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Treatment of chronic urticaria with omalizumab: the experience of Hospital de Braga

Tratamento de urticária crónica com omalizumab: a experiência do Hospital de Braga

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Abstract

Introduction: Omalizumab is approved for the treatment of severe chronic spontaneous urticaria (CSU), unresponsive to quadruple doses of nonsedative H1 antihistamine. Few data are available to help predict the response to omalizumab in the Portuguese population. **Objective:** Characterize the population of CU patients treated with omalizumab in Hospital de Braga and identify variables that help predict a better response to omalizumab. **Methods:** Retrospective chart-review study of CU patients treated with omalizumab in Hospital de Braga. Statistical analysis was performed using the chi-square, odds ratio analysis and generalized linear models. **Results:** 21 patients were included (three men and 18 women). 16 patients had CSU, two had solar urticaria, two cholinergic urticaria, and one cold urticaria. They all had at least 6 months of treatment with omalizumab. Prior to omalizumab, they all had been treated with quadruple doses of nonsedating H1 antihistamines. Using generalized linear models, patients showed a significant reduction of the UAS and UAS7 scores. Women and patients with intermediate levels of immunoglobulin (Ig)—IgE presented a bigger reduction. Women had higher total serum IgE. **Conclusion:** The female gender and patients with intermediate levels of IgE had a better response to omalizumab. In this study, the female gender seems to have higher total serum IgE.

Keywords: Antihistamines. Chronic urticaria. IgE levels. Omalizumab. Urticaria.

Resumo

Introdução: O omalizumab está aprovado para o tratamento de urticária crónica espontânea que resistente a terapêutica quádrupla com anti-histamínicos. Há pouca informação disponível que ajude a prever a resposta ao omalizumab na população portuguesa. **Objetivos:** Caracterizar a população de doentes com urticária crónica tratados com omalizumab no Hospital de Braga e identificar variáveis que ajudem a prever uma melhor resposta ao omalizumab. **Métodos:** Foi efetuado um estudo retrospetivo dos doentes com urticária crónica tratados com omalizumab no Hospital de Braga. Realizou-se análise estatística com estatística descritiva, *chi-square*, análise de risco e modelo linear generalizado. **Resultados:** Foram incluídos 21 doentes (3 homens e 18 mulheres). 16 doentes apresentavam urticária crónica espontânea, 2 tinham urticária solar, 2 urticária colinérgica e 1 urticária ao frio. Todos estavam a ser tratados com omalizumab há pelo menos 6 meses. Antes do

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omalizumab todos tinham sido tratados com terapêutica anti-histamínica quádrupla. Modelos lineares generalizados mostraram que os doentes apresentaram uma redução significativa dos scores Urticaria Activity Score (UAS) e UAS7. Estas reduções foram mais proeminentes nos doentes do sexo feminino e em doentes com níveis intermédios de IgE. As mulheres apresentaram níveis de IgE mais elevados. **Conclusão:** O género feminino e doentes com níveis intermédios de IgE apresentaram melhor resposta ao omalizumab. Neste estudo o género feminino parece estar associado a níveis de IgE mais elevados.

***Palavras-chave*:** Anti-histamínico. Urticária crónica. IgE. Omalizumab. Urticária.

Introduction

Urticaria is a common disease presenting with wheals and/or angioedema[1].

The classification of urticaria is mainly based on clinical criteria: acute and CU, whether the lesions appear over a period of up to 6 weeks or over > 6 weeks, respectively. The acute form affects 20% of the general population and CU up to 5%[2].

Chronic urticaria comprises both CSU and chronic inducible urticaria, which includes physical and non-physical urticaria.

In CU patients, mental health and physical impairment can be comparable to patients with moderate and severe psoriasis[3]. For the assessment of disease activity, quality of life, and the impact on daily activities, a number of detailed questionnaires have been developed. The urticaria activity score 7 (UAS7) assesses the number of wheals and itch intensity on seven consecutive days and was shown to correlate with the impact on quality of life, sleep and daily activities[4,5].

Currently, nonsedating antihistamines and omalizumab, an anti-immunoglobulin E antibody, are recommended for the therapy of CU. Omalizumab is approved for the treatment of severe CSU, unresponsive to quadruple dose of nonsedative H1 antihistamine[6]. Few data are available to help predict the response to omalizumab in the Portuguese population.

The purpose of this case series is to characterize the population of patients with CU that are being treated with omalizumab in Hospital de Braga and try to identify variables that may help predict a better response to omalizumab.

Methods

A retrospective chart review study of patients with CU being treated with omalizumab in the Immunoallergology and Dermatology Departments of Hospital de Braga between January and December 2020.

Patients were characterized according to demographic and clinical data, such as age, gender, presence of atopic comorbidities, age of onset and duration of CU, age at the beginning of omalizumab, previous treatments, initial omalizumab dose, total serum IgE, and results of other complementary studies, including the autologous serum test (AST) and antithyroid antibodies (ATA).

Clinical response to omalizumab was evaluated with the UAS and UAS7, validated in the Portuguese language, and calculated before and during treatment. Patients started omalizumab associated with their previous medications, which were later discontinued according to their clinical improvement.

Patients were characterized according to their response to omalizumab as:

- Complete responders–need of antihistamines in SOS besides omalizumab to keep UAS ≤ 6;
- Partial responders–need of daily medication besides omalizumab to keep UAS ≤ 6, but showed a clinical improvement since the start of omalizumab
- Nonresponders–patients that showed no improvement after 6 months of omalizumab treatment.

The adverse reactions were monitored by the nursing staff after each administration.

Statistical analysis and descriptive statistics of the data were performed using the Statistical Package for the Social Sciences software version 23.0 (IBM Corporation), using the chi-square, odds ratio analysis, and generalized linear models. A p-value < 0.05 was considered statistically significant.

Results

In this study, 21 patients with CU were included (18 women and three men). The descriptive statistics are shown in tables 1 and 2. They all started omalizumab at the dose of 300 mg every 4 weeks.

A total of 16 patients had CSU; two had solar urticaria, two cholinergic urticaria and one cold urticaria.

About six patients had atopic comorbidities (n = 6 and 28.6%), namely atopic dermatitis, allergic rhinitis, asthma, and allergic eczema.

Table 1. Descriptive statistics of CU patients treated with omalizumab in Hospital de Braga

Characteristics	Mean ± standard deviation	Median (min and max)
Age at onset of urticaria (years)	37 ± 12	33 (17, 62)
Age at onset of omalizumab (years)	41 ± 12	39 (22 and 63)
Time between urticaria onset and omalizumab treatment (years)	4 ± 4	2 (0.5 and 12)
Duration of omalizumab treatment (months)	20 ± 13	18 (6 and 60)
Total serum IgE (kU/L)	335.9 ± 319.5	326.5 (3 and 1187)
Initial UAS	5.19 ± 0.87	5 (3 and 6)
Final UAS	0.95 ± 1.28	1 (0 and 4)
Initial UAS7	19.71 ± 5.64	20 (9 and 38)
Final UAS7	± 2.67	0 (0 and 21)

A total of 14 patients had their total serum IgE measured before the start of treatment: three patients had IgE > 500 kU/L, seven between 100 and 500 kU/L and four under 100 kU/L. Only one patient underwent an AST guided by the patient's clinical history, and it was negative. They all had negative antithyroid antibodies.

Prior to omalizumab, they all had been treated with quadruple doses of nonsedating H1 antihistamines, 12 with systemic corticotherapy, 10 with cyclosporine, eight with montelukast, one with hydroxychloroquine, one with intravenous immunoglobulin, one with oxybutynin, and one with ultraviolet B (UVB) phototherapy. This last patient also had allergic eczema.

Currently, 19 patients are being treated with omalizumab (medium duration of treatment: 19.9 months). One patient discontinued omalizumab for pregnancy reasons.

There were 11 complete responders in this study, 10 partial responders (two needed dose increase to 450 mg every 4 weeks) and one nonresponder. The nonresponder is a 40-year-old female patient with CSU, no atopic comorbidities and low serum IgE, previously treated with montelukast and cyclosporine. This patient was switched to dupilumab since recent knowledge shows dupilumab may be a promising novel treatment option for patients with CU and low IgE levels.

Patients well controlled with omalizumab have started to increase the time intervals between each dose of omalizumab, but none has yet stopped this treatment.

There were no adverse reactions after the administration of omalizumab.

Statistical analysis

The urticaria activity was determined with the assessment of the UAS score before the start of omalizumab and 6 months after starting treatment.

The results are shown in tables 3 and 4.

Using the paired samples *t*-test, there was a significant difference between the initial and final scores for UAS and UAS7. The patients showed a reduction of 4.2 points on the UAS score ($p < 0.001$) and of 17.0 points on the UAS7 ($p < 0.001$), in comparison to the scores before the start of treatment.

According to gender, women showed a UAS score reduction of 4.3 points and men of 3.7 points ($p < 0.001$). Considering UAS7, women showed a score reduction of 17.3 points and men of 15.3 points.

When the results were evaluated according to the total serum IgE of each patient, patients with IgE < 100 kU/L showed a reduction of 4.0 points and 16.3 points on the UAS and UAS7 scores, respectively, patients with IgE 100-500 kU/L showed a reduction of 4.7 and 19.8 points on the UAS and UAS7 scores respectively, and patients with IgE > 500 kU/L showed a reduction of 3.3 points on the UAS and of 15.0 points on the UAS7 score.

We searched for an association between gender and the total serum IgE. The chi-square test showed an association ($p < 0.05$), women presented with more elevated values of IgE.

Discussion

Omalizumab is approved as an add-on therapy for CSU[7]. Few studies have tried to find predictor factors for omalizumab response in CSU in the Portuguese population.

To be able to predict the response to omalizumab is important for clinical practice since it is an expensive therapy, and not all patients respond to it.

About 17-48% of patients with CSU do not have a complete or significant response to omalizumab[8-10]. In this study, 52% didn't have a complete response to omalizumab. So, it seems important to try and find ways to select those patients that will benefit more from omalizumab.

One study showed that female patients seem to have a faster and better response to omalizumab, which is in line with our results. It also concluded that patients

Table 2. Descriptive statistics of the 21 CU patients treated with omalizumab in Hospital de Braga

Patient	Sex	CU type	Age of urticaria onset	Age at the beginning of omalizumab	Time between urticaria onset and omalizumab treatment (years)	Duration of omalizumab treatment at 30th November 2020 (months)	Atopic comorbidities	Previous medications	Total serum IgE	AST	ATA
1	m	C	17	26	9	12	AD	anti-H, CyA, and montelucaste	504	ND	ND
2	f	CSU	42	52	10	60	-	anti-H, CCT, and IVIg	34	ND	ND
3	f	CSU	33	35	2	12	AD and allergic rhinitis	Anti-H, CyA, and CCT	487	ND	ND
4	f	CSU	42	45	3	24	Allergic rhinitis	Anti-H, CyA, CCT	ND	ND	ND
5	f	CSU	62	63	1	18	-	Anti-H, CyA, and montelucaste	ND	ND	neg
6	f	CSU	42	42	0.5	18	-	Anti-H, CyA, and CCT	ND	ND	neg
7	f	CSU	25	39	11	12	-	Anti-H and CCT	291	ND	neg
8	f	CSU	33	34	2	18	Asthma	Anti-H and montelucaste	39	ND	neg
9	f	CSU	29	29	0.5	24	-	Anti-H	3	ND	neg
10	f	CSU	33	34	1	16	-	Anti-H, CCT, and montelucaste	ND	ND	ND
11	f	CSU	41	47	6	24	-	Anti-H, CyA, and CCT	172	ND	neg
12	f	CSU	25	37	12	24	-	Anti-H, CyA, and montelucaste	3	neg	neg
13	f	CSU	25	28	3	12	-	Anti-H and CCT	122	ND	neg
14	f	CSU	50	54	4	48	-	Anti-H, CCT, and montelucaste	401	ND	neg
15	f	CSU	38	41	3	12	-	Anti-H, CCT, and montelucaste	ND	ND	neg
16	m	CSU	37	39	1.5	18	-	Anti-H, CyA, and HCQ	38	ND	neg
17	f	S	28	31	3	6	-	Anti-H and CyA	362	ND	neg
18	f	CSU	60	62	2	18	-	Anti-H and CCT	463	ND	neg
19	m	Cold	30	31	1	18	Asthma and allergic rhinitis	Anti-H and montelucaste	1187	ND	ND
20	f	C	58	60	2	6	Allergic eczema	Anti-H, CyA, and UVB	606	ND	neg
21	f	S	21	22	1	18	-	Anti-H, CyA, CCT, and oxybutynin	ND	ND	neg
Patient	Sex	Age at the beginning of urticaria	Age at the beginning of omalizumab	Time between the beginning of urticaria and the beginning of omalizumab (years)	Duration of omalizumab treatment at 30th November 2020 (months)	Atopic comorbidities	Previous medications	Total serum IgE	AST	ATA	
1	m	17	26	9	12	AD	Anti-H, CyA, and montelucaste	504	-	-	
2	f	42	52	10	60	-	Anti-H, CCT, and IVIg	34	-		

(continues)

Table 2. Descriptive statistics of the 21 CU patients treated with omalizumab in Hospital de Braga *(continued)*

Patient	Sex	CU type	Age of urticaria onset	Age at the beginning of omalizumab	Time between urticaria onset and omalizumab treatment (years)	Duration of omalizumab treatment at 30th November 2020 (months)	Atopic comorbidities	Previous medications	Total serum IgE	AST	ATA
3	f	33	35	2	12	AD, allergic rhinitis	Anti-H, CyA, CCT	487	-	-	
4	f	42	45	3	24	Allergic rhinitis	Anti-H, CyA, CCT	-	-	-	
5	f	62	63	1	18	-	Anti-H, CyA, and montelucaste	-	-	neg	
6	f	42	42	0.5	18	-	Anti-H, CyA, and CCT	-	-	neg	
7	f	25	39	11	12	-	Anti-H, CCT	291	-	neg	
8	f	33	34	2	18Asthma		Anti-H and montelucaste	39	-	neg	
9	f	29	29	0.5	24	-	Anti-H	3	-	neg	
10	f	33	34	1	16	-	Anti-H, CCT, and montelucaste	-	-	-	
11	f	41	47	6	24	-	Anti-H, CyA, and CCT	172	-	neg	
12	f	25	37	12	24	-	Anti-H and montelucaste	3	neg	neg	
13	f	25	28	3	12	-	Anti-H and CCT	122	-	neg	
14	f	50	54	4	48	-	Anti-H, CCT, and montelucaste	401	-	neg	
15	f	38	41	3	12	-	Anti-H, CCT, and montelucaste	-	-	neg	
16	m	37	39	1.5	18	-	Anti-H, CyA, and HCQ	38	-	neg	
17	f	28	31	3	6	-	Anti-H and CyA	362	-	neg	
18	f	60	62	2	18	-	Anti-H and CCT	463	-	neg	
19	m	30	31	1	18	Asthma, allergic rhinitis	Anti-H and montelucaste	1187	-	-	
20	f	58	60	2	6	Allergic eczema	Anti-H, CyA, and UVB	606	-	neg	
21	f	21	22	1	18	-	Anti-H, CyA, CCT, and oxybutynin	-	-	neg	

AST: autologous serum test; ATA: antithyroid antibodies; AD: atopic dermatitis; anti-H: quadruple dose nonsedating H1 antihistamines; C: cholinergic urticaria; Cold: cold urticaria; CSU: chronic spontaneous urticaria; CyA: cyclosporine; CCT: corticotherapy; IVIg: intravenous immunoglobulin; HCQ: hydroxychloroquine; ND: not done; S: solar urticaria; UVB: Ultraviolet B phototherapy.

Table 3. Urticaria activity score and UAS7 reduction in each group of patients according to gender and total serum IgE levels

Variables	UAS reduction	UAS7 reduction
All patients	4.2 ($p < 0.001$)	17.0 ($p < 0.001$)
Female	4.3 ($p < 0.001$)	17.3 ($p < 0.001$)
Male	3.7 ($p < 0.001$)	15.3
IgE < 100 kU/L	4.0	16.3 ($p < 0.001$)
IgE 100-500 kU/L	4.7 ($p < 0.001$)	19.8 ($p < 0.001$)
IgE > 500 kU/L	3.3 ($p < 0.001$)	15.0

Table 4. Type of response to omalizumab

Response to omalizumab	Number of patients
Total response	11
Partial response	9
No response	1

with more elevated total serum IgE levels had a better response to omalizumab. However, in this study, patients with intermediate levels of total serum IgE presented a bigger improvement[11]. This could have also happened because there were only 3 patients with total serum IgE > 500 in this study.

One Portuguese study applied generalized linear models to evaluate the progression of the UAS score in response to omalizumab. They showed a medium reduction of the UAS score of 16% and of UAS7 of 20% per monthly administration of omalizumab. These reductions were also more prominent in female patients and in patients with higher total serum IgE levels[12].

There was an association between the female gender and higher levels of total serum IgE, and this could be a possible explanation for the better response to omalizumab in the female group.

Most patients presented with a total response to omalizumab (n = 11 and 52.4%), some have already started interval prolongation, but none have yet stopped treatment. The nonresponder patient was switched to dupilumab and has shown improvement.

Some limitations of this study are the fact that it's a retrospective study, the global sample is small, in particular the male gender. Also, the scores used are subjective; the literature shows women tend to have initial higher scores than men.

Not all patients had every laboratory study, like total serum IgE or antithyroid antibodies, and there are other clinical parameters that can affect the response to treatment and weren't evaluated, like body weight, eosinopenia, and others.

Conclusion

The female gender and patients with intermediate levels of IgE had a better response to omalizumab in this study. The female gender seems to have higher total serum IgE, and maybe that is the reason they had a better response to omalizumab. This study's population is small to extrapolate conclusions to the general Portuguese population.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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