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Angioedema is an unfavorable factor for the response to omalizumab in chronic spontaneous urticaria: A retrospective study

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Abstract

Antihistamines are the first-line treatment option for chronic urticaria. In recent years, omalizumab, an anti-immunoglobulin-E humanized monoclonal antibody, has been used in patients with recalcitrant disease. The present study aimed to retrospectively evaluate the efficacy and safety of omalizumab and determine whether there was a difference between complete and partial responses to omalizumab with respect to age, gender, disease duration and coexistence of angioedema. From May 2014 to December 2016, a total of 40 refractory chronic urticaria patients were treated with omalizumab. Complete response was observed in 19 (47.5%) patients, and partial response was observed in 18 (45%) patients. There were no statistically significant differences between the rates of complete and partial responses in patients with respect to gender, age, and disease duration. However, complete response was more frequent (60%) in patients without angioedema. Remission was observed in 40.5% (n = 15) of patients, and the follow-up time was 5.5 ± 2.4 months. There was a statistically significant association between remission and coexistence of angioedema (p < .05). Eighty-seven percent (13/15) of the remission patients did not have angioedema. Thus, omalizumab can be used effectively and safely in refractory chronic urticaria patients. However, the coexistence of angioedema may be an unfavorable factor for complete response and remission.

KEYWORDS

angioedema, chronic, omalizumab, urticaria

1 | INTRODUCTION

Chronic urticaria is characterized by pruritic wheals, that recur or last for >6 weeks. Recently, the term 'chronic spontaneous urticaria' (CSU) has been used instead of 'chronic idiopathic urticaria' and 'chronic autoimmune urticaria'. Second-generation H1-antihistamines are the first-line medications in CSU treatment, with a dose increase if patients are unresponsive to the treatment (Song, Stern, Giruparajah, Berlin, & Sussman, 2013). Omalizumab is a recombinant humanized IgG1 monoclonal antibody that selectively binds free immunoglobulin E (IgE) antibodies. Circulating IgE binds the high-affinity (FcεRI) and low affinity (FcεRII, CD23) receptors on basophils and mast cells, resulting in the release of histamine and other mediators of the allergic response. Omalizumab binds the high-affinity receptor-binding domain (Cε3) on the Fc portion of free IgE (Chia & Mydlarski, 2016). Omalizumab has recently been approved for the treatment of refractory chronic urticaria.

The aim of this retrospective observational study was to evaluate the effectiveness and safety of omalizumab and the follow-up results in Turkish patients with CSU.

2 | MATERIAL AND METHODS

Records of patients with CSU treated with omalizumab at the Department of Dermatology, Mustafa Kemal University, Hatay, Turkey between May 2014 and December 2016 were retreived in this retrospective study. Clinical diagnosis had been made based on the clinical symptoms and patient's history. Biopsy had been performed in a few patients to rule out urticarial vasculitis. Demographic data and clinical variables such as age, gender, duration of disease, prior treatments,

comorbidities, and the presence of angioedema (AE) were recorded. This retrospective study was approved by the Ethics Commitee of Mustafa Kemal University (Hatay, Turkey).

2.1 | Definitions

Indications for omalizumab treatment Patients unresponsive to antihistamines, despite dose incriments and the use of medications such as cyclosporine, corticosteroids, and montelukast.

Omalizumab treatment protocol Once a month, 300 mg, subcutaneously. Omalizumab was stopped every 6 months. If symptoms recurred, treatment was restarted.

Response to Omalizumab Clinical response to treatment was evaluated monthly according to the symptoms in patients and the need for additional antihistamine drugs. If urticaria attacks were improved, patients were recommended to stop additional medications in the first months of treatment.

Complete response (CR) Complete resolution of symptoms without adding medications other than omalizumab.

Partial response (PR) Resolution or improvement of symptoms with the addition of antihistamines (Armengot-Carbo et al., 2013).

Duration of relapse From the last omalizumab injection until recurrence of an urticaria attack.

2.2 | Statistical analysis

Data were analyzed using SPSS for Windows (version 19; SPSS Inc., Chicago, IL). A chi-square test, Fisher's exact test and Mann–Whitney *U* test were used for statistical analysis. Values are presented as the mean ± *SD* or median, and $p < .05$ was considered significant.

3 | RESULTS

A total of 40 CSU patients (19 females, 21 males) treated with omalizumab were enrolled in this retrospective study. The mean age was 43.1 ± 12.1 years (range, 19–76 years), and the duration of disease was 56.8 ± 63.6 months (range, 5–264 months; median, 36 months). AE was present concomitantly in 30% ($n = 12$) of the patients. Demographic and clinical characteristics and previous treatments of the patients are displayed in Table 1.

Omalizumab was discontinued because of treatment failure in three patients (7.5%). Two of the patients received three and one received five doses of omalizumab. The rest of the patients received 5–23 injections. CR was observed in 47.5% ($n = 19$) of the patients, and PR was observed in 45% ($n = 18$) of the patients. There were no statistically significant differences between the rates of CR and PR with respect to gender ($p = .254$) and age ($p = .761$). There was no statistically significant difference between the CR (median, 48 months; range, 5–264 months) and PR (median, 30 months; range, 12–264 months) groups with respect to the disease duration either ($p = .702$). However, the disease duration was much longer in the patients with CR. No statistically significant difference was detected between these two groups regarding the coexistence of AE ($p = .129$). However, CR was more frequent (60%, $n = 15$) in the patients without AE (Table 2). Unresponsive patients ($n = 3$) were not included in the statistical analysis because of the low number of patients.

TABLE 1 Demographic and clinical characteristics of the patients

	Number (%)
Gender	
Female	19
Male	21
Age (year; mean ± *SD*)	43.1 ± 12.1 (range, 19–76)
Disease duration (month; median)	36 (range 5–264).
Angioedema	12 (30)
Other diseases (comorbidities)	
Thyroid disease	2 (5)
Asthma	6 (15)
Other (hypertension, DM, cardiovascular)	10 (25)
Previous treatments	
H1 antihistamines	40 (100)
Corticosteroids	18 (45)
Cyclosporine	2 (5)
Montelukast	2 (5)

Remission was observed in 40.5% ($n = 15$) of patients, and these patients received 3–9 omalizumab injections. The follow-up time was 3–10 months. Only five of these patients received antihistamines after the cessation of omalizumab, three for pruritus and two for infrequent urticarial symptoms. There was a statistically significant correlation between remission and the presence of AE ($p = .043$; $p < .05$). Eighty-seven percent (13/15) of the remission patients did not have AE (Table 3). The present authors did not detect a statistically significant association between remission and the gender ($p = .942$), disease duration ($p = .297$) and age ($p = .111$).

Recurrence of urticaria attacks occured in 30–90 days ($n = 20$) at the end of the first 6-month period, 30–70 days ($n = 8$) at the end of the second 6-month period, and 45–180 days ($n = 4$) at the end of the third 6-month period in the CR and PR patients. The duration of recurrence was similar in every period. Only one patient was asymptomatic for 180 days after the end of the third 6-month period.

Reversable adverse effects of omalizumab were observed in two patients (5%). One had an injection site reaction, and the other had palpitations.

4 | DISCUSSION

In this retrospective study, the present authors detected a statistically significant association between remission and the absence of

TABLE 2 Characteristics of patients with complete response and partial response to the treatment

	Complete response	Partial response
Patient no (%)	19 (47.5)	18 (45)
Gender (male/female)	12/7	8/10
Age	42.7 ± 11.9	41.2 ± 10.7
Disease duration (month)	48 (5–264)	30 (12–264)
Angioedema (+)/(–)	4/15	8/10

TABLE 3 Coexistence of angioedema in patients with and without remission

	Remission			
	No	Yes		
	Number	Number	Total number (%)[a]	*p*[b]
Angioedema				.043
Yes	10	2	12 (32.4)	
No	12	13	25 (67.6)	
Total	22 (59.5)	15 (40.5)	37 (100.0)	

[a] Column persentage.
[b] Fisher's exact test (one-sided).

AE. Although the difference was not statistically significant, CR was more frequent (60%, *n* = 15) in patients without AE. Similarly, Ghazanfar et al. have reported that complete responders were more frequent among patients without AE and AE was not included as a predictor of a favorable response to treatment (Ghazanfar, Sand, & Thomsen, 2016).

CR and PR rates were 47.5% and 45%, respectively, in our study. Recurrence of symptoms started just before the next omalizumab injection in patients with PR (generally, 10 days or 1 week before). In a few studies, CR has been defined as complete resolution of symptoms without adding drugs other than omalizumab, similar to our study. Rottem et al. have reported that the incidence of CR was 57% and that of PR was 43% (Rottem et al., 2014). Labrador et al. have reported that 60% of patients could stop concomitant medications and remain asymptomatic with omalizumab alone (Labrador-Horrillo et al., 2013). In another retrospective study, the authors have reported that 83% of patients were complete responders (Metz, Ohanyan, Church, & Maurer, 2014). The CR rate was lower in our study than in other studies, which could be explained by differences in study designs.

Remission was observed in 40.5% of patients in our study. Remission rates have been different in other retrospective studies. In one retrospective study, omalizumab was stopped in 37.3% of patients with CR; however, in 47.5% of those, omalizumab was restarted because of recurrence (Labrador-Horrillo et al., 2013). Song et al. have reported that of the 14 patients (88%) who initially benefited, four remained in remission for more than 9 months after their last treatment (Song et al., 2013). Ghazanfar et al. have reported that their remission were 7% (Ghazanfar et al., 2016).

In conclusion, the remission rate was higher in our study than that in other studies. The follow-up time was 3–9 months in our study. However, a longer follow-up duration can alter the rate of remission. The present authors also detected that the presence of AE was an unfavorable factor for remission and CR. Therefore, CSU patients with AE may need longer treatment.

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CONFLICT OF INTEREST

There is no conflict of interest to declare.

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