,61 ($p=0,004$); CU-Q2oL -21,38 ($p=0,01$); SF-36 17,53 ($p=0,04$); UAS7 ronchas -8,23 ($p=0,004$), UAS7 prurito -10,69 ($p=0,004$).

Conclusiones: Existió muy buena respuesta en T1, que se mantuvo en T6 y T12. Los pacientes con urticaria crónica espontánea tratados con omalizumab presentaron buenos resultados con reducción de la actividad de UCE y mejora de su CdV.

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What is known?

Little is known about this condition. Few studies measure the impact of quality of life in patients with chronic urticaria and the symptoms which most affect and concern them.

What does this paper contribute?

Exhaustive data collected from general and specific quality of life questionnaires, in patients with chronic urticaria treated with omalizumab for two years. It shows the repercussions on their quality of life and forms a base for nursing intervention to minimise impairment.

Introduction

Chronic spontaneous urticaria (CSU) is highly prevalent in the general population and despite its low mortality may be devastating for the quality of life (QoL) of whomever suffers from it.¹ Prevalence is calculated to be between 0.1% and 1%.^{2,3} This disorder affects females twice as frequently as males and it peaks between the ages of 20 and 40.² Its

cause is usually unknown in 80% of cases.^{4,5} Urticaria is characterised by the sudden appearance of hives and/or angio oedema. It must be distinguished from other clinical conditions where hives and/or angio oedema may also occur, such as anaphylaxis, auto-inflammatory syndromes, hereditary angio oedema and in skin tests performed for allergy diagnoses.⁶

The hive is defined by three standard traits:

1. Central inflammation of variable size, almost always surrounded by reflexive erythema.
2. It is associated with itchiness or sometimes burning.
3. Evanescent: the skin usually recovers its normal appearance within a period of 1–24 h.

Angio oedema is characterised by:

1. Sudden, marked inflammation, with skin coloured erythema, at deep dermis and hypodermis level, often with involvement below the mucous membranes.⁶
2. On occasion pain instead of itchiness. Resolution is slower than that of hives (up to 72 h).⁶

Chronic spontaneous urticaria refers to erythematous hives that occur spontaneously, fleetingly, are recurrent and last for a period of at least 6 weeks.^{2,6–9} In 40% of cases they are associated with angio oedema.^{2,8} CSU has a negative impact on health and on the subjective satisfaction of patients suffering from it. The individual perception of each patient with regards to their quality of life is a good way of

assessing the limitations which the patients may experience as a result of their disorder.²

Regarding prognosis, CSU frequently spontaneously remits but its duration is currently unpredictable. Approximate calculations indicate that the symptoms of 50% of patients with CSU disappear after 6 months, although the patients often suffer from recurrences.¹⁰

Urticaria is physically and psychologically debilitating due to its chronicity changing patients' QoL.^{2,11-13} For example, O'Donnell et al.¹¹ demonstrated that the scores for the state of health of the patients with CSU were comparable to that of patients with coronary arteriopathy. Furthermore, both state of health and subjective satisfaction of patients with CSU have a poorer score than those of healthy subjects and those with respiratory allergy,⁷ which falls within the group of serious allergy disorders.⁶

QoL studies quantify symptoms from the patient's perspective. The psychological repercussions of organic problems vary for each individual. Thus patients with the same disorder may suffer from it in differently ways.

Pharmacological treatment of symptoms

Patient wishes and preferences should be taken into consideration when treating urticaria.^{2,6}

The need for treatment may vary over time.⁶

First line treatment consists of second-generation antihistamines (anti-H₁) with no anticholinergic effects and minimal or no sedative effects.¹⁴ They should preferably be taken on a regular basis, not on demand. If symptoms persist for longer than 2 weeks 2nd line treatment begins where it is recommended to increase the dose of these anti-H₁ to 4 times a day and not combine them with any other type of anti-H₁.^{6,7} Safety data exist on their continued use for several years.¹⁵ Prior to changing to an alternative therapy, it is recommended to wait 1–4 weeks to allow for complete efficacy.⁶ Omalizumab has been demonstrated to be effective as 3rd line treatment of CSU for those patients who are resistant to anti-H₁. This has been proven in isolated cases, case series and in double-blind placebo control studies, in patients resistant to anti-H₁.^{16,17}

Omalizumab is a humanised monoclonal antibody obtained by means of recombinant DNA technology, from hamster ovary cell lines.¹⁸ It reduces CSU activity, lowers the need for additional medication to control symptoms and improves quality of life.³ It is effective at doses between 150 and 300 mg/4 weeks regardless of the total IgE serum level.¹⁹ This treatment is expensive, has a safety profile and very good clinical efficacy.^{3,6} The risk/benefit ratio in long-term use is higher than that of corticosteroids.

After reviewing the references we observed that there are few studies which measure the impact on QoL in CSU patients and on their appreciation of the seriousness of the disorder.¹³

All studies were performed with few patients,¹² which may be considered a limitation. Kaplan et al.²⁰, conducted a study with 12 patients, 60% of whom had complete remission after 16 weeks treatment and a significant reduction in the use of rescue treatment.³

An important function in nursing is to contribute scientific knowledge to improve the quality of care for ill people by assessing their needs and concerns.²¹

We evaluated the impact on QoL of CSU resistant to anti-H₁ in a group of patients, in addition to its alternation as a result of the effect of omalizumab. Both physical and psychological aspects were measured throughout the length of the study (at the beginning, after one month, after six months and at one year).

Method

Design: Longitudinal observational descriptive and evolutionary quality of life study.

Sample: 18 patients ≥ 12 years with CSU refractory to antihistamine treatment at high doses who had been referred for treatment with omalizumab. They were recruited from January 2014 until March 2015, with final data being collected in December 2015. 13 patients were female with a mean ($\pm$ standard deviation) age of 43 (± 18) years and 5 were male with a mean ($\pm$ standard deviation) age of 47 (± 20) years. The study was conducted in the Navarre Health Service Allergy Department. Almost the entire population of Navarre is treated in this Department.

Inclusion criteria: all patients with CSU ≥ 12 years of age who had been treated with omalizumab since January 2014, all of whom were treated with new generation anti-H₁, and who, on receiving information about the study, agreed to sign an informed written consent and complete monthly quality of life questionnaires.

Exclusion criteria: patients with cognitive limitations and all those who presented added complications and/or did not wish to complete questionnaires. All the patients were able to revoke their authorisation at any time.

As this was an observational study, no additional patient tests other than the specific questionnaires were intended.

Procedure: the nurse provided the validated questionnaires to each patient monthly and they had to complete them during the waiting time after the administration of omalizumab (Cu-Q2oL, SF-36 and visual analogue scale [VAS]) except UAS7 which each person completed in their home seven days prior to each visit. Follow-up and control of responses was conducted in this manner.

Assessment was performed at the beginning of the study with the 1st dose of omalizumab (T0), and subsequently at one month (T1), at 6 months (T6) and at 12 months (T12) for the patients who continued with the treatment. There were patients who withdrew from the treatment for different reasons. Statistical data were evaluated with the number of active patients at each time.

Tool for measuring. The questionnaires determined the QoL impairment and the disorder's activity of the patient with CSU. All questionnaires are available in paper format.

- **Visual analogue scale of symptoms VAS.** This evaluates the symptoms prior to the visit on a Likert scale. It is regularly represented with a horizontal line of 100 mm anchored by two end points which range from 0 (no symptoms) to 10 (very strong symptoms), along a continuous line where the patient marks perpendicularly to show how they perceive their situation. There are intermediate values.²²

Table 1 UAS7 score system for assessing urticaria activity.

Score	Number of hives (last 24 h)	
0	None	0 hives
1	Mild	≤20 hives
2	Moderate	Between 21 and 50 hives
3	Severe	Over 50 hives
Score	Itch severity (last 24 h)	
0	None	Absent
1	Mild	Present without being a nuisance
2	Moderate	Uncomfortable but without interfering in daily activities or disturbing sleep
3	Severe	Severely interferes in daily activities and disturbs sleep

- *Specific QoL questionnaire for patients with CSU CU-Q2oL.*

This is the only specific questionnaire to assess QoL in CSU. It has been validated and includes physical, emotional, social and practical aspects of the disorder.^{6,13,23,24} It fulfils validity standards, has internal consistency, credibility and is change sensitive.^{6,9,25}

There are 23 items, which conceptualise a quality of life into 6 main areas: itchiness (2 items), repercussion in life activities (6 items), problems sleeping (5 items), limits (3 items), appearance (5 items) and swelling (2 items).¹³

A five-point scale from 1 (never) to 5 (a lot) is used for response scores.¹³

To calculate scores, the pre-coded numerical values have to be converted on a scale of 0–100 points, using the following formula:

$$\left(\sum \text{items} - \min \sum \text{items} \right) / \left(\max \sum \text{items} - \min \sum \text{items} \right) \times 100$$

Example:

Item 1: response 3.

Item 2: response 2.

Item 3: response 4.

Item 4: response 5.

$\sum \text{Items: } (3 + 2 + 4 + 5) = 14.$

$\min \sum \text{items: } (1 + 1 + 1 + 1) = 4.$

$\max \sum \text{items: } (5 + 5 + 5 + 5) = 20.$

Formula: $(14 - 4) / (20 - 4) \times 100 = 62.5\%.$

Higher scoring denotes after impact on QoL.

- *UAS7* evaluates the activity and impact of the CSU, where the itchiness is measured (from none to intense) on a scale of 0–3 and number of hives (from none to ≥50) also using a scale of 0–3 (Table 1), where minimum score is 0 and maximum 3. Scores are added up: 0–6 every day and summarised at the end of a week (maximum 42).^{3,6,7,26} This is used as an additional tool to assess urticaria activity.⁸

Table 2 Main traits of the SF-36 health survey.

	Number of items	Number of levels	Score ^a
Physical functioning	10	21	0–100
Physical role	4	5	0–100
Bodily pain	2	11	0–100
General health	5	21	0–100
Vitality	4	21	0–100
Social functioning	2	9	0–100
Emotional role	3	4	0–100
Mental health	5	26	0–100
Transition ^b	1	5	–
Physical summary	35	–	50 (10)
Mental summary	35	–	50 (10)

^a Scores of 0–100 are in that range and are interpreted as the worst or best state of health, respectively; in scores of 50 (10) the benchmark population has a mean of 50 with a standard deviation of 10, and the values above or below 50 indicate a better or worse state of health, respectively, than the benchmark population.

^b Change in the general state of health compared with the previous year. This item is not used to calculate any of the 8 main areas.

The scores for itchiness and hives were analysed separately in this study.

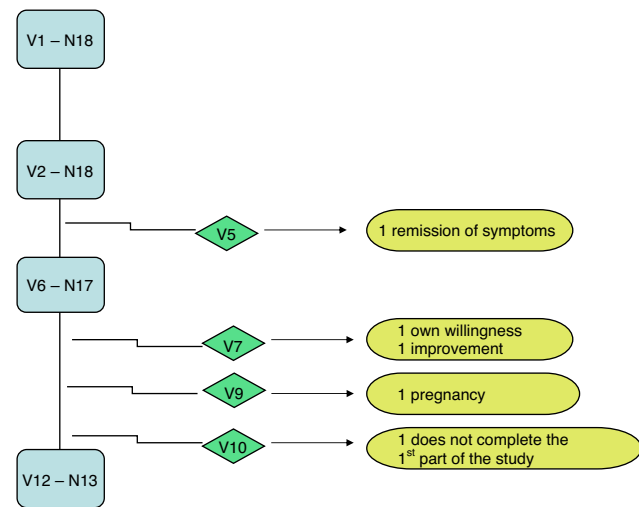
- *Health questionnaire SF-36:* this is a validated generic tool to assess general level of health and well-being and the ability to carry out basic activities.^{27,28}

It contains 36 items designed by Ware et al., in 1993, which covers 8 aspects of state of health with the same profile. It is divided into 2 areas: physical and mental and general impact on habits is scored¹² (Table 2). Scores over or under 50 indicate a better or poorer state of health to the benchmark population mean. Higher scores denote a better state of health (Table 3).

The study was approved by the Ethics Committee of the Navarre Health Service. Statistical analysis was performed with the SPSS version 20 software programme. Data analysis was made by calculating means and standard deviation of scores of the different scales in the baseline 1 visit (T0), visit 2 (T1), visit 6 (T6) and visit 12 (T12).

Table 3 Means and standard deviations of scores obtained for the tools of disorder activity (VAS, UAS-7 itchiness, UAS-7 hives) and effect on QoL (CU-Q2oL and SF-36) at four moments of assessment: at the beginning of treatment, one month after, 6 months after and 12 months after.

	Pretto T-0 Basal	T-1 Seg 1 month	T-6 Seg 6 months	T-12 Seg 12 months	Comparison post-pre (1 months)	Comparison post-pre (6 months)	Comparison post-pre (12 months)
VAS	7.19 (2.28)	2.47 (2.48)	2.76 (2.79)	1.92 (2.43)	-4.72 (3.40)	-4.26 (2.94)	-9.61 (16.74)
CU-Q2oL	52 (15.53)	35.61 (8.60)	32.88 (9.64)	32.23 (11.23)	-16.38 (14.92)	-18.94 (16.89)	-21.38 (19.49)
SF-36	114.17 (21.01)	129.61 (14.52)	130.24 (17.86)	129.85 (20.48)	15.44 (20.66)	15.41 (25.13)	17.53 (27.44)
UAS7 v-hives	10.78 (4.44)	3.50 (5.63)	3.18 (4.59)	2.08 (3.32)	-7.27 (6.03)	-7.41 (5.03)	-8.23 (5.89)
UAS7 itchiness	13.28 (6.56)	4.56 (5.26)	5.71 (6.25)	3.15 (3.55)	-8.72 (9.06)	-7.11 (6.89)	-10.69 (8.47)

**Figure 1** Patient withdrawal in the different visits.

In each case the difference between visit 1 and visit 2 (18 patients) was calculated, between visit 1 and 6 at 6 months (17 patients) and between visit 1 and 12 at 12 months (13 patients), also showing the mean and deviation of the differences. Measurement time scores were compared using the *t*-test for paired samples (variables CU-Q2oL, SF-36) and the Wilcoxon (VAS, UAS7 hives and UAS7 itchiness) range test.

Review of the literature was performed using the CUIDEN database and no article related to QoL in CSU was found. MEDLINE/Pubmed and the Service's own library were used to find all journals related to allergy treatment.

Results

At the baseline visit there were 18 patients, and at the final visit there were 13 patients. There were different reasons for withdrawing from treatment and therefore abandoning the study. One was due to a remission of symptoms at visit 5. Two withdrew at visit 7 (one because they wanted to and the other due to improvement). One withdrew at visit 9 due to pregnancy and the last was only included in visits 1, 2 and 6 and withdrawal was therefore due to non completion of the study time (Fig. 1).

Comparative analysis showed there were significant statistical differences in the comparisons of follow-up time with regard to the pre-treatment moment, detecting an increase in scores of questionnaire SF-36 and a reduction in the VAS, CU-Q2oL and UAS7 which implies an improvement in QoL in all questionnaires.

Means and confidence intervals at 95% were calculated from the scores given in visits 1, 2, 6 and 12 (Fig. 2).

According to CU-Q2oL and SF-36, the symptoms which most affected patients (Fig. 3) were itchiness which presented in 61.1% of patients; impairment in general health and limitation in physical activity in 55.5%; welts, swelling and nervousness in 50%; depression and embarrassment about the blemishes in 38.8%; side effects of drugs in 33%; fatigue and sleepiness in 27.7%; difficulties in work in 22.2%; problems in choosing clothes and physical pain in 16.67% and changes in social relations in 11.1%.

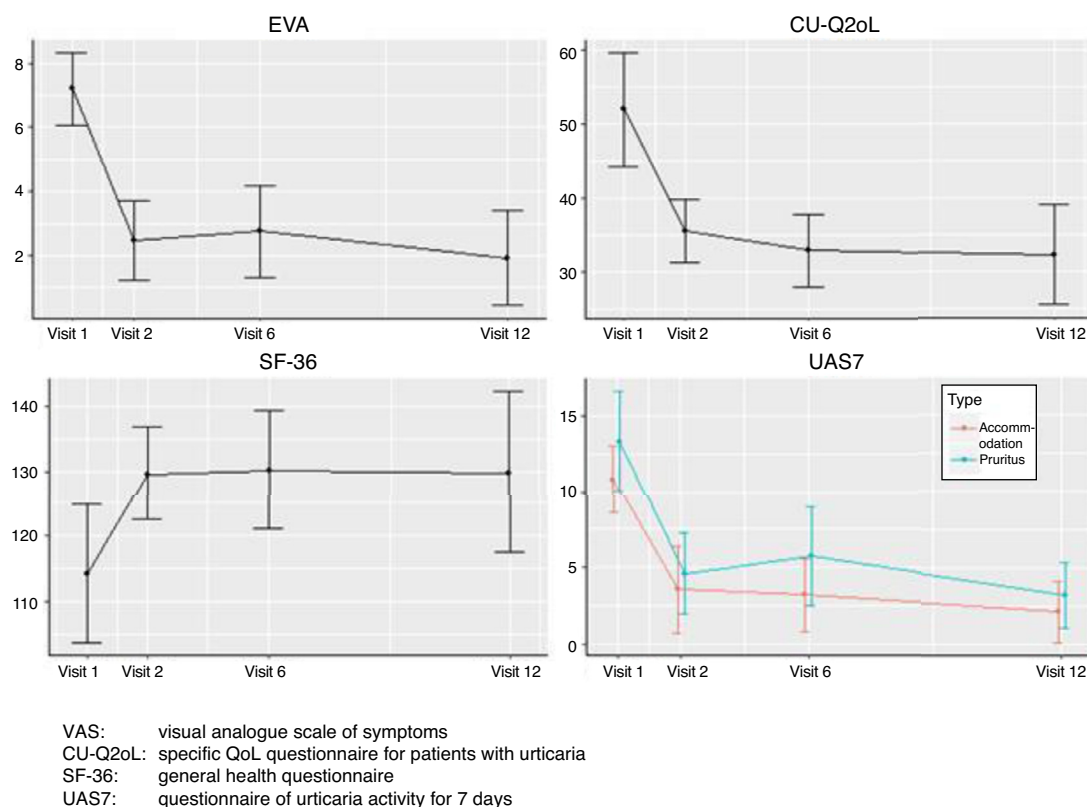


Figure 2 Comparative graphs of the questionnaires in the different visits.

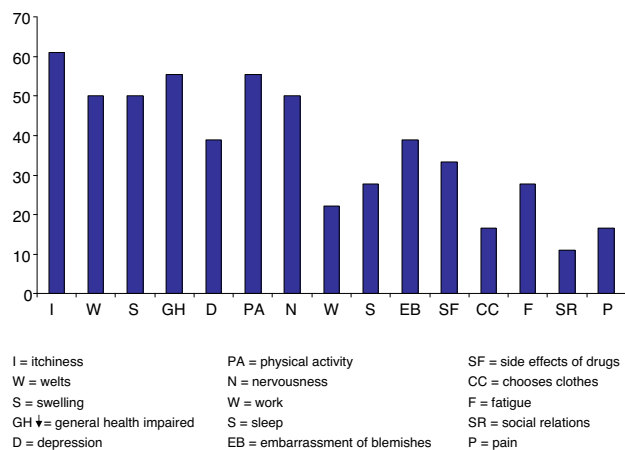


Figure 3 Percentage of patients with different symptoms.

There were no adverse reactions to the administration of omalizumab.

Discussion

In reviewing the literature we detected the absence of studies which simultaneously assessed general questionnaires regarding general state of health (SF-36, VAS) and specific questionnaires on urticaria (CU-Q2oL, UAS7).

The questionnaires used enable us to measure and monitor the activity of the disorder and QoL. The SF-36 health

questionnaire is one of the most frequently used validated generic tools to be translated in the field of QoL measurement.^{27,28} This measurement facilitates information on the disorder and its impact on the patient's life in a standardised, comparative and objective manner (Goldsmith 1972 and 1973), contributes sufficient evidence on its credibility, validity and sensitivity.²⁷ Different pathologies may be compared and strategies in healthcare planning may thus be established. In the case of CSU this is insufficient since several aspects are irrelevant for these patients and others of greater importance to them such as physical appearance, are omitted.²³ For this reason we include a specific validated tool such as CU-Q2oL^{3,23-25} because it succinctly reflects QoL in patients with CSU, it is simple to use and has proven its validity.⁹ It is more sensitive to changes in the patient's state of health than generic measurements.

The VAS has demonstrated its validity and credibility in measuring the intensity of symptoms, being highly used in clinical environments and preferred by patients for its simplicity.²²

Both in clinical care and clinical trials, the activity of CSU should be assessed with the help of the UAS7 scale which is a simple, unified and validated scoring system.^{6,26} In this system the signs and symptoms are assessed by the patient him or herself, and this makes it a particularly useful tool. The evaluation of the main symptoms of urticaria (hives and itchiness) are measured for seven consecutive days. This questionnaire helps to compare the findings of the studies conducted in other centres.

The results we had from all questionnaires used were congruent with one another and similar to those of other studies.^{12,13} It has been observed that the CSU has an impact on state of health and on subjective satisfaction of patients, affecting daily life, limiting it and impairing both physical and emotional functions.

Analysis of the questionnaires has allowed us to see that they are complementary to one another and reflect the overall reality of the patient. We have analysed all their perceptions, highlighting the most relevant such as itchiness. This symptom is presumed to be merely physical but there is a sensation of impaired health more on an emotional level. Both have a direct effect on other areas of their life such as sleep, depression, etc.

Treatment with antihistamines and/or corticosteroids make the symptoms of urticaria temporarily disappear, but not the cause. On stopping treatment, the cutaneous eruption reappears and this is experienced as a therapeutic failure. When this process stops, they may believe this is an indication of a more serious and profound disorder.

One of the limitations of this study was withdrawal from treatment with omalizumab and the consequent dropping out of these patients from the study.

To conclude, we would say that CSU is a challenge for the professional and for the patient. The nurse plays an important role in caring for patients with CSU who are receiving treatment with omalizumab, both in its administration and data collection regarding their QoL. However, to offer good care, the health professionals must first know what patients' specific needs, concerns, and symptoms are, etc.

When the nurse is aware of the aspects which most strongly affect the QoL of CSU patients and their improvement after omalizumab they may communicate this so that the professionals may tell their patients who are initiating treatment that a satisfactory response is expected from it. In this way anxiety and uncertainty is alleviated, which in itself may contribute to impairment in QoL.

With regards to the results, we think it is important to promote research by nurses in this area, with the opportunity in each visit of evaluating possible interventions in order to offer quality attention to this growing population.

Conflict of interests

The authors have no conflict of interest to declare.

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