Clínica Universidad de Navarra

UNIDAD CENTRAL DE ENSAYOS CLÍNICOS

INFORME RESUMEN DEL ESTUDIO CLÍNICO

TITULO

Estudio multicéntrico aleatorizado, doble ciego, controlado con placebo, con grupos paralelos, para evaluar la eficacia y seguridad de Omalizumab (Xolair ®) en una nueva indicación: urticaria colinérgica

Promotor: Clínica Universidad de Navarra

Número EUDRACT: 2013-002770-43

Código del protocolo: CUN-OMAL-UCOL

Fecha de finalización del ensayo clínico: 20-06-2017

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INFORMACIÓN DEL ENSAYO CLÍNICO

IDENTIFICACIÓN DEL ESTUDIO

TÍTULO: Estudio multicéntrico aleatorizado, doble ciego, controlado con placebo, con grupos paralelos, para evaluar la eficacia y seguridad de omalizumab (xolair ®) en una nueva indicación: urticaria colinérgica

Código del promotor: CUN-OMAL-UCOL

Número EUDRACT: 2013-002770-43

Otros identificadores, si procede: ClinicalTrials.gov Identifier: NCT02012387

IDENTIFICACIÓN DEL PROMOTOR

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DATOS PEDIÁTRICOS REGLAMENTARIOS

El ensayo clínico NO forma parte de un plan de investigación pediátrica.

CENTROS DE REALIZACIÓN DEL ESTUDIO E INVESTIGADORES PRINCIPALES

Clínica Universidad de Navarra. Departamento

Investigador Principal: Marta Ferrer Puga

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FASE DE ANÁLISIS DE RESULTADOS

Fecha de estudio: Fecha de inicio del estudio: 20 Diciembre 2013

Fecha en la que el último paciente completó el estudio: 20-06-2017

Fechas de análisis de resultados:

Análisis intermedio: No ha habido análisis intermedio

Análisis final: 18 abril 2018

No quedan resultados por analizar.

INFORMACIÓN GENERAL SOBRE EL ENSAYO CLÍNICO

Adjuntamos a continuación información sobre los resultados del ensayo:

Introduction

Cholinergic urticaria consists on the appearance of itching, pin-point sized wheals induced by an active (e.g. exercise) or passive (e.g. hot bath) increase in core body temperature that fade away upon cooling off the body1. It is highly disabling2 with a great impact on patients' daily life activities and work performance. Each patient has his or her threshold, which could be triggered by minimal stimuli as climbing stairs, entering a heated building from street chilly temperature.

It starts at a young age. Most patients, in contrast with other inducible urticarias, that have times of relapse or less intensity, suffer the condition along their life. Consequently, they get used to the disease, avoiding those activities that trigger the urticaria and changing daily life habits without seeking medical treatment.

The etiology and pathogenesis of hive formation remains unknown3, though it is recognized mast cells are clearly involved. It has been hypothesized that through interaction between acetylcholine and mast cells and due to hypersensitivity to sweat antigens. However, there are reports informing

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that among patients with anhidrosis and/or hypohidrosis is frequent to present cholinergic urticaria4. As it is the case for other inducible urticarias, desensitization or tolerance could be induced in cholinergic urticaria. There are two prospective prevalence studies, the first prospective study5 in 499 high school and university students by questionnaire and some exercise challenge test found 11.2% prevalence. The second study in an younger Indian population6 calculates a 4.16% prevalence. In both cases, the condition was mostly mild

Despite the high morbidity of this disease and the impact on quality of life, there is no available treatment. Antihistamines that usually control other types of urticaria could only partially alleviate cholinergic urticaria. There is only one paper that shows efficacy doubling the dose of cetirizine above the recommended dosage7.

Omalizumab, in small isolated case reports, has shown to be effective in control cholinergic urticaria not respondent to conventional therapies at maximum or off-label doses8-12. A negative response was also reported13. Our rationale for the utilization in this type of urticaria is that Omalizumab exerts an inhibitory action on mast cell activation14, 15, as it has been demonstrated in other inducible urticarias16 as dermographism12 and cold urticaria17. We hypothesize that Omalizumab is able to revert the basophil or mast cell activation present in those urticaria types14, 15.

For that reason, we performed a Multicenter Randomized, Double-blind, Placebo-controlled Parallel Clinical Trial to Assess Efficacy and Safety of Omalizumab (Xolair®) in patients suffering from cholinergic urticaria non respondent to double dose of antihistamines.

Material and Methods

Study population

We performed a multicenter randomized, double-blind, placebo-controlled Parallel Clinical Trial clinical trial (ClinicalTrials.gov Identifier: NCT02012387). It was performed in 7 sites distributed along Spain: Clínica Universidad de Navarra and Complejo Hospitalario de Navarra (Pamplona), Hospital Clinic, Hospital Vall d'Hebron (Barcelona), Hospital Universitari Joan XXIII (Tarragona), Hospital General Universitario Gregorio Marañón (Madrid), and Hospital Universitario Central de Asturias (Oviedo).

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The study was approved by the Navarra State Ethic Commite (Ref # 51/2013) and The Spanish Drug Agency (AEMPS) (Eudra CT#2013-002770-43). Each patient signed a written consent.

Patients with a clinical diagnosis of cholinergic urticaria by history and a positive exercise challenge test were treated with double license dose of cetirizine (20 mg) for two weeks and the exercise challenge test was repeated. If the test was again positive, they were randomized to start the study. All patients presented hives upon exercise and or passive warming. None of the patients suffered from exercise induced anaphylaxis, respiratory, gastrointestinal or cardiovascular symptoms while presenting hives. Apart from intense exercise that triggered hives in all patients, 12 patients suffered urticaria upon minimal activity (climbing stairs, briskly walking). All patients reported symptoms upon passive warming, 6 also with spicy foods, and stress. Demographics and clinical features are included in Table 1. We did not find any statistical difference between the placebo and active treatment group. We include demographic and clinical features by intervention group in Table 2.

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Table 1. Demographics and clinical features of the sample

	TOTAL
N	22
Age (years)	34.1 (15.0)
Male, n (%)	16 (72.7)
Race, caucasic, n (%)	22 (100)
Tobacco, n (%)	
Smoker	5 (22.73)
Non smoker	15 (68.18)
Ex-smoker (>1 year)	1 (4.55)
NA	1 (4.55)
Alcohol, n (%)	
Non consumer	7 (31.8)
Occasionally	14 (63.6)
NA	1 (4.55)
Diabetes mellitus, n (%)	
No	19 (86.4)
Missing data	3 (13.6)
Hypertension, n (%)	
No	19 (86.4)

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Missing data	3 (13.6)
Asthma, n (%)	
No	14 (63.6)
Yes	5 (22.7)
Missing data	3 (13.6)
Other conditions, n (%)	16 (72.7)
Cholinergic urticarial history	
Time from diagnosis (months), Median (p25, p75)	22.0 (2.2 - 39.1)
Symptoms trigger, n (%)	
Intense exercise and sweating	11 (50)
Moderate activity (briskly walking, climbing stairs)	12 (54.6)
Mild activity, elevated background temperature	18 (81.8)
Other	6 (27.3)
Lesions localization, n (%)	
Face and neck	15 (68.2)
Trunk	22 (100)
Extremities	20 (90.9)
Other	0 (0)
Frequency of onset, n (%)	
Daily	17 (77.3)
Other [See Table 1.C (supplementary)]	5 (22.7)

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Time to disappear, n (%)	
20-60 minutes	15 (68.2)
1-3 hours	6 (27.3)
>3 hours	1 (4.6)
Associated itching, n (%)	22 (100)
Other accompanying symptoms, n (%)	
Epiphora	1 (4.6)
Diarrhea	0 (0)
Wheezes	0 (0)
Dizziness	0 (0)
Hyper salivation	0 (0)
Shortness of breath	0 (0)
Nausea	0 (0)
Other	0 (0)
Previous UCOL treatment, n (%)	
Cold application on the skin	5 (22.7)
Antihistamines	22 (100)
Corticosteroids	6 (27.3)
Other	1 (4.6)
Vital signs	
Systolic BP	126 (13.7)

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Diastolic BP	73.1 (8.3)
Pulse	79.7 (18)
BMI (kg/m^2)	26.3 (4.4)
Exercise challenge test (selection visit)	
Time to start sweating (minutes)	4.9 (3)
Localization, n (%)	
Face and neck	13 (59.1)
Trunk	20 (90.9)
Extremities	16 (72.7)
No skin lesions	1 (4.6)
Time to break up in hives(minutes), N=19	5.5 (4)
Time to hives disappearance (minutes), N=18	84.2 (89.7)
Total IgE(kU/l)	294.7 (347.5)

BMI: Body Mass Index, BP: Blood pressure, NA: Not Available. Data are presented as mean (standard deviation), unless otherwise stated.

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Table 2. Demographic and clinical features by intervention group.

	Placebo	Treatment	P value
N	9	13	
Age (years)	32.3 (13.8)	35.4 (16.2)	0.641
Male, n (%)	6 (66.7)	10 (76.9)	0.655
Race, caucasic, n (%)	9 (100)	13 (100)	-
Tobacco, n (%)			
Smoker	3 (33.3)	2 (15.4)	0.375
Non smoker	5 (55.6)	10 (76.9)	
Ex-smoker (>1 year)	0 (0)	1 (7.7)	
NA	1 (11.1)	0 (0)	
Alcohol, n (%)			
Non consumer	4 (44.4)	3 (23.1)	0.235
Occasionally	4 (44.4)	10 (76.9)	
NA	1 (11.1)	0 (0)	
Diabetes mellitus, n (%)			
No	8 (88.9)	11 (84.6)	0.999
Missing data	1 (11.1)	2 (15.4)	
Hypertension, n (%)			
No	8 (88.9)	11 (84.6)	0.999
Missing data	1 (11.1)	2 (15.4)	

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Asthma, n (%)			
No	5 (55.6)	9 (69.2)	0.819
Yes	3 (33.3)	2 (15.4)	
Missing data	1 (11.1)	2 (15.4)	
Other conditions, n (%)	6 (66.7)	10 (76.9)	0.655
Cholinergic urticarial history			
Time from diagnosis (months), Median (p25, p75)	22.5 (1.1 - 119)	12.4 (3.5 – 36.4)	0.483
Symptoms trigger, n (%)			
Intense exercise and sweating	5 (55.6)	6 (46.2)	0.999
Moderate activity (briskly walking, climbing stairs)	5 (55.6)	7 (53.9)	0.999
Mild activity, elevated background temperature	8 (88.9)	10 (76.9)	0.616
Other	2 (22.2)	4 (30.8)	0.999
Lesions localization, n (%)			
Face and neck	6 (66.7)	9 (69.2)	0.999
Trunk	9 (100)	13 (100)	-
Extremities	8 (88.9)	12 (92.3)	0.999
Other	0 (0)	0 (0)	-
Frequency of onset, n (%)			
Daily	8 (88.9)	9 (69.2)	0.360

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Other	1 (11.1)	4 (30.8)	
Time to disappear, n (%)			
20-60 minutes	8 (88.9)	7 (53.9)	0.242
1-3 hours	1 (11.1)	5 (38.5)	
>3 hours	0 (0)	1 (7.7)	
Associated itching, n (%)	9 (100)	13 (100)	-
Other accompanying symptoms, n (%)			
Epiphora	0 (0)	1 (7.7)	-
Diarrhea	0 (0)	0 (0)	-
Wheezes	0 (0)	0 (0)	-
Dizziness	0 (0)	0 (0)	-
Hyper salivation	0 (0)	0 (0)	-
Shortness of breath	0 (0)	0 (0)	-
Nausea	0 (0)	0 (0)	-
Other	0 (0)	0 (0)	-
Previous UCOL treatments, n (%)			
Cold application on the skin	2 (22.2)	3 (23.1)	0.999
Antihistamines	9 (100)	13 (100)	-
Corticosteroids	3 (33.3)	3 (23.1)	0.655
Other	1 (11.1)	0 (0)	0.409
Vital signs			

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Systolic BP	121 (16)	130 (10)	0.130
Diastolic BP	69 (9)	76 (7)	0.070
Pulse	79 (19)	80 (18)	0.936
BMI (kg/m^2)	27 (5)	25 (4)	0.318
Exercise challenge test (selection visit)			
Time to start sweating (minutes)	5.4 (3.9)	4.4 (1.8)	0.256
Localization, n (%)			
Face and neck	4 (44.4)	9 (69.2)	0.384
Trunk	8 (88.9)	12 (92.3)	0.999
Extremities	6 (66.7)	10 (76.9)	0.655
No skin lesions	1 (11.1)	0 (0)	0.409
Time to break up in hives(minutes), N=19	5.5 (4.3)	5.5 (4.0)	0.999
Time to hives disappearance (minutes), N=18	31.9 (16.7)	126 (103)	0.004
Total IgE(kU/l)	283.3 (335.1)	302.5 (369.2)	0.973

BMI: Body Mass Index, BP: Blood pressure, NA: Not Available. Data are presented as mean (standard deviation), unless otherwise stated.

After a 2-week screening period, and repeated exercise challenge test. If the test was positive, patients were randomized to placebo or active treatment for 12 weeks receiving a monthly dose during the blinded period. From week 16th, all patients received omalizumab and performed

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exercise challenge test in each visit. We followed up patients three months after the last dose performing an exercise challenge test. We include a design scheme of the study in Figure 1.

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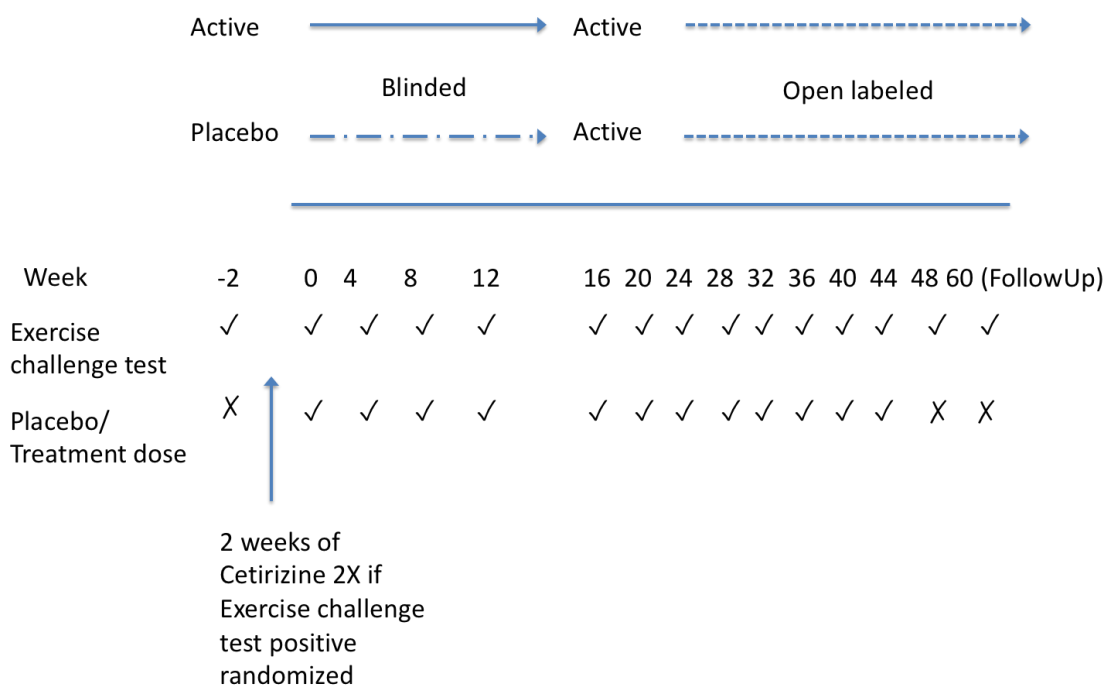
Figure 1. Study design



A total of 29 patients were recruited. After receiving 20 mg of cetirizine in the pre-screening visit, 6 patients were negative in the exercise challenge test and were excluded, and 23 patients were randomized. One patient dropped out after randomization, before receiving the first placebo dose. Finally, 22 randomized patients received the corresponding intervention. The mean age of patients was 34.1 years (SD:15); 16 were men and 7 were women. During the blinded period of the study, 9 patients received placebo and 13 patients received omalizumab. During the open labeled period of the study, all patients received omalizumab from the 4th visit (after basal visit) at week 16th. Figure 2 shows a Flow chart of the study.

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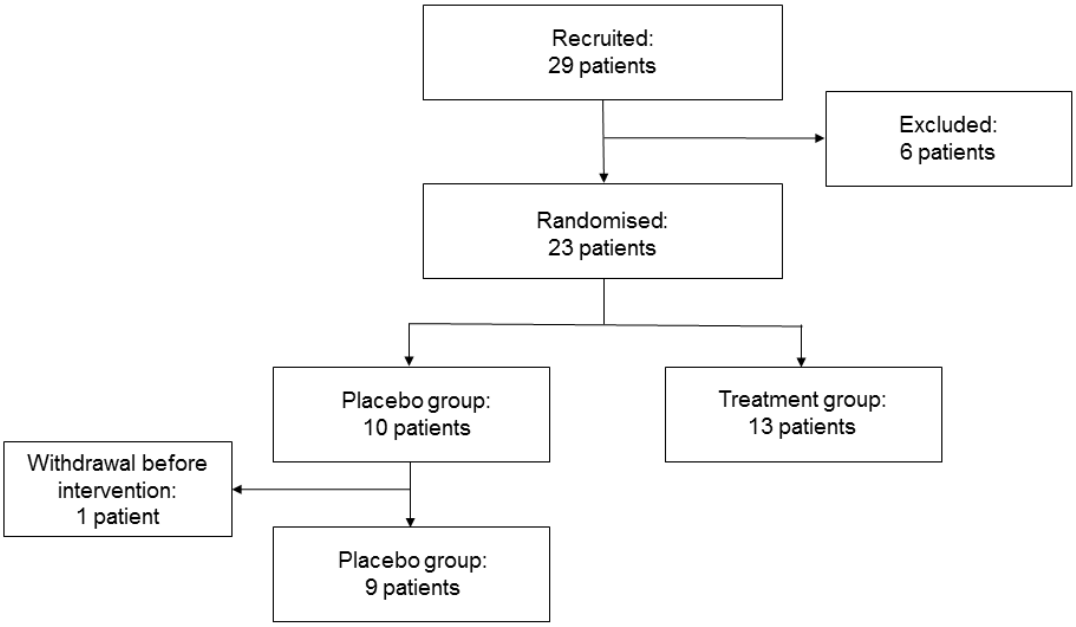
Figure 2. Flowchart of the clinical trial.



Non-respondent to supra therapeutic doses of antihistamines (defined as 2x the maximal dose included in the drug labeling of cetirizine, 20 mg) were included. We excluded patients suffering from chronic spontaneous urticaria associated with cholinergic urticaria or patients suffering from other inducible urticarias. Patients with pruritus related to other skin condition, any systemic disease that hampers follow up or interpretation of data, patients having received omalizumab treatment within the previous 12 months were excluded. Patients with any exclusion criteria included in the drug labeling or other conditions that do not allow the accomplishment of the clinical trial requisites, such as the abuse of drugs or alcohol were also excluded.

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Primary and secondary outcome measures:

Our primary endpoint was the negativization of the exercise challenge test. We performed the exercise challenge test following the European Guidelines18 for cholinergic urticaria. All centers followed the same center standardized protocol. The patient exercised in treadmill running to the point of sweating and following for 15 more minutes, wearing warm clothing in a warm room. We registered time of skin lesions appearance, disappearance and skin lesions extension as well as time to sweat.

The test was considered positive if exercise challenge leads to the typical rash over 10 minutes. Challenge exercise test was performed subsequently each 4 week up to 12 months and at the follow up visit after three months of the last dose.

We included as secondary Outcome Measures: Quality of life, evaluated through the Spanish validated version of Chronic Urticaria quality of life CUQ2oL 19, each patient filled up the questionnaire upon each visit. Symptoms score, Visual Analogue Score (VAS), patient's diary symptoms, and use of rescue medication. Additional measures of efficacy were as well number of dropouts in each treatment group, sick leave days due of cholinergic urticaria and Emergency Department visits. Safety was assessed by means of recording and evaluation of adverse events throughout the study.

Daily symptoms score

We elaborated a daily symptom score (UCOL Score) that combines the stimuli that elicit the reaction and skin extension with a minimum of 0 and a maximum of 6 score.

Table 3. UCOL score (0-6 points)

Stimuli	Extension

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	Score		Score
None	0	No skin lesions	0
Intense exercise with profuse sweating	1	Isolated hives in upper trunk	1
Moderate activity: briskly waking, climbing stairs	2	Hives in trunk and arms or legs	2
Minimal activity, warm external temperature	3	Hives in trunk, arms, legs, neck, face	3

Statistics

All analyses were carried out on the basis of the intention-to-treat principle. We calculated means (and standard deviations) and frequencies of baseline demographic and clinical characteristics variables for the whole sample and separately by study arm. Differences between interventions groups in quantitative outcomes were tested using independent samples t-tests and changes between means of quantitative outcomes from baseline to follow-up visits were tested using paired samples t-tests. Differences in the distribution of categorical variables were tested using the chi-square test or the Fisher's exact test. The correlation between negativization outcome and visit was quantified using the Spearman's rank correlation coefficient. Statistical significance was defined using a 2-sided α level of 0.05. All analyses were performed using IBM SPSS Statistics 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) and Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

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Results

Exercise challenge test

All patients (including the placebo group) received omalizumab during the open labeled period. The treatment group received omalizumab during the blinded and the open labeled periods (from baseline), whereas the placebo group received omalizumab only during the open labeled period (from visit 4th, week 16th). We observed a significant correlation between negativization outcomes and visit (Spearman Rho: 0,65; p=0,004). We found an average negativization increase of 2.9 percentage points (IC 95%: 1,5; 4,2) per visit. The highest values of negativization were observed at Visit 5th (week 20th), 38.1%, and at Visit 11th (week 44th), 37.5% (Figure 3).

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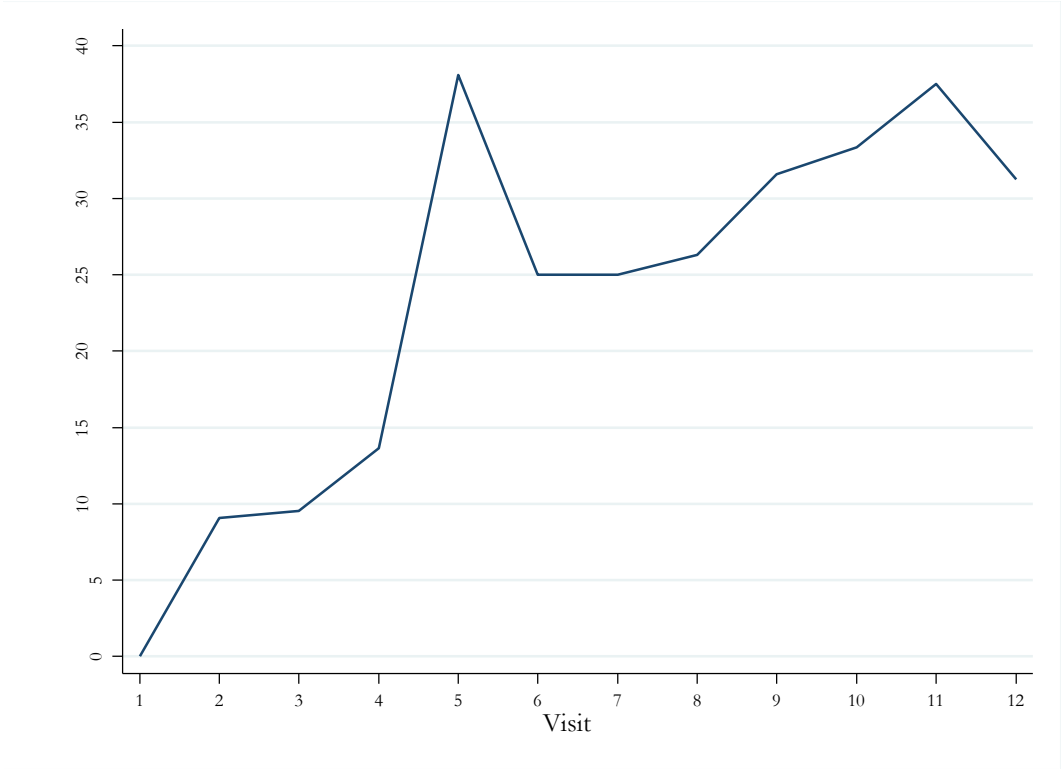
Figure 3. Negativization of exercise challenge test along study visits.



UCOL Score

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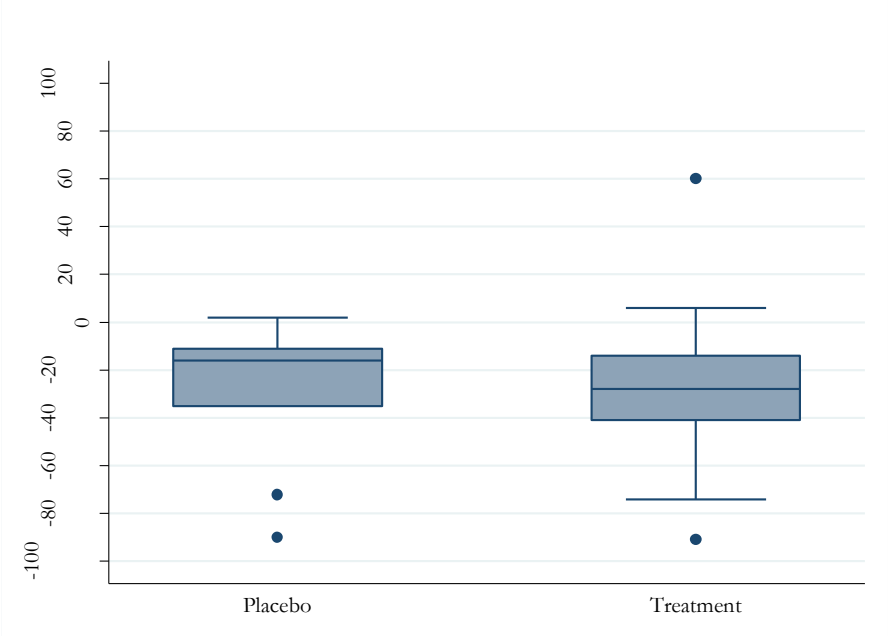
During the blinded period, both intervention groups showed a decrease in the UCOL score. This decrease was higher in the treatment group compared with the placebo group, although it was not statistically significant (p=0.825). The median UCOL decrease for the placebo group was -16 (p_{25}:-35; p_{75}:-11) and the median decrease for the treatment group was -28 (p_{25}:-41; p_{75}:-14) (Figure 4A).

When comparing UCOL score before treatment and after receiving 4 doses of omalizumab, we observed a statistically significant improvement (p=0.0015). When comparing UCOL score before treatment and after receiving 8 doses of omalizumab, we also observed a statistically significant improvement (p=0.0005). After finishing treatment with Omalizumab, there was a statistically significant increase in UCOL score in the follow-up visit (week 60th) compared with the last visit that evaluated the effect of the last dose of Omalizumab (visit 12, week 48th). (Figure 4B)

Figure 4.A. Change in UCOL score according to intervention group.



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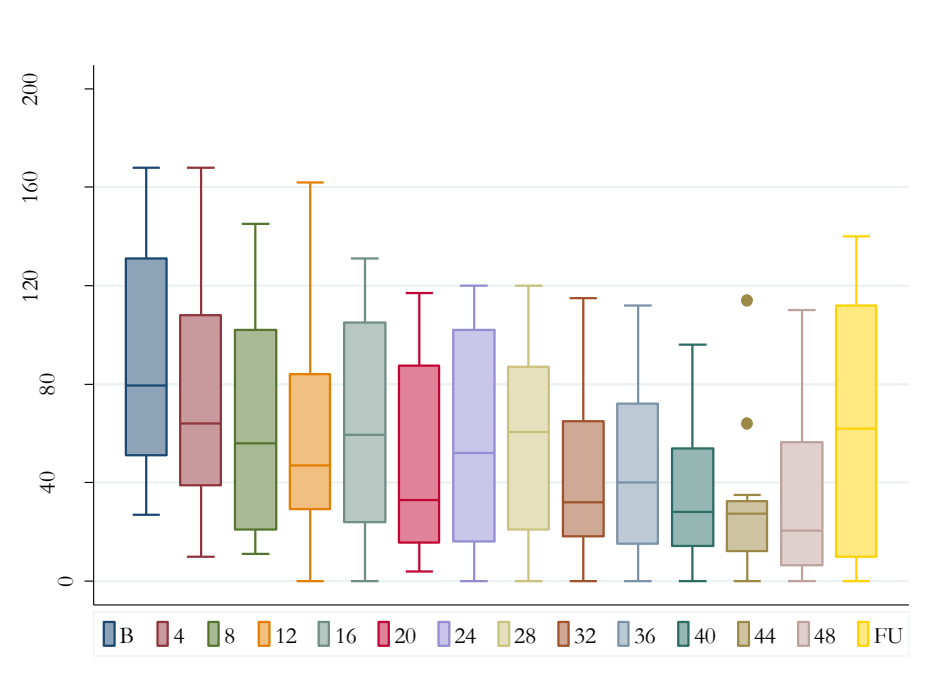
The line inside the box represents the median value. The upper and lower ends of the box represent the percentiles 75 and 25 values, respectively.

Figure 4.B. UCOL score by visits (weeks) in the total study sample.



B: Basal visit. FU: Follow-up visit (after three 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 percentiles 75 and 25 values, respectively.

Quality of life (CU2-QoL)

During the blinded period, both intervention groups showed a decrease in the CU2-QoL score (which indicates an improvement in quality of life for both groups). This decrease (improvement) was higher in the treatment group compared with the placebo group, although it was not statistically significant (p=0.7176). The median CU2-QoL score decrease

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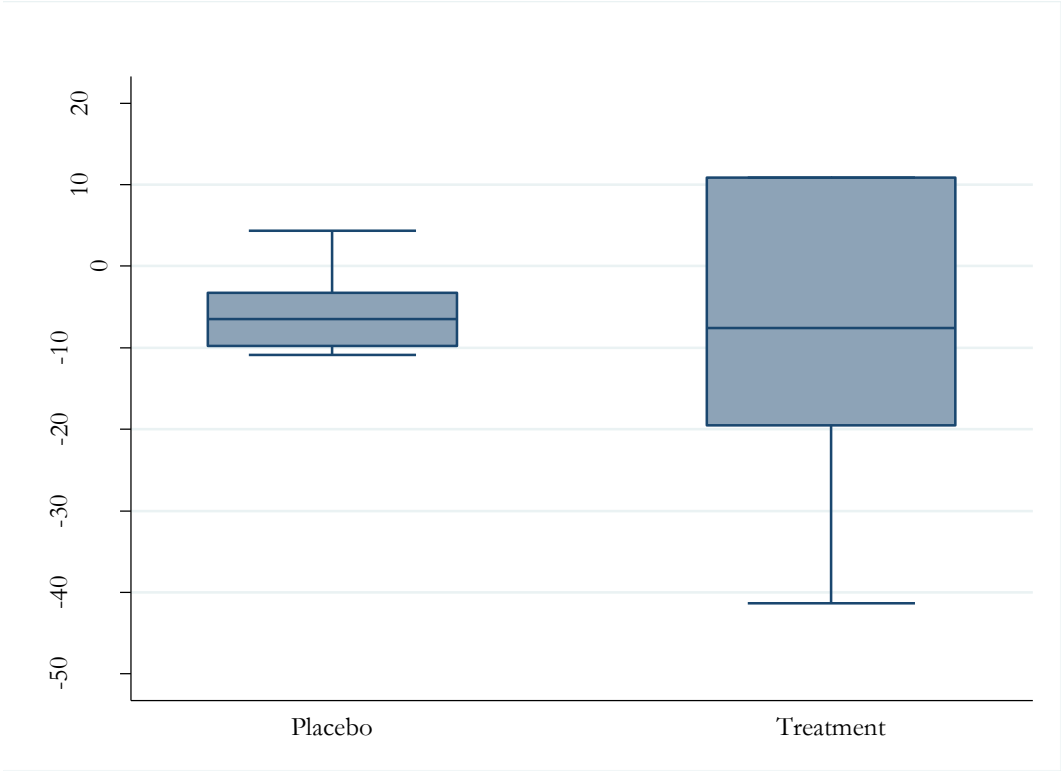
for the placebo group was -6.5 (p_{25}: -9.8; p_{75}: -3.3) and the median decrease for the treatment group was -7.6 (p_{25}: -19.6; p_{75}: 10.9) (Figure 5A).

When comparing CU2-QoL score before treatment and after receiving 4 doses of omalizumab, we observed a slight improvement that was not statistically significant (p=0.1069). When comparing CU2-QoL score before treatment and after receiving 8 doses of omalizumab, we observed a statistically significant improvement (p=0.0105)

After finishing treatment with Omalizumab, there was a statistically significant increase in CU2-QoL score in the follow-up visit (week 60th) compared with the last visit that evaluated the effect of the last dose of Omalizumab (visit 12, week 48th). (Figure 5B).

Figure 5.A. Change in CU2-QoL score according to intervention group.



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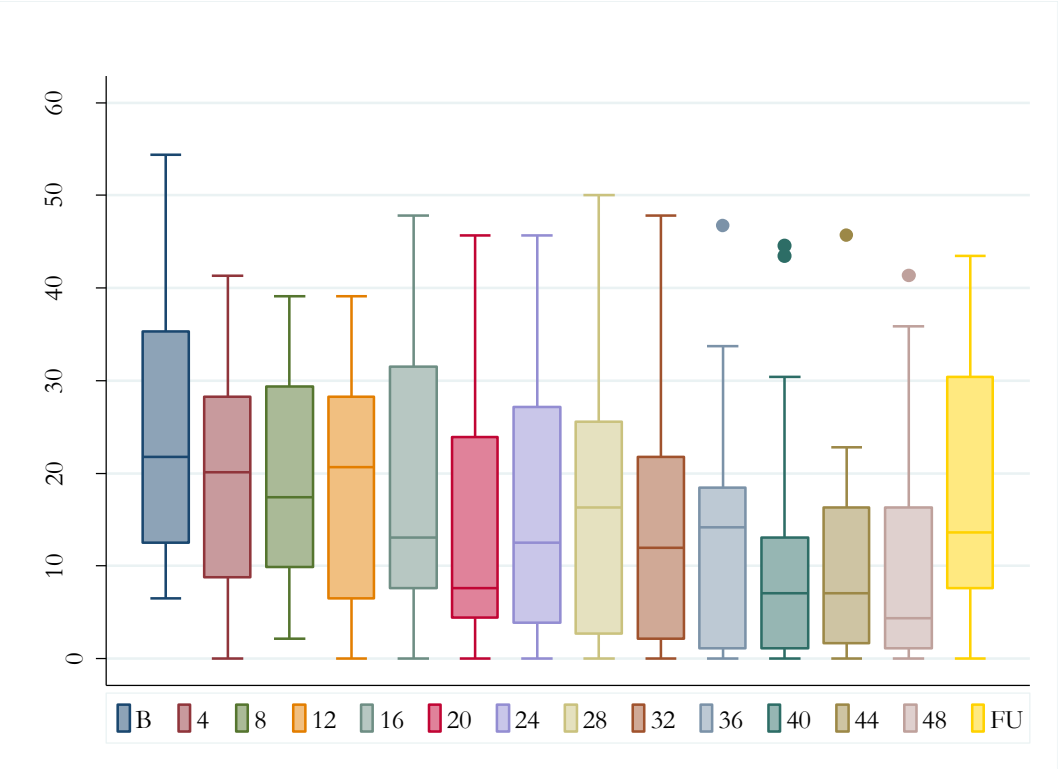
The line inside the box represents the median value. The upper and lower ends of the box represent the percentiles 75 and 25 values, respectively.

Figure 5.B. CU2-QoL score by visits (weeks) in the total study sample.



B: Basal visit. FU: Follow-up visit (after three 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 percentiles 75 and 25 values, respectively.

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Visual Analogue Score (VAS)

During the blinded period, both intervention groups showed a similar decrease in the VAS score (p=0.9555). The median VAS decrease for the placebo group was -10 (p_{25}: -40; p_{75}: -5) and the median decrease for the treatment group was -10 (p_{25}: -50; p_{75}: 0) (Figure 6A). When comparing VAS score before treatment and after receiving 4 doses of omalizumab, we observed a statistically significant improvement (p=0.0108). When comparing VAS score before treatment and after receiving 8 doses of omalizumab, we also observed a statistically significant improvement (p=0.0008). After finishing treatment with Omalizumab, there was a statistically significant increase in VAS score in the follow-up visit (week 60th) compared with the last visit that evaluated the effect of the last dose of Omalizumab (visit 12, week 48th). (Figure 6B).

Figure 6.A. Change in VAS score according to intervention group.

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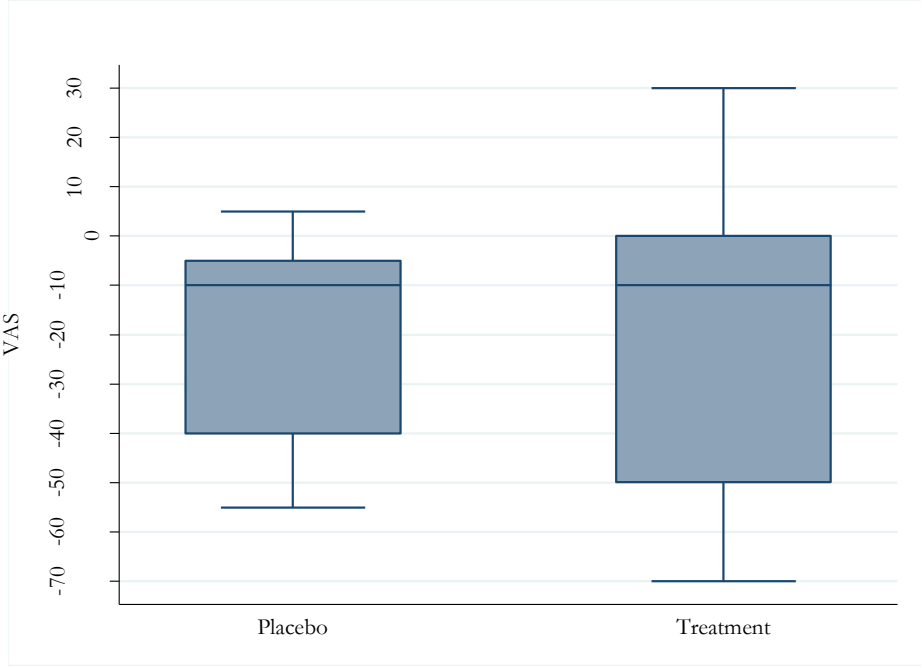

The line inside the box represents the median value. The upper and lower ends of the box represent the percentiles 75 and 25 values, respectively.

Figure 4.B. VAS score by visits (weeks) in the total study sample.

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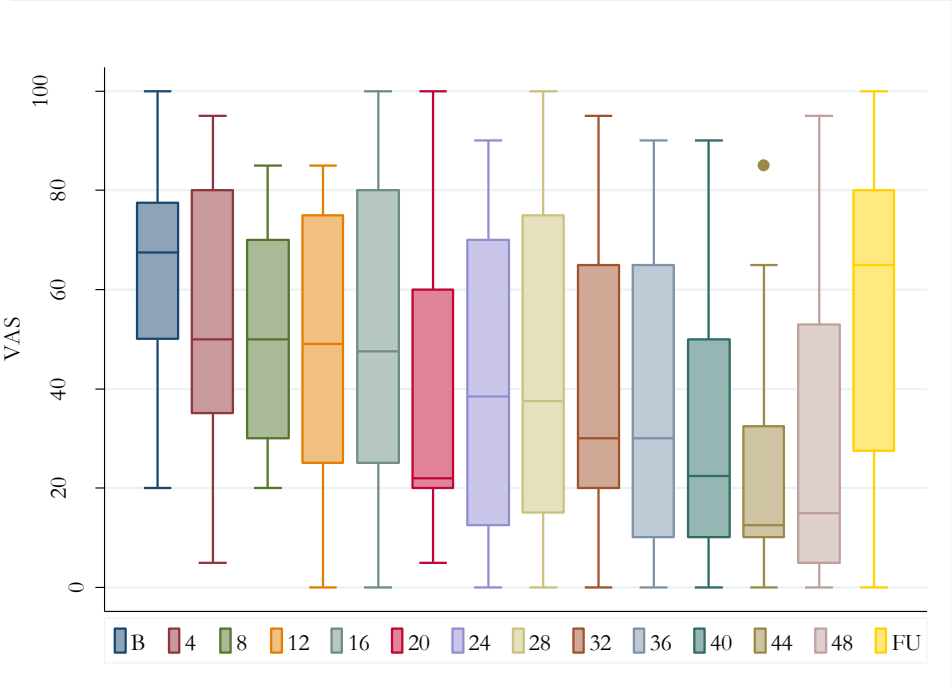

B: Basal visit. FU: Follow-up visit (after three months of the last omalizumab dose). The line inside the box represents the median value. The upper and lower ends of the box represent the percentiles 75 and 25 values, respectively.

Patients' diary symptoms: days with symptoms

During the blinded period, both intervention groups showed a decrease in days with symptoms. The median of days with symptoms decrease for the placebo group was -4 (p_{25}: -9; p_{75}: -2) and the median decrease for the treatment group was -3 (p_{25}: -8; p_{75}: 0) (Figure 7A). The difference between intervention groups was not statistically significant (p=0.4117).

When comparing days with symptoms before treatment and after receiving 4 doses of omalizumab, we observed a statistically significant decrease (p=0.0125). When comparing

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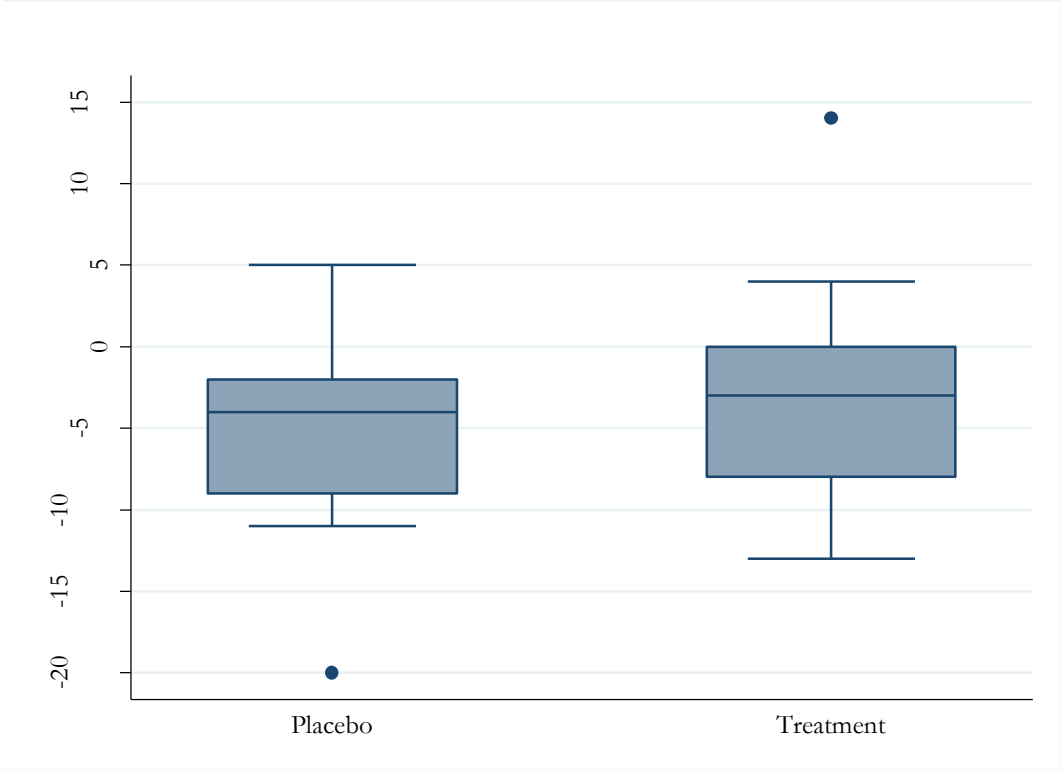
days with symptoms before treatment and after receiving 8 doses of omalizumab, we also observed a statistically significant improvement (p=0.0144). After finishing treatment with Omalizumab, there was a statistically significant increase in days with symptoms in the follow-up visit (week 60th) compared with the last visit that evaluated the effect of the last dose of Omalizumab (visit 12, week 48th). (Figure 7B).

Figure 7.A. Change in days with symptoms according to intervention group.



The line inside the box represents the median value. The upper and lower ends of the box represent the percentiles 75 and 25 values, respectively.

Figure 7.B. Days with symptoms by visits (weeks) in the total study sample.

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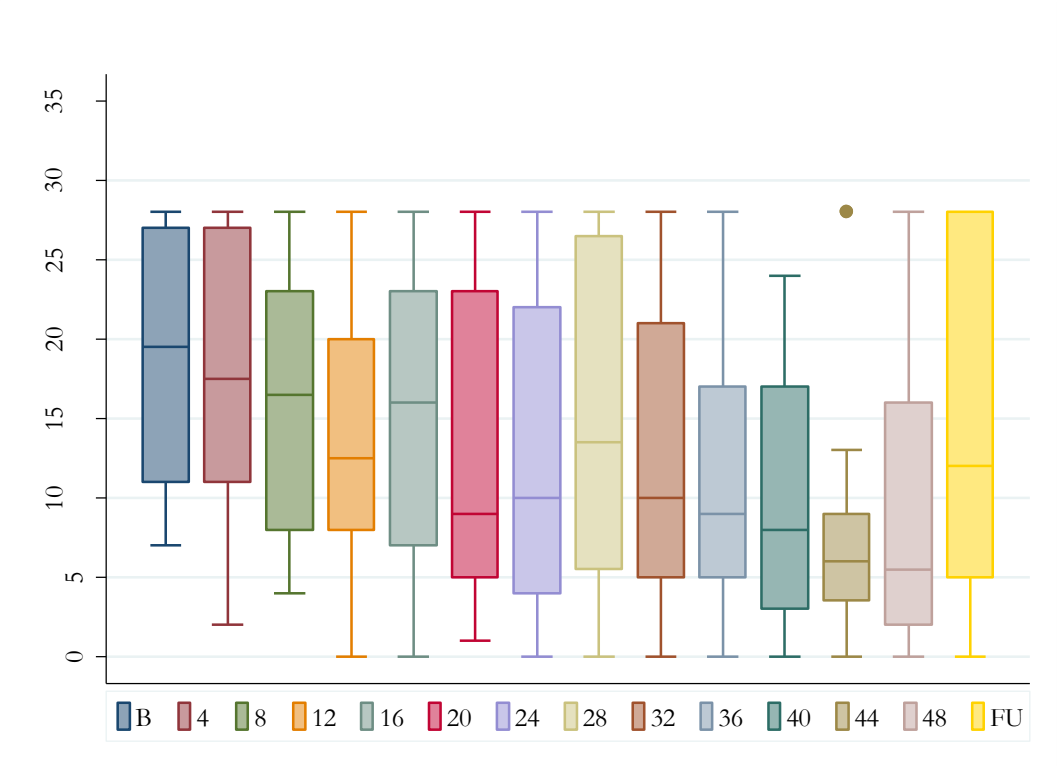

B: Basal visit. FU: Follow-up visit (after three months of the last omalizumab dose). The line inside the box represents the median value. The upper and lower ends of the box represent the percentiles 75 and 25 values, respectively.

Only two sick leave work days were taken by the total study sample. Likewise, no patient required emergency visits along the study due to their cholinergic urticaria.

Time to skin lesions to appear and disappear

During the blinded period, both intervention groups showed an increase in lapse time to skin lesions to appear. The median increase time (minutes) to hives to appear for the placebo group was 5 (p_{25}: 0; p_{75}: 7) and the median increase time for the treatment group

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was 0 (p_{25}: -2; p_{75}: 4). The difference between intervention groups was not statistically significant (p=0.2). We did not observe a significant difference when comparing an increase on time to hives to appear before treatment and after receiving 4 or 8 doses Omalizumab.

Likewise, when comparing decreasing time in hives disappearance after the exercise challenge test, during the blinded period, both intervention groups showed a decrease in lapse time to skin lesions to disappear. The median decrease time (minutes) to hives to disappear for the placebo group was -3 (p_{25}: -30; p_{75}: 5) and the median increase time for the treatment group was -16.5 (p_{25}: -92.5; p_{75}: 0). The difference between intervention groups was not statistically significant (p=0.3). We did not observe a significant difference when comparing an increase on time to hives to appear before treatment and after receiving 4 or 8 doses Omalizumab.

Rescue medication

During the blinded period, the placebo group required antihistamines to be prescribed as rescue medication 29 times (78,3%) in the placebo arm and in 17 occasions in the treatment arm (43,59%). Corticosteroids were prescribed twice in the placebo arm (5,41%) and 3 times in the treatment arm (7,69%). In Table 4 we include information regarding rescue medication.

Table 4. Rescue medication prescription

	By intervention group during blind period		
Rescue medication	**Placebo**	**TREATMENT**	**Total**
Antihistamines	29	17	46

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%	78.38	43.59	60.53
Corticosteroids	2	3	5
%	5.41	7.69	6.58
Others	6	19	25
%	16.22	48.72	32.89
Total	37	39	76
	100.00	100.00	100.00

Safety

There were reported 13 adverse events, 4 in the placebo group and 9 in the treatment arm. 11 were not related with the study and two unlikely related. 8 were classified as mild, 4 moderate and 1 severe because required hospitalization due to a scheduled surgery. None of the AA caused withdrawal from the study, and all of them were solved. In Table 5 we include the AA.

Table 5. List of Adverse events

AA	Number of patients
Headache	2
Pharyngitis	2
Metallic flavor	1
Sciatica	1
Low back pain	1

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Restless legs syndrome	1
Paraphimosis	1
Phimosis surgery	1
Cold with bronchial hyperreactivity	1
Food poisoning (seafood)	1
Ankle sprain	1

Conclusions from the study

1. Omalizumab seems a good choice for those cholinergic urticaria patients non-respondent to high dose of antihistamines. Patients treated with omalizumab showed a negativization of the exercise challenge test, a significant improvement of the UCOL score, patient daily symptoms, and quality of life.
2. Omalizumab showed an excellent safety and tolerability profile.
3. On the opposite of what it was observed in the chronic urticaria clinical trials were a number of patients show a very fast response, in our study the response was slower and progressive. We hypothesize that those non respondent patients could have responded with higher omalizumab dose.
4. Although reported, we did not have any patient with hypo or anhydrosis and did not find any difference in time to sweat on omalizumab response.
5. Cholinergic urticaria, as the case for other inducible urticarias, is respondent to high doses of antihistamines. In our study, 6 out of 29 patients achieved control symptoms with double doses of cetirizine. Omalizumab may be positioned as second line therapy for those patients not controlled with antihistamines.
6. In spite of moderate to severe intensity, patients suffering from cholinergic urticaria, did not take sick leave days or attended emergency department,

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suggesting that they are used to their condition and adapt they daily life to its limitations.

7. Although statistical significance was not demonstrated in the comparison of outcomes between placebo and treatment groups during the blinded period, the magnitud of the differences between groups (mainly favoring treatment) could be of clinical relevance. A study with a longer blinded period may be warranted.
8. UCOL score seems a sensitive tool to monitorize cholinergic urticaria and response to treatment that it should be validated with larger samples.

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Declaración del solicitante con respecto a la exactitud de la información presentada.

Los abajo firmantes suscriben que el presente estudio se realizó de acuerdo con el protocolo aprobado y cumpliendo las normas de Buena Práctica Clínica.

El presente resumen del informe contiene toda la información relevante del estudio y refleja de forma completa y precisa los datos generados durante el mismo.

Marta Ferrer Puga

Investigador principal

CUN

7 mayo 2018

Firma Fecha

Enrique Aubá Guedea

Representante del promotor.

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Firma Fecha

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