Original Article

Efficacy and Safety of Omalizumab (Xolair) for Cholinergic Urticaria in Patients Unresponsive to a Double Dose of Antihistamines: A Randomized Mixed Double-Blind and Open-Label Placebo-Controlled Clinical Trial

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What is already known about this topic? Cholinergic urticaria (UCOL) is an inducible urticaria triggered by active or passive increase in core body temperature. It is highly disabling. There is no available treatment for this condition. Antihistamines that usually control other types of urticaria can only partially alleviate UCOL.

What does this article add to your knowledge? This is the first clinical trial with omalizumab for UCOL. We observed a significant improvement in our main outcome, which is a negative exercise challenge test result from week 16, with significant improvements in the UCOL score, daily symptoms, and quality of life. A slow and progressive response to the treatment was observed.

How does this study impact current management guidelines? Omalizumab shows evidence of the safety and potential efficacy in patients with UCOL.

BACKGROUND: Cholinergic urticaria (UCOL) is a highly disabling inducible urticaria triggered by an increase in core body temperature.

OBJECTIVE: To explore the safety and efficacy of omalizumab in controlling UCOL.

METHODS: We conducted a multicenter randomized mixed double-blind and open-label (first 4 months blinded followed by 8 months open-label) placebo-controlled clinical trial in 22 patients suffering from UCOL who were unresponsive to a double dose of antihistamines. We performed an exercise challenge test during each visit as our main outcome variable.

RESULTS: The overall rate of exercise challenge test negative at week 48 was 31.3%, with an average increase in exercise challenge test negative rate of 2.9% points (95% CI, 1.5-4.2) per visit. Statistically significant differences in the negative exercise challenge test rate between the placebo and active intervention groups were not observed during the blinded period (first 4 months of the study). However, from the fourth dose, a

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Abbreviations used
AE- Adverse event
CU2-QoL questionnaire- Chronic urticaria quality of life questionnaire
UCOL- Cholinergic urticaria
VAS- Visual analog scale

progressive improvement was observed. When comparing before and after treatment, statistically significant improvements in all secondary outcome measures were noted after 4 doses (UCOL score: $P = .0015$; visual analog scale score: $P = .0108$; days with symptoms: $P = .0125$) and after 8 doses (UCOL score: $P = .0005$; chronic urticaria quality of life questionnaire: $P = .0105$; visual analog scale score: $P = .0008$; and days with symptoms: $P = .0144$). In the follow-up visit after the cessation of treatment, the symptoms reappeared, with positive exercise challenge test result and significant increases in all variables. Only 4 of 22 patients remained asymptomatic after 3 months of no treatment. No adverse effects were reported.

CONCLUSIONS: This randomized mixed double-blind and open-label placebo-controlled trial showed evidence of the safety and potential efficacy of omalizumab in patients with UCOL. **(J Allergy Clin Immunol Pract 2019;7:1599-609)**

Key words: *Cholinergic urticaria; Omalizumab; Clinical trial; Exercise; Exercise challenge test; Cholinergic urticaria; UCOL score*

INTRODUCTION

Cholinergic urticaria (UCOL) consists of the appearance of itching, pin-point wheals induced by an active (eg, exercise) or passive (eg, hot bath) increase in core body temperature, which fade away when the body cools.[1] It is highly disabling,[2] with a substantial impact on patients' daily activities and work performance. Each patient has his or her own stimulus threshold, and symptoms can be triggered by minimal activity such as climbing stairs or entering a heated building from the cooler outside temperature.

UCOL starts at a young age. In contrast to patients with other inducible urticarias, who have periods of remission or diminished intensity, most patients with UCOL suffer the condition their entire lives.[3] Consequently, they become accustomed to the disease, avoiding activities that induce urticaria and changing their daily habits without seeking medical treatment.

The etiology and pathogenesis of hive formation remains unknown, although it has been recognized that mast cells and basophils are clearly involved.[4] It has been hypothesized that cellular activation could occur through the interaction between acetylcholine and mast cells or basophils and may be due to a hypersensitivity to sweat antigens.[5-8] However, UCOL has also been observed in patients with anhidrosis and/or hypohidrosis.[9] As in other inducible urticarias, specific IgE antibodies against serum proteins have been found in passive transfer experiments on UCOL.[10] The prevalence of UCOL was 11.2% in a study of 499 German high school and university students[11] and 4.2% in a study in a young Indian population.[12] In both cases, the condition was mostly mild.

Despite the high morbidity of UCOL and its impact on patient quality of life, there is no available treatment for this condition. Antihistamines that usually control other types of urticaria can only partially alleviate UCOL. There have only been 4 controlled studies, which have been reviewed elsewhere,[13] and 1 of them showed the partial efficacy of doubling the recommended dose of the second-generation antihistamine cetirizine.[14]

In small isolated case reports, omalizumab has been shown to be effective at controlling UCOL in patients who are unresponsive to conventional therapies at maximum or off-label doses.[15-18] In a recent retrospective study comprising 16 patients suffering from UCOL, 7 combined with other types of urticaria including chronic spontaneous urticaria and 9 with isolated UCOL, a positive response was observed in 3 of them and a major response in other 3 patients.[19] A negative response was also reported.[20] Our rationale for the utilization of omalizumab in this type of urticaria is that it exerts an inhibitory action on mast cell and basophil activation,[21,22] as has been demonstrated in other inducible urticarias[23] such as dermographism[24] and cold urticaria.[25] We hypothesize that omalizumab is able to revert the basophil or mast cell activation present in urticaria.[21,22]

We conducted a multicenter randomized mixed double-blind and open-label placebo-controlled clinical trial with the aim of evaluating the efficacy and safety of omalizumab (Xolair) in patients suffering from UCOL who are unresponsive to a double dose of antihistamines.

METHODS

Study population

A multicenter randomized mixed double-blind and open-label placebo-controlled parallel clinical trial was performed (ClinicalTrials.gov identifier: NCT02012387; Eudra CT#2013-002770-43). It was conducted at 7 sites distributed across Spain. Each patient signed a written consent form.

The eligibility criteria included female and male patients aged 14 years or older with a diagnosis of UCOL according to clinical history and a positive exercise challenge test result who were unresponsive to supratherapeutic doses of antihistamines (defined as 2 × [maximal dose included in the drug labeling]) and who provided written informed consent. The exclusion criteria were the presence of pruritus related to dermatitis or other skin conditions; the presence of any systemic disease that hampered follow-up or the interpretation of data; the administration of omalizumab treatment within the previous 12 months; the presence of any exclusion criteria included on the drug label; and the presence of any other conditions that did not allow the accomplishment of the clinical trial requisites, such as the use of illicit drugs or alcohol abuse.

Patients with a clinical diagnosis of UCOL according to their clinical history and positive exercise challenge test results were treated with double the licensed dose of cetirizine (20 mg) for 2 weeks, and then the exercise challenge test was repeated. If the test result was positive, patients were randomized to either the placebo group or the active treatment group for 16 weeks, receiving a monthly dose during the blinded period. Starting in week 16, all patients received omalizumab and performed an exercise challenge test during each visit. This design allowed to achieve a 2-fold objective: maximizing the sample size of a unique group receiving

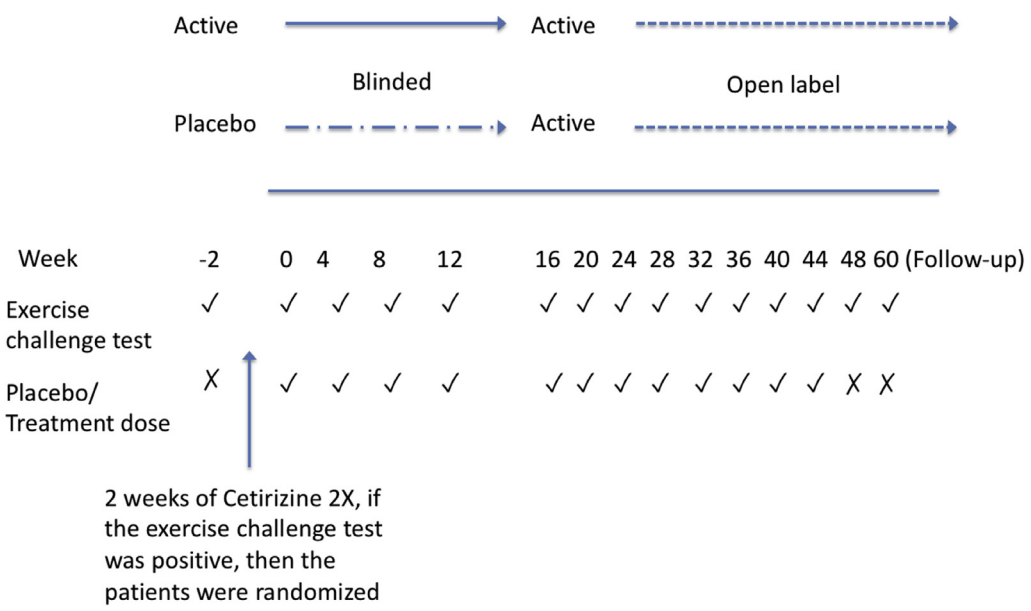

FIGURE 1. Scheme of the study design. The X mark indicates "not done," and the ✓ mark indicates "done."

TABLE I. The cholinergic urticaria score (0-6 points)

Stimuli	Score	Extent of skin lesions	Score
None	0	No skin lesions	0
Intense exercise with profuse sweating	1	Isolated hives on upper trunk	1
Moderate activity, such as brisk walking or climbing stairs	2	Hives on trunk and arms or legs	2
Minimal activity, warm external temperature	3	Hives on trunk, arms, legs, neck, and face	3

omalizumab in order to evaluate the global negative rate, while keeping the possibility of comparing blinded and parallel groups of omalizumab and placebo. Three months after the last dose, the patients returned for another follow-up visit during which they performed a final exercise challenge test. We include a schematic of the study design in Figure 1.

Treatment administration

The active intervention group received omalizumab (300-mg dose, subcutaneous route, independent of total IgE levels, weight, or height). Two injections of 150 mg were administered every 4 weeks for 4 months (4 doses within 16 weeks). The placebo consisted of a saline serum (subcutaneous route, 0.6 mL saline serum with the same volume as the active treatment). Two injections were administered every 4 weeks for 4 months (4 doses within 16 weeks). After the double-blind period, all patients from both arms received the active intervention for 8 months (open-label period). Two injections of 150 mg were administered every 4 weeks for 8 months (8 doses within 32 weeks).

Exercise challenge test

We performed the exercise challenge test following the European guidelines[26] for UCOL. All centers followed the same standardized protocol. The patients exercised by running on a treadmill until they started sweating and then continued running for an additional 15 minutes. We registered the time intervals between the start of the test and the first appearance of sweat and the first appearance of skin lesions and the extent and duration of symptoms.

The test result was considered positive if the exercise challenge led to the typical rash within 10 minutes from starting sweating.

Daily symptoms score

We created a daily symptom score (UCOL score) that combines the stimuli that elicit the reaction, from passive warming up to intense exercise, with the extent of the skin lesions, from isolated trunk hives to generalized hives, with a minimum score of 0 and a maximum score of 6 (Table I). We wanted a simple, easy, and feasible scoring tool. We adapted the measure tool from the Urticaria Activity Score because is already validated and has a high patient adherence.

Basophil activation test with sera from patients with UCOL

The basophil activation test was performed as previously described.[27] Blood from healthy donors was centrifuged, and cells above the red-blood cell layer were collected and resuspended in stimulation buffer containing IL-3. Thereafter, the cells were stimulated with 50 μL of sera from UCOL patient. After 30 minutes at 37°C, the stimulation was stopped, and the serum was eliminated by washing the samples with cold washing buffer (PBS, 2 mM EDTA). Samples were labeled with anti-IgE fluorescein isothiocyanate (FITC) and anti-CD63 phycoerythrin (PE) for 30 minutes at 4°C. The erythrocytes were lysed for 10 minutes at room temperature, and the samples were washed twice before analyzing them in a FACSCanto II flow cytometer (FACScan, Becton Dickinson, NJ). Data were analyzed with FlowJo Tree Star software (Ashland, Ore). In all cases, dead cells were eliminated on the basis of their forward and side scattering profiles.

Primary and secondary outcomes

Our primary outcome was a negative exercise challenge.

We included the following as secondary outcome measures: quality of life, evaluated through the validated Spanish version of the

TABLE II. Demographic and clinical features of the entire study population and stratified by the intervention group

Characteristic	Total	Placebo	Treatment	*P* value
N	22	9	13	
Age (y)	34.1 ± 15.0	32.3 ± 13.8	35.4 ± 16.2	.641
Sex: male, n (%)	16 (72.7)	6 (66.7)	10 (76.9)	.655
Race, white, n (%)	22 (100)	9 (100)	13 (100)	—
UCOL history				
Time from diagnosis (mo), median (p25, p75)	22.0 (2.2-39.1)	22.5 (1.1-119)	12.4 (3.5- 36.4)	.483
Symptom trigger, n (%)				
Intense exercise and sweating	11 (50)	5 (55.6)	6 (46.2)	.999
Moderate activity (briskly walking, climbing stairs)	12 (54.6)	5 (55.6)	7 (53.9)	.999
Mild activity, elevated ambient temperature	18 (81.8)	8 (88.9)	10 (76.9)	.616
Other	6 (27.3)	2 (22.2)	4 (30.8)	.999
Lesion localization, n (%)				
Face and neck	15 (68.2)	6 (66.7)	9 (69.2)	.999
Trunk	22 (100)	9 (100)	13 (100)	—
Extremities	20 (90.9)	8 (88.9)	12 (92.3)	.999
Other	0 (0)	0 (0)	0 (0)	—
Frequency of onset, n (%)				
Daily	17 (77.3)	8 (88.9)	9 (69.2)	.360
Other	5 (22.7)	1 (11.1)	4 (30.8)	
Time required for lesions to disappear, n (%)				
20-60 min	15 (68.2)	8 (88.9)	7 (53.9)	.242
1-3 h	6 (27.3)	1 (11.1)	5 (38.5)	
>3 h	1 (4.6)	0 (0)	1 (7.7)	
Associated itching, n (%)	22 (100)	9 (100)	13 (100)	—
Previous UCOL treatments, n (%)				
Cold applied to the skin	5 (22.7)	2 (22.2)	3 (23.1)	.999
Antihistamines	22 (100)	9 (100)	13 (100)	—
Corticosteroids	6 (27.3)	3 (33.3)	3 (23.1)	.655
Other	1 (4.6)	1 (11.1)	0 (0)	.409
Exercise challenge test (selection visit)				
Time to start sweating (min)	4.9 (3)	5.4 (3.9)	4.4 (1.8)	.256
Lesion localization, n (%)				
Face and neck	13 (59.1)	4 (44.4)	9 (69.2)	.384
Trunk	20 (90.9)	8 (88.9)	12 (92.3)	.999
Extremities	16 (72.7)	6 (66.7)	10 (76.9)	.655
No skin lesions	1 (4.6)	1 (11.1)	0 (0)	.409
Time to appearance of hives (min), N = 19	5.5 ± 4	5.5 ± 4.3	5.5 ± 4.0	.999
Time to disappearance of hives (min), N = 18	84.2 ± 89.7	31.9 ± 16.7	126 ± 103	.004
Total IgE (kU/L)	294.7 ± 347.5	283.3 ± 335.1	302.5 ± 369.2	.973

BMI, Body mass index; *BP*, blood pressure; *NA*, not available.
Data are presented as mean ± SD unless otherwise stated.

chronic urticaria quality of life (CU2-QoL) questionnaire[28]; the UCOL score; and the visual analog scale (VAS) score. Patient symptom diaries with all incidences, use of rescue medication, and adverse events were also collected. Each patient completed the CU2-QoL questionnaire at each visit. Additional measures collected were the number of study dropouts in each treatment group, the number of sick leave days used because of UCOL, and the number of emergency department visits. The use of rescue medication was also recorded. Safety was assessed by means of the evaluation of adverse events throughout the study.

Assuming an expected negative challenge rate of 11%,[24] 21 patients would have been necessary to provide a 70% power to detect a difference, with an expected 30% response rate, with a 2-sided *P* value of .05 indicating statistical significance.

Participants were randomly assigned following simple randomization procedures (computerized random numbers) with a 1:1 allocation to receive either the placebo or active intervention during the blinded portion of the study. The allocation sequence was concealed until the intervention was assigned by central randomization. The patients and physicians were blinded to the allocation. After the double-blind period, all patients from both arms received the active drug for 8 more months (open-label period).

Statistical methods

All analyses were carried out on the basis of the intention-to-treat principle. We calculated the means (and SDs) or median (percentile 25 [p_{25}]; percentile 75 [p_{75}]) and frequencies of the baseline demographic and clinical characteristics for the whole study population

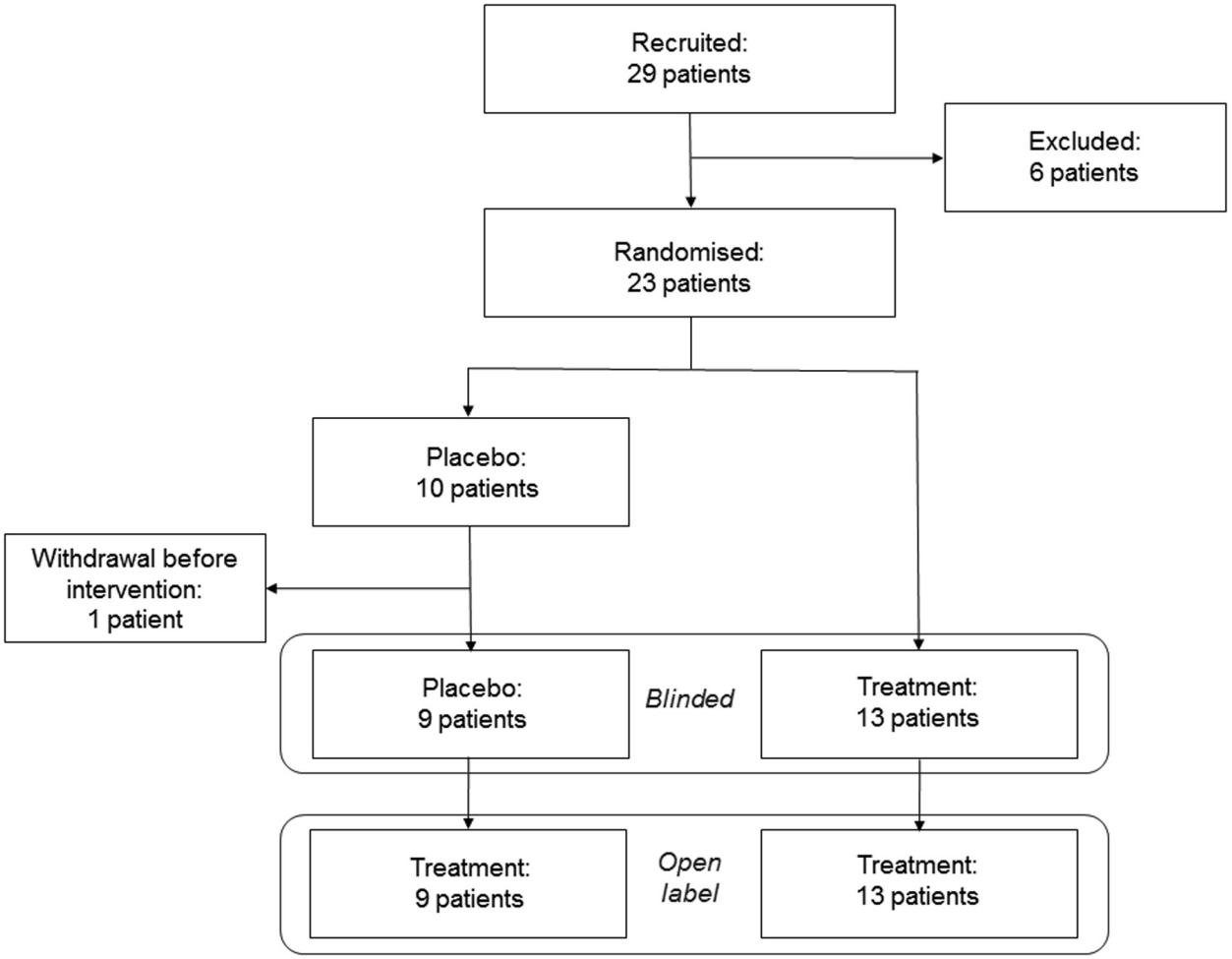

FIGURE 2. Flowchart of the clinical trial.

and separately by study arm. Differences in quantitative outcomes between intervention groups were tested using independent sample *t* tests. The Mann-Whitney test was used if the normal distribution of the outcome could not be assumed. Changes in the means of quantitative outcomes from the baseline to follow-up visits were tested using paired sample *t* tests. The Wilcoxon matched-pairs signed-ranks test was used when the normality assumption was violated. Normality was checked using the Shapiro-Wilk test. Differences in the distributions of categorical variables were tested using the chi-square test or Fisher exact test. A binomial probability test was used to compare the negative challenge after the last active intervention visit with the expected negative challenge rate. Statistical significance was defined using a 2-sided α level of 0.05. All analyses were performed using IBM SPSS Statistics version 20 (IBM Corp, Released 2011, IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY) and Stata version 14 (StataCorp LP, 2015, Stata Statistical Software: Release 14, College Station, Texas).

RESULTS

All patients presented hives after exercise and/or passive warming at the beginning of the study. None of the patients suffered from exercise-induced anaphylaxis or respiratory, gastrointestinal, or cardiovascular symptoms while presenting hives. Twelve patients suffered urticaria induced by minimal activity (climbing stairs, briskly walking), and 6 suffered urticaria induced by spicy foods and stress.

In total, 29 patients were recruited. After receiving 20 mg of cetirizine at the prescreening visit, 6 patients tested negative on the exercise challenge test and were excluded, and 23 patients tested positive and were randomized. One patient dropped out after randomization before receiving the first study dose. Finally, 22 randomized patients received the intervention. The mean age of the patients was 34.1 $\pm$ 15 years; 16 were men, and 6 were women (Table II).

The clinical and demographic features of the patients in the 2 intervention groups were fairly well balanced at randomization, although those allocated to the placebo group appeared to have faster time to disappearance of hives at baseline than did the treatment group (Table II).

During the blinded period of the study, 9 patients received placebo and 13 patients received omalizumab. During the open-label period of the study, all patients received omalizumab starting at week 16 and ending at week 44. Figure 2 shows a flowchart of the study.

Exercise challenge test

After the open-label period, during which all patients received the active intervention, the overall negative challenge rate at week

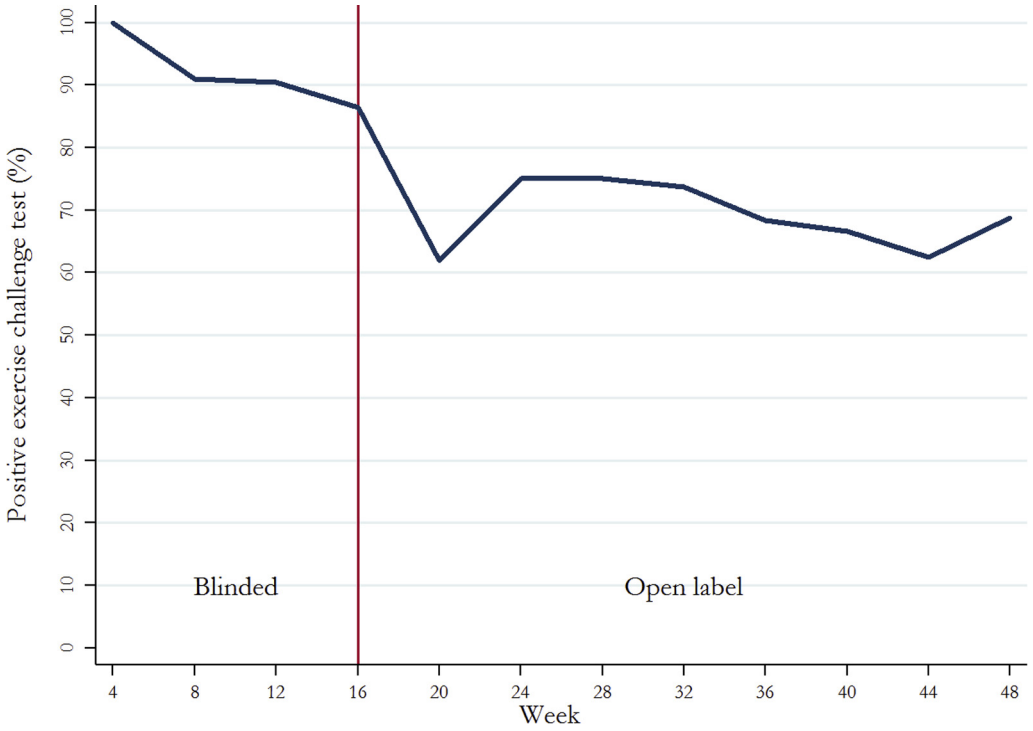

FIGURE 3. Negative challenge of the exercise challenge test in the whole sample over time. A progressive increase in negative challenge rates over time was observed. The overall negative challenge rate at week 48 was 31.3%, which differed significantly from a theoretical response of 11% ($P = .02$). In the first 16 weeks of placebo-active comparison, the negative challenge rate in the placebo group was 2 of 9 (22.2%) and in the active group was 1 of 13 (7.7%) ($P = .544$). Data represent results for all placebo and active patients combined (n = 22). Week 4 (n = 19), week 6 (n = 22), week 12 (n = 21), week 16 (n = 22), week 20 (n = 21), week 24 (n = 20), week 28 (n = 20), week 32 (n = 19), week 36 (n = 19), week 40 (n = 18), week 44 (n = 16), and week 48 (n = 16).

48 was 31.3%, which differed significantly from a theoretical response of 11% ($P = .02$). We observed an average negative challenge increase of 2.9 percentage points (95% CI, 1.5-4.2) per visit. The highest negative challenge rates were observed at week 20 (38.1%) and at week 44 (37.5%) (Figure 3). Two of the 9 patients in the placebo group experienced negative challenge at the end of the blinded period, whereas negative challenge was observed in 1 of 13 patients in the treatment group ($P = .544$).

The UCOL score

During the blinded period, both intervention groups showed a decrease in the UCOL score. The median UCOL score decrease in the placebo group (n = 9) was −16 (p_{25}: −35; p_{75}: −11), and the median decrease in the treatment group (n = 13) was −28 (p_{25}: −41; p_{75}: −14), although this difference was not statistically significant ($P = .8247$).

When comparing UCOL scores of the whole sample of patients (n = 22) before treatment (median, 66; p_{25}: 51; p_{75}: 108) and after receiving 4 (median, 40; p_{25}: 20; p_{75}: 82) or 8 doses of omalizumab (median, 40.5; p_{25}: 7; p_{75}: 65), we observed a statistically significant improvement ($P = .0015$ and $P = .0005$, respectively). After stopping treatment with omalizumab, there was a statistically significant increase in the UCOL score at the follow-up visit (week 60: median, 62; p_{25}: 10; p_{75}: 112) compared with the last visit that evaluated the effect of the last dose of omalizumab at week 48 (median, 20.5; p_{25}: 6.5; p_{75}: 56.5; $P = .0156$) (Figure 4).

Quality of life (CU2-QoL questionnaire)

During the blinded period, both intervention groups showed a decrease in CU2-QoL questionnaire scores (which indicates an improvement in the quality of life for both groups). This decrease (improvement) was greater in the treatment group (median, −7.6; p_{25}: −19.6; p_{75}: 10.9) than in the placebo group (median, −6.5; p_{25}: −9.8; p_{75}: −3.3), although the difference was not statistically significant ($P = .7176$).

When comparing the CU2-QoL questionnaire scores of the whole sample of patients before treatment (median, 16.9; p_{25}: 9.2; p_{75}: 29.9) and after receiving 8 doses of omalizumab (median, 7.6; p_{25}: 1.6; p_{75}: 20.1), we observed a statistically significant improvement ($P = .0105$). Likewise, after stopping treatment with omalizumab, there was a statistically significant increase (worsening) in the CU2-QoL questionnaire score at the next follow-up visit (week 60: median, 13.6; p_{25}: 7.6; p_{75}: 30.4) compared with the score at the visit that evaluated the effect of the last dose of omalizumab at week 48 (median, 4.4; p_{25}: 1.1; p_{75}: 16.3; $P = .0002$) (Figure 5).

The VAS score

During the blinded period, decreases in the VAS score of the treatment group (median, −10; p_{25}: −50; p_{75}: 0) and the placebo group (median, −10; p_{25}: −40; p_{75}: −5) were similar ($P = .9555$).

When comparing VAS scores of the whole sample of patients before treatment (median, 60; p_{25}: 40; p_{75}: 80) and after receiving 4 (median, 30; p_{25}: 20; p_{75}: 70) or 8 doses of

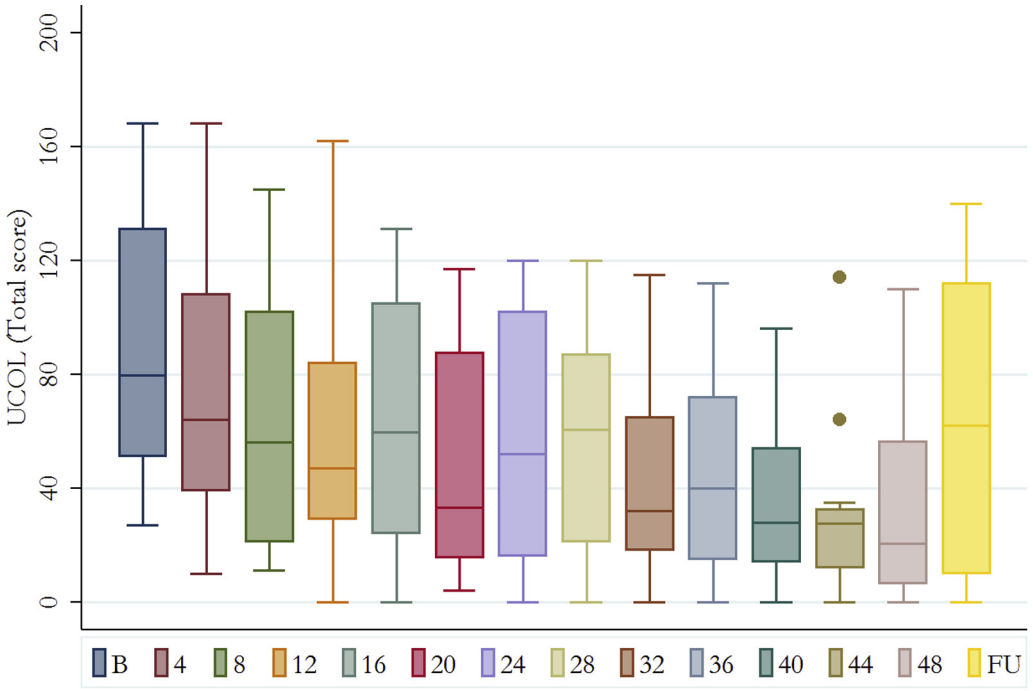

FIGURE 4. The UCOL score by weeks in the total study population. *B*, Basal visit; *FU*, follow-up visit (week 60, after 3 months of the last omalizumab dose). The line inside the box represents the median value. The upper and lower ends of the box represent the 75th and 25th percentiles, respectively. Circles represent values outside the box-whisker. A progressive decrease in UCOL score over time was observed. After stopping the intervention, a rise in the UCOL score at follow-up visit (week 60) was observed. Data represent results for all placebo and active patients combined (n = 22).

omalizumab (median, 25; p_{25}: 5; p_{75}: 64), we observed a statistically significant improvement ($P = .0108$ and $P = .0008$, respectively). After completing treatment with omalizumab, there were statistically significant increases in VAS scores at the follow-up visit (week 60: median, 65; p_{25}: 27.5; p_{75}: 80) compared with the visit that evaluated the effect of the last dose of omalizumab at week 48 (median, 15; p_{25}: 5; p_{75}: 53; $P = .0002$) (Figure 6).

Patient symptom diaries: Number of days with symptoms

During the blinded period, both groups showed similar decreases in the number of days with symptoms (median for placebo, −4, p_{25}: −9, p_{75}: −2; median for treatment, −3, p_{25}: −8, p_{75}: 0; $P = .4117$).

When comparing the number of days with symptoms before treatment (median, 18; p_{25}: 11; p_{75}: 23) and after receiving 4 (median, 10; p_{25}: 5; p_{75}: 21) or 8 doses of omalizumab (median, 9; p_{25}: 2; p_{75}: 20), we observed a statistically significant improvement ($P = .0125$ and $P = .0144$, respectively). After stopping treatment with omalizumab, there was a statistically significant increase in days with symptoms at the follow-up visit (week 60: median, 12; p_{25}: 5; p_{75}: 28) compared with the visit that evaluated the effect of the last dose of omalizumab at week 48 (median, 5.5; p_{25}: 2; p_{75}: 16; $P = .0333$) (Figure 7).

Only 2 sick leave days were taken by the entire study population. Likewise, no patient required emergency visits during the study due to UCOL.

Basophil activation test

Greater than 15% CD63 expression was considered positive. None of the patients' serum samples activated normal basophils. The activation value obtained was 0.75% (Q_{25}: 0.4; Q_{75}: 2.78) CD63 activation.

Time to the appearance and disappearance of skin lesions

During the blinded period, both intervention groups showed increases in the time elapsed between the start of exercise and the appearance of skin lesions and decreases in the time to the disappearance of the skin lesions; however, we did not observe a significant difference when comparing these times before treatment and after receiving 4 or 8 doses of omalizumab.

Rescue medication

Fourteen patients (63.3%) required rescue medication with antihistamines and/or corticosteroids. The median (minimum, maximum) number of patients receiving antihistamine prescriptions in the placebo and treatment groups was 1 (0, 15) and 1 (0, 5), respectively. The number of patients receiving 3 or more prescriptions of antihistamines was 4 (44.4%) in the placebo group and 2 (15.4%) in the treatment group, although this apparent difference was not large enough to demonstrate a statistically significant association between a group during the blinded period and the need for rescue medication ($P = .178$). Two patients received corticosteroids (1 patient in the placebo group received 2 prescriptions, and 1 patient in the treatment group received 3 prescriptions).

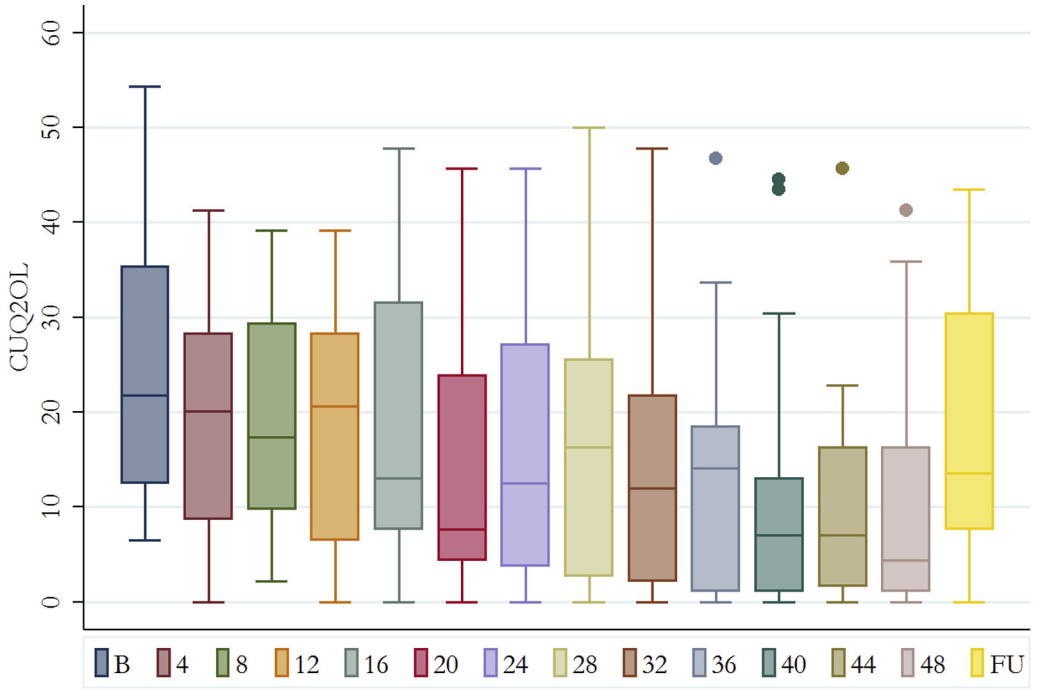

FIGURE 5. CU2-QoL questionnaire score by weeks in the total study population. *B*, Basal visit; *FU*, Follow-up visit (week 60, after 3 months of the last omalizumab dose). The line inside the box represents the median value. The upper and lower ends of the box represent the 75th and 25th percentiles, respectively. Circles represent values outside the box-whisker. A progressive decrease (improvement) in the CU2-QoL questionnaire score over time was observed. After stopping the intervention, a rise (worsening) in the CU2-QoL questionnaire score at follow-up visit (week 60) was observed. Data represent results for all placebo and active patients combined (n = 22).

Safety

There were 13 adverse events (AEs), 4 in the placebo group and 9 in the treatment arm. Eleven AEs were not related to the study, and 2 were unlikely to be related. Eight AEs were classified as mild, 4 were moderate, and 1 was classified as severe because the patient required hospitalization due to a scheduled surgery. None of the AEs caused withdrawal from the study, and all of them were resolved. In Table E1 in this article's Online Repository at www.jaci-inpractice.org, we include the AEs in the list of events.

DISCUSSION

In this study, we observed an overall negative challenge rate of the exercise challenge test of 31.3% in patients with UCOL who did not respond to a double dose of antihistamines after receiving omalizumab treatment for 8 months (placebo group) or 12 months (active intervention group). This negative challenge rate was significantly higher than the expected rate of 11%.[24] We did not find statistically significant differences between the placebo and active intervention groups at the end of the blinded period (first 4 months of the study). However, we observed a significant progressive improvement along time starting from the fourth dose. We also noted improvements in the daily symptoms and quality-of-life scores after active intervention compared with the baseline values. Omalizumab treatment was well tolerated and presented a good safety profile.

In contrast to what was observed in the chronic spontaneous urticaria clinical trials,[29] where a number of patients showed a very fast response, in our study, the response was slower and progressive. This is also in contrast with the very recent publication[19] on omalizumab in real life in patients with UCOL, where a 6-week response is reported. However, it is difficult to compare with our results because the study is a retrospective nonplacebo comparison analysis of 16 patients from which 7 had other concomitants types of urticaria including chronic spontaneous urticaria, patients received different doses, and it is not clear whether an exercise challenge test was performed at each visit. This fact may support in theory the role of IgE in the pathogenesis of the disease,[5,7,8] with similar timing of omalizumab-induced reductions in allergen skin mast cell response,[30] mast cell skin receptors, or basophil function.[31] Consequently, the mechanism of action of omalizumab in UCOL could be the sequestering of specific IgE against serum or sweat proteins rather than direct action on the cells. In the future, measuring specific IgE against known antigens could serve as a good predictive marker of the response to omalizumab. It would also be very interesting to profile omalizumab response according to different subtypes of UCOL.[32] Thus, we want to highlight the importance of maintaining omalizumab treatment for more than 4 months to start assessing improvement.

As was the case in chronic spontaneous urticaria, we observed a reappearance of symptoms in the 12-week posttreatment follow-up visit.

Statistically significant differences between the placebo and treatment groups in main outcomes were not demonstrated during the blinded period (4 months). Exploring the impact of a longer blinded period and a larger sample size may be warranted. The fact that the placebo group had a significantly faster time to hive disappearance at baseline could also be relevant to such pattern of response. We should also take into account that as is the case in all urticarias, there are spontaneous remissions.

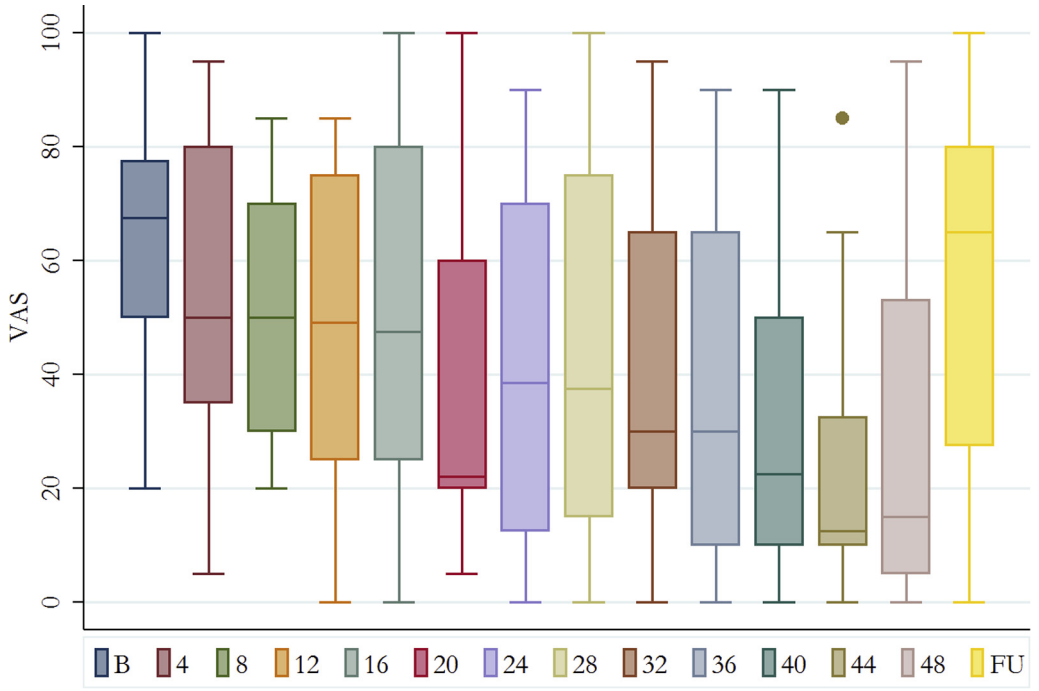

FIGURE 6. The VAS score by weeks in the entire study population. *B*, Basal visit; *FU*, Follow-up visit (week 60, after 3 months of the last omalizumab dose). The line inside the box represents the median value. The upper and lower ends of the box represent the 75th and 25th percentiles, respectively. Circles represent values outside the box-whisker. A progressive decrease in the VAS score over time was observed. After stopping the intervention, a rise in the VAS score at follow-up visit (week 60) was observed. Data represent results for all placebo and active patients combined (n = 22).

There is a need of a treatment option for those patients who are unresponsive to antihistamines. The need is even more urgent for patients with UCOL for whom no treatment apart from antihistamines exists. To date, there have been no randomized controlled clinical trials on omalizumab for UCOL. Moreover, the data published are all based on case reviews, without assessing the response to treatment by exercise challenge test, except in 1 case, or by symptom score. The data previously published are mainly based on subjective self-reported symptoms. The first case report of a complete response in 1 patient[17] observed a complete response starting in week 5, with a negative challenge of the exercise challenge test. Furthermore, a significant response in a patient was also reported on the basis of quality-of-life questionnaire and self-reported exercise tolerance[33]; both of the aforementioned patients received 300 mg of omalizumab monthly. Other publication reported a lack of response to omalizumab[20] in a patient receiving 300 mg every 2 weeks. However, that patient had an IgE level of 1523 kU/mL and might have needed a higher dose of omalizumab. The next isolated case[15] also reported a significant symptom response to 300 mg of omalizumab administered every 7 weeks, with a significant response starting in the ninth week of treatment and a complete response at week 21, which agree with our observation of a slow response pattern. Our response rate was 31.3%, which was similar to that reported by Metz et al[34] in a retrospective analysis, wherein they describe a complete response in 5 of 8 patients and a significant response in 1 patient. However, no description of the outcome measures was provided, and the patients received different doses of omalizumab; 4 patients started with 150 mg, 2 had their doses increased to 300 mg, 1 received 450 mg, and 1 patient received 300 mg monthly from the beginning. A retrospective case review[35] reported a response in 3 of 4 patients reviewed, with few data available on the response assessment. The latest study published to date[19] raises a very interesting point, which is that they obtained a positive response in those nonrespondent patients by raising doses. Studies with higher doses in nonresponders should be performed.

Another important contribution of our study is the clinical tool, the *UCOL score*, that we designed. It is not always feasible or practical to perform an exercise challenge test in the daily routine clinical setting; however, severity and response to treatment should be objectively measured. There is a reliable and validated clinical tool, the Urticaria Activity Score summed over 7 days,[36] to measure spontaneous chronic urticaria symptom severity; however, it is not applicable to UCOL because Urticaria Activity Score summed over 7 days registers the number of hives and itch severity over the last 24 hours and over 7 days. Moreover, our tool not only measures skin symptoms but also reflects the impact of the disease on daily activities and serves to monitor treatment response in real life. Our tool seems to be a sensitive instrument for monitoring UCOL and the patient response to treatment. However, it is yet to be validated against the exercise test, and subsequently with a larger sample size. It should be validated as a tool to measure antihistamine response. Once validated, it would also be interesting to establish the threshold for deciding when a patient could be classified as unresponsive to any given treatment. This is especially important when an expensive treatment is an option, and the physician has to decide when a patient is unresponsive to antihistamines.

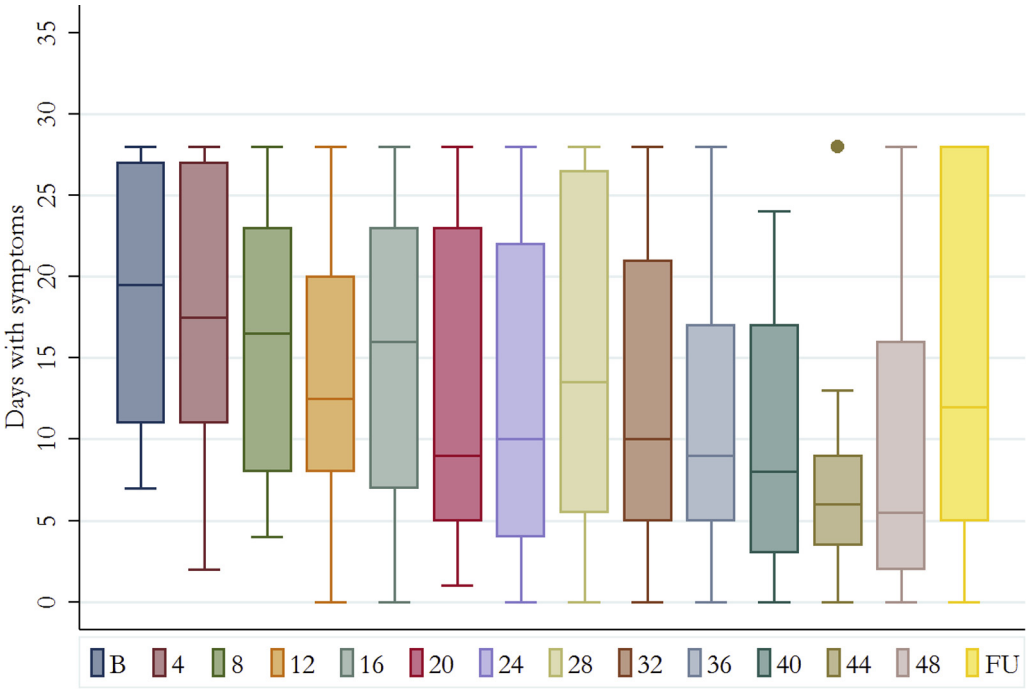

FIGURE 7. Days with symptoms by weeks in the entire study population. *B*, Basal visit; *FU*, Follow-up visit (week 60, after 3 months of the last omalizumab dose). The line inside the box represents the median value. The upper and lower ends of the box represent the 75th and 25th percentiles, respectively. Circles represent values outside the box-whisker. A progressive decrease in days with symptoms over time was observed. After stopping the intervention, a rise in the days with symptoms at follow-up visit (week 60) was observed. Data represent results for all placebo and active patients combined (n = 22).

We used a 300-mg omalizumab dose because this dose showed better outcomes in all types of urticaria in previous studies.[29,37,38] Future dose-response studies with UCOL should be performed. Moreover, as was the case for chronic spontaneous urticaria, real-life studies would provide better insights.

UCOL, as is the case for other inducible urticarias, is responsive to high doses of antihistamines. In our study, 6 of 29 initially included patients achieved control of the symptoms with double doses of cetirizine. In the only study published[14] on this topic, with 11 patients, 20 mg of cetirizine was able to partially control UCOL symptoms. As is the case for chronic spontaneous urticaria, omalizumab may be useful as a second-line therapy for those patients whose symptoms are not controlled with high doses of antihistamines.

In spite of the moderate to severe intensity of their symptoms, the patients suffering from UCOL did not take sick leave days or attend emergency departments, suggesting that they are accustomed to their condition and have adapted their daily life to its limitations. Likewise, there is a lack of awareness of this type of inducible urticaria; consequently, this inducible urticaria might be overlooked.

As expected, none of the patients' serum samples were able to activate normal basophils; in chronic spontaneous urticaria, this autoimmune property is found in 40% of patients[39]; this finding reinforces the concept that different pathophysiological pathways underlie various types of inducible urticarias.

Sweat allergy has been postulated as a pathomechanism factor for UCOL.[5-8] This fact was challenged because of the high frequency of anhidrosis in patients with UCOL. This apparent paradox was explained by poral occlusion causing sweat leaking and subsequent reaction.[40] In our study, as it is depicted in Table II, we did not have any patients with hypo- or anhidrosis and did not find any difference in the time to the appearance of sweat with the response to omalizumab. This fact makes it less likely to have a sweat allergen mechanism.

Statistically significant differences were not observed between the placebo and active intervention groups during the blinded period (first 4 months of the study). Despite what is a negative result at 16 weeks, the data are useful to present in the literature as a real-world experience of omalizumab therapy in UCOL. It suggests a slow onset of effect, contrary to several retrospective experiences, or open-label trials. The use of a larger blinded period (>4 months) may be warranted for the treatment impact evaluation in future studies. Overall, we found a progressive negative challenge of the exercise challenge test, with a 31.3% negative challenge rate at week 48, with significant improvements in the UCOL score, daily symptoms, and quality of life. In addition, on ending treatment, the symptoms tended to reappear. Our study could contribute to the knowledge of efficacy of omalizumab in patients suffering from UCOL not responding to double doses of antihistamines and for whom no other treatment is at hand, and to improve UCOL patients' daily life. In conclusion, this randomized mixed double-blind and open-label placebo-controlled trial showed evidence of the safety and potential efficacy of omalizumab in patients with UCOL. Notably, the response in UCOL is slower than that observed in chronic spontaneous urticaria.

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TABLE E1. List of Adverse Events

Adverse Event	No. of patients
Headache	2
Pharyngitis	2
Metallic flavor	1
Sciatica	1
Low back pain	1
Restless legs syndrome	1
Paraphimosis	1
Phimosis surgery	1
Cold with bronchial hyperreactivity	1
Food poisoning (seafood)	1
Ankle sprain	1