Omalizumab in Chronic Spontaneous Urticaria: A Brazilian Real-Life Experience

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Key Words
Urticaria · Omalizumab · Treatment

Abstract
Background: Current guidelines on chronic spontaneous urticaria (CSU) suggest a treatment based on a 3-step approach that aims at total symptom control, starting with H1-antihistamines. However, a significant number of patients present an antihistamine-resistant urticaria that must be treated with an alternative third-line therapy such as omalizumab. Methods: Patients with a history of CSU who did not respond to treatment with high doses of modern antihistamines were treated with 150 or 300 mg of omalizumab every 4 weeks. The response to treatment was recorded as complete (CR), partial (PR) or no response. A dose adjustment was proposed according to response. Results: We treated 47 CSU patients with omalizumab (40 females), of whom 39.5% had evidence of autoimmunity. The average number of treatments was 11.4 (range 2–87). All patients had been refractory to high-dose modern antihistamines. A CR was seen in 84.6% of patients who started with 300 mg and in 60% of those who started with 150 mg. Only 1 patient had no response to both the 150- and 300-mg doses. In 6 of the PR patients with 150 mg, a higher dose of 300 mg was proposed and 4 had a CR. Four patients discontinued the treatment. No severe adverse events were reported in the patients who finished the study. Discussion: Although good results were seen in both groups, CR rates were higher in those under a high-dose initial treatment. Our data strongly suggest that the therapy should be individualized.

Introduction
Chronic spontaneous urticaria (CSU) affects 1–1.3% of the population and has a significant impact in quality of life [1]. Current guidelines suggest a treatment based on a 3-step approach that aims at total symptom control.
The first and second steps consist of using modern second-generation H1-antihistamines drugs, firstly in standard doses, with up to a 4-fold increase in the original dose in nonresponders. However, a significant number of patients present an antihistamine-resistant urticaria that must be treated with an alternative third-line therapy: leukotriene receptor antagonist (LRA), cyclosporine and/or omalizumab [2].

The level of evidence for the efficacy of LRA in CSU is low. In addition, cyclosporine is effective but has the potential for severe side effects. On the other hand, omalizumab has shown significant efficacy and safety in treating patients with CSU [2].

Omalizumab is a humanized anti-IgE monoclonal antibody already approved for the treatment of recalcitrant CSU in several countries [3]. Although it has been used for a long time in asthma treatment, it is not registered for CSU in Brazil. The aim of this study was to describe the initial experience with omalizumab for off-label CSU treatment in this country.

**Materials and Methods**

This was a retrospective, real-life study with severe, refractory CSU patients treated with omalizumab at seven Brazilian centers from June 2012 to December 2014. Patients with a history of urticaria for more than 6 weeks who did not respond to treatment with high doses of modern antihistamines for at least 2 weeks were included. Omalizumab was administered subcutaneously every 4 weeks in all centers (in doses of 150 or 300 mg according to its availability). The response to treatment was recorded as follows: complete response (CR), defined as total absence of hives and itching, partial response (PR), when there was a significant improvement in symptoms and quality of life, but still presenting hives and itching, and no response. For the patients who did not have a CR with 150 mg after 12 weeks, a higher dose (when available) was administered.

**Results**

We evaluated 47 CSU patients treated with omalizumab (40 females) aged from 16 to 74 years (mean 38.9). The mean level of total IgE was 158.6 kU/l (range 0.16–774) among the 27 patients from whom total IgE levels were available. Autoimmunity, as defined by the presence of a positive autologous serum skin test and/or the presence of antithyroid or antinuclear antibodies was investigated in 43/47 patients, and 39.5% of them had evidence of autoimmunity.

The average number of treatments was 11.4 (range 2–87). The mean duration of CSU prior to omalizumab therapy was 4.5 years. Ten patients had an associated induced urticaria (4 dermatographic and 6 delayed pressure). All the patients had been treated with modern antihistamines in a 4-fold dose monotherapy or in a double-dose combination of two different antihistamines. In 2 patients 100 mg cyclosporine was given in combination with the antihistamines.

In this study 26 of the 47 patients received omalizumab at an initial dose of 300 mg/month. An improvement in urticaria symptoms was reported in the majority of them, with 22 (84.6%) showing CR and 4 PR. In 8 patients with a CR, a reduction to a 150-mg dose was proposed after 6 months of therapy, and 4 (50%) of them had their symptoms controlled with this dose.

Of the 20 patients who started the treatment with 150 mg of omalizumab, 12 (60%) had CR. In 6 of the partial responders, a higher dose of 300 mg was used. Four (66.7%) had CR with 300 mg but 2 still have symptoms. The other 2 partial responders had no access to a higher dose of 300 mg. One patient did not respond to either 150 or 300 mg of omalizumab, but is currently under remission with cyclosporine 150 mg/day monotherapy (fig. 1). Four patients discontinued the treatment: 1 for lack of response, 1 for an abortion (not related to the study drug) and 2 due to limited access to drugs. No severe adverse events were reported in the patients who continued the treatment.

**Discussion**

The treatment of patients with CSU aims at complete symptom control. Options for antihistamine-refractory CSU patients include LRA, cyclosporine and omalizumab, as recommended by international guidelines [2]. Although the efficacy and safety of omalizumab for CSU has been described, the drug is still off label for treating urticaria in Brazil.

We report the effects of omalizumab in 47 antihistamine-refractory CSU patients. Medical experts in seven different centers in Brazil carried out the diagnosis, and the drug was prescribed in doses according to the availability for each patient. Although good results were seen in both groups, the CR rates were higher in those under a starting treatment of 300 mg/month (84.6%) compared with those treated with an initial dose of 150 mg/month (57.1%; p = 0.0386, Fisher’s exact test). However, half of
those controlled with higher doses continued under remission when doses were decreased to 150 mg, and 44.4% of those partially controlled with a 150-mg dose achieved total control with a higher dose. Furthermore, this positive clinical response was accompanied by decreases in other antiurticarial medications.

Within this cohort of CSU patients, only 1 was considered as a nonresponder to omalizumab treatment. She did not show any specific clinical feature that could have explained this outcome. A recent study did not find any specific autoimmune marker or even clinical characteristics as a predictor of responsiveness to omalizumab [4].

Only 4 patients treated initially with 300 mg of omalizumab showed a PR, but we did not evaluate whether they would have improved by using a higher dose. Surprisingly, a dose-ranging study of single-dose omalizumab was evaluated and the 600-mg omalizumab group was inferior to the 300-mg group in all the analyzed treatment outcomes [5].

The limitations of this study include its small sample size and the limited availability of omalizumab as an off-label treatment for CSU in Brazil. Also, standardized urticaria scores were not evaluated in this real-life study. Nevertheless, our data strongly suggest that the therapy should be individualized, especially in a country where access to treatment is limited by economic issues in the general population. Our results are similar to those already described in other real-life studies [1, 6, 7], demonstrating safety and efficacy of omalizumab in antihistamine-refractory CSU patients.

Fig. 1. Outcomes of treatment with omalizumab among patients with antihistamine-refractory CSU.
References


