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Original Article DERMATOLOGY

Antihistamines and omalizumab combination treatment in patients with chronic spontaneous urticaria: Real-world experience from a tertiary care hospital

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ABSTRACT

OBJECTIVE: Chronic spontaneous urticaria is characterized by recurrent hives and/or angioedema that persists for more than six weeks, with unknown triggers. This study aimed to gather and analyze real-world data from adult patients diagnosed with chronic spontaneous urticaria who were receiving omalizumab treatment.

METHODS: This retrospective observational study included adults who received omalizumab between September 2022 and February 2024.

RESULTS: A total of 64 patients were included in the study, with a mean age of 44.3 years. Among them, 40 (62.5%) were female, and 24 (37.5%) were male. The mean duration of urticaria diagnosis was 46.6 months, with a mean omalizumab use of 23.6 months. Prior to omalizumab treatment, the most commonly used treatments were the highest dose of second-generation antihistamines (60.9%), and combination therapy with antihistamines and oral corticosteroids (31.3%). All patients received omalizumab 300 mg once every four weeks from the start of treatment and continued using antihistamines. No significant correlation was observed between the antihistamine dosage and treatment response (p=0.06). An observed interval extension and/or dose increase was noted in 23.4% of the patients. The mean Urticaria Control Test (UCT) score, weekly Urticaria Activity Score (UAS7), and Dermatology Life Quality Index (DLQI) scores significantly improved from the first visit before omalizumab treatment to the last visit after treatment (all p<0.001). Of the patients, 98.4% responded moderately or above to the treatment, 26.6% responded thoroughly, and 46.9% responded well. Only three patients (3.1%) experienced myalgia as a side effect of omalizumab therapy, with no severe adverse events reported.

CONCLUSION: Combination therapy with antihistamine and omalizumab is a reliable and beneficial therapy for managing chronic spontaneous urticaria.

Keywords: Antihistamine; chronic spontaneous urticaria; omalizumab; treatment.

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Urticaria, characterized by symptoms such as wheals and angioedema, is an inflammatory disease that can manifest as acute or chronic (lasting > six weeks) [1]. CSU, a type of chronic urticaria, causes a significant decrease in an individual's quality of life, with unpredictable attacks and unknown triggers [2].

Treatment guidelines recommend a stepwise approach for the treatment of CSU as follows: standard-dose second-generation H1 antihistamines (sgAHs), high-dose sgAHs, standard-dose omalizumab treatment, high-dose omalizumab treatment, and cyclosporine treatment [3]. Omalizumab is recommended for adults and ado-

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lescents with chronic spontaneous urticaria who do not respond to antihistamines. To evaluate its effectiveness, scales such as the Urticaria Activity Score (UAS) (ranging from 0 to 6 points), weekly Urticaria Activity Score (UAS7) (ranging from 0 to 42 points), and Dermatology Quality of Life Index (DLQI) (ranging from 0 to 30 points) were used [4]. The effectiveness of omalizumab can vary depending on the individual. This unpredictability adds to the difficulties encountered indisease management [2].

Data on the use of omalizumab have been available in literature since 2006 [5]. Although the effectiveness and safety of this drug are still being studied, it is generally considered safe. Real-life data are expected to guide physicians in managing challenging patients in clinical practice, particularly those who require higher doses [5]. Furthermore, an increase in real-life data will help resolve the uncertainty surrounding the timing and methods of discontinuing omalizumab treatment [3].

This study aimed to assess the overall effectiveness and side effects of omalizumab in patients with chronic spontaneous urticaria in a real-world clinical setting.

MATERIALS AND METHODS

This study included patients aged ≥18 years who were diagnosed with CSU and were treated with omalizumab at our dermatology outpatient clinic between September 2022 and February 2024. These patients received omalizumab 300 mg at least every four weeks and were evaluated at least one month after the start of treatment. Patients with missing data or poor data reliability were excluded from the study. Approval with the number AEŞH-EK1-2023-050 was received on April 26, 2023, from the Ethics Committee of Ankara Etlik City Hospital. This study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Urticaria severity was assessed using the Urticaria Control Test (UCT) and weekly Urticaria Activity Score (UAS7). The impact on the quality of life was evaluated using the Dermatology Life Quality Index (DLQI). The scores on these scales were compared before the patient's first application of omalizumab and after the last application. The final response to omalizumab treatment was categorized as follows: complete response if there was complete improvement in urticaria, good response if there was a reduction of at least 90%, moderate response if there was a reduction of 30–89%, and poor response if there was a reduction of less than 30%.

Highlight key points

- Omalizumab is used in patients with chronic spontaneous urticaria who do not respond to antihistamine therapy.
- Before starting omalizumab treatment, the most commonly used treatments were the highest dose of second-generation antihistamines alone, and combination therapy with antihistamines and oral corticosteroids.
- Patients receiving omalizumab continued their antihistamine therapy, and no significant relationship was found between antihistamine dose and treatment response.
- Most patients treated with omalizumab showed a moderate or above response to treatment, and no serious side effects were observed during omalizumab treatment.
- Combination therapy with antihistamines and omalizumab can be used as a safe and effective treatment for chronic spontaneous urticaria.

Statistical Analysis

The statistical analysis in this study was conducted using two software tools: JASP (Version 0.18.3.0, Computer Software, Amsterdam, The Netherlands) and Jamovi (Version 2.3.28, Computer Software, Sydney, Australia). Continuous (numeric) variables are presented in tables, which include the mean±standard deviation, median, minimum, and maximum values depending on their distribution. Descriptive statistics were analyzed using cross-tabs and chi-squared tests. Additionally, we performed a paired t-test to compare patients' evaluation scores from their initial and final visits. Categorical variables were summarized as numbers and percentages. We conducted Kolmogorov-Smirnov and Shapiro-Wilk tests to assess the normality of the numerical variables. Statistical significance was set at $p<0.05$.

RESULTS

Of the patients, 62.5% (n=40) were female and 37.5% (n=24) were male. Their ages ranged from 20 to 75 years, with an average of 44.3±13.7 years. However, the mean age at which urticaria first appeared was 46.6±40.7 years. The duration of urticaria ranged from 7 to 198 months, with a mean of 46.6±40.7 months. The average duration of omalizumab use by the patients was found to be 23.6±30.3 months. The mean follow-up period for the patients was 27.0±31.0 months. At the time of admission, the average blood eosinophil % value was 1.74±1.31. Additionally, 40.6% (n=26) of the patients had a history of angioedema and 21.9% (n=14) had elevated total IgE levels (Table 1).

Table 1. Clinical and demographic characteristics of all patients

	Mean±SD	Min–Max	n	%
Age	44.3±13.7	20–75		
Age of onset of urticaria	40.2±13.7	12–71		
Urticaria duration, months	46.6±40.7	7–198		
Omalizumab use duration, months	23.6±30.3	1–192		
Patient follow-up period, months	27.0±31.0	1–192		
Blood eosinophil levels, %	1.74±1.31	0–5.9		
Gender				
Female			40	62.5
Male			24	37.5
Age category, years				
18–65			61	95.3
>65			3	4.7
Urticaria duration category				
6–12 months			4	6.3
12–36 months			30	46.9
3–5 years			11	17.2
>5 years			19	29.7
Increased total IgE			14	21.9
Presence of angioedema			26	40.6

SD: Standard deviation; Min: Minimum; Max: Maximum.

Before starting omalizumab therapy, patients received dapsone, oral corticosteroids (OCS), anti-leukotrienes (ALKs), and second-generation antihistamines (sgAHs). Among patients, the most frequently used treatment was sgAH alone at the maximum dose, accounting for 60.9% (n=39). The second most commonly used treatment was the combination of sgAHs and OCS, which accounted for 31.3% (n=20) of patients. Of the patients treated with omalizumab, 96.9% (n=62) used sgAHs, whereas 3.1% (n=2) used a combination of sgAHs and dapsone. The sgAH doses used by patients receiving omalizumab were as follows: 1X dose (39.1%, n=25), 4X dose (34.4%, n=22), 2X dose (21.9%, n=14), and 3X dose (4.7%, n=3). No significant correlation was observed between the antihistamine dosage and treatment response (p=0.06). During the follow-up period, changes were made to the dose or duration of omalizumab in 23.4% (n=15) of patients. These changes included extended intervals (12.5%, n=8) and increased doses (10.9%, n=7) (Table 2).

Seven patients (10.9%) discontinued the omalizumab treatment. The reasons for discontinuation were transfer to another center (4 patients, 6.3%), completion of treatment (2 patients, 3.1%), and treatment failure (1 patient, 1.6%). Moreover, discontinuation occurred most often before six months. During follow-up, myalgia was observed as a side effect of omalizumab in 4.7% (n=3) of the patients (Table 2).

The final response status of patients to omalizumab treatment, in decreasing order of frequency, was as follows: good response (≥90% reduction, n=30, 46.9%), complete response (complete recovery, n=17, 26.6%), moderate response (30–89% reduction, n=16, 25%), and poor response (<30% reduction, n=1, 1.6%) (Table 2).

During the evaluation of the patients on their first visit before receiving omalizumab treatment and on their last visit after receiving omalizumab treatment, a statistically significant difference was observed in the follow-up assessments of UCT, UAS7, and DLQI scores (all p<0.001) (Table 3). Data on the UCT, UAS7, and DLQI scores for all patients at the first and last visits are presented in Figure 1 and Table 3.

Table 2. Detailed data on the treatment of all patients (n=64)

	%
Previous treatments	
sgAHs (highest dose)	60.9
sgAHs+ OCS	31.3
sgAHs combination	3.1
sgAHs + ALKs	1.6
sgAHs+ Dapsone	1.6
sgAHs + ALKs + OCS	1.6
Concurrent treatments	
sgAHs	96.9
sgAHs + Dapsone	3.1
Use of sgAHs dose	
sgAHs + Dapsone	3.1
1X dose	39.1
2X dose	21.9
3X dose	4.7
4X dose	34.4
OMA dose or duration change	
Present	23.4
Treatment change type	
Extended intervals	12.5
Increasing dose	10.9
Discontinuation of treatment	
Present	10.9
Reasons for discontinuing treatment	
Treatment failure	1.6
Completion of treatment	3.1
Transfer to another center	6.3
Timing of discontinuing the OMA	
<6 months	6.3
6 months – 1 year	1.6
1–2 years	3.1
Omalizumab side effect	
Present	4.7
Absent	95.3
Omalizumab side effect type	
Myalgia	3.1
Arthralgia	–
Headache	–
Regional injection site reaction	–
Other	–
Final response to treatment	
Other	–
Complete response (complete recovery)	26.6
Good response (≥90% reduction)	46.9
Moderate response to treatment (30–89% reduction)	25
Poor response to treatment (<30% reduction)	1.6

sgAHs: Second generation antihistamines; OMA: omalizumab; ALKs: Anti-leukotrienes; OCS: Oral corticosteroids.

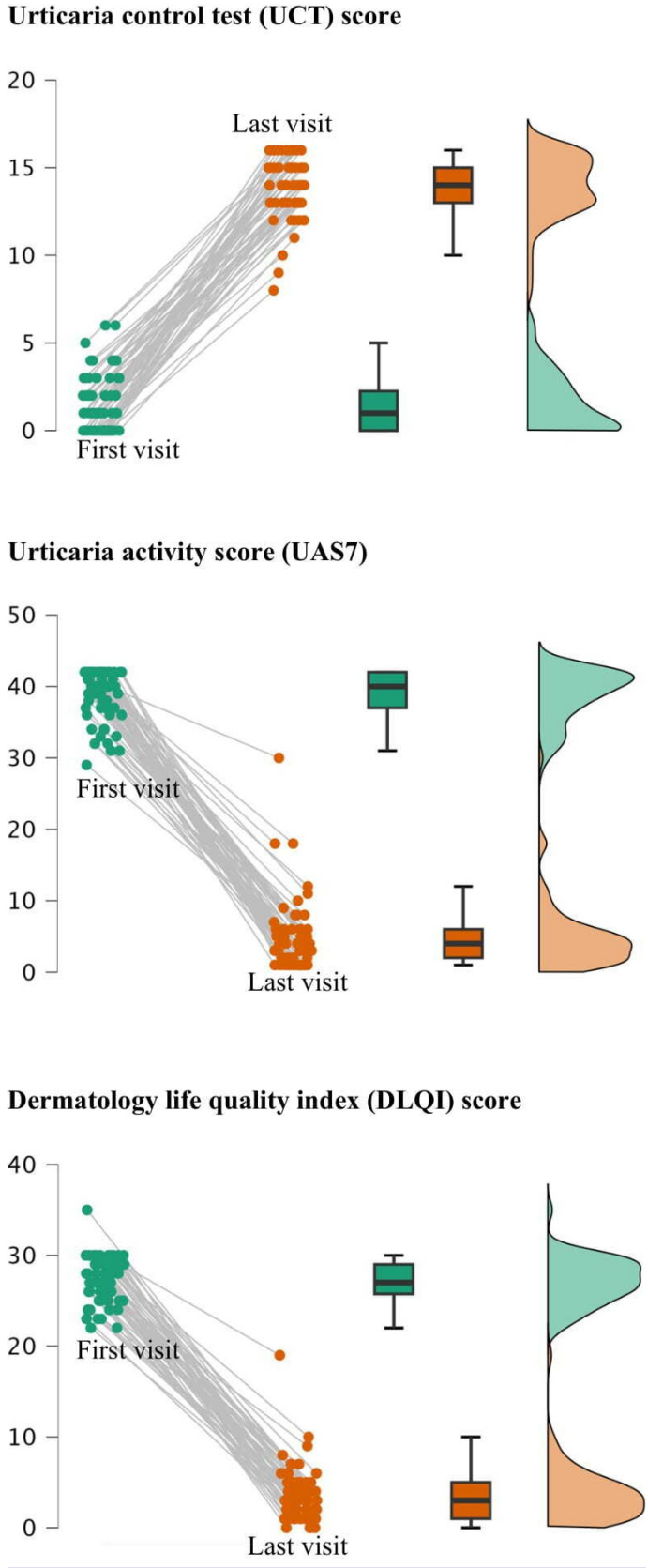

Figure 1. Changes in patients' UCT, UAS7, and DLQI scores at the first and last visit.

TABLE 3. Data on all patients' UCT, UAS7, and DLQI scores at the first and last visit (n=64)

Category, (%)	First visit	Last visit	p
UCT score, mean±SD	1.47± 1.61	13.9±1.76	**<0.001**
0–7	100	–	
8–11	–	7.8	
12–16	–	92.2	
UAS7 score, mean±SD	38.7±3.57	4.86±4.79	**<0.001**
0–6	–	82.8	
7–15	–	12.5	
16–27	–	3.1	
28–42	100	1.6	
DLQI score, mean±SD	27.1±2.45	3.52±3.00	**<0.001**
0–1	–	29.7	
2–5	–	54.7	
6-10	–	14.1	
11–20	–	1.6	
21–30	100	–	

*: Paired t-test; SD: Standard deviation; UCT: Urticaria control test; UAS7: Weekly urticaria activity score; DLQI: Dermatology Life Quality Index.

DISCUSSION

An initial dose of 300 mg, administered once every four weeks, is recommended for treating CSU with omalizumab, according to international guidelines. The current licensed doses for this medicine are 150 mg and 300 mg. A dose of 300 mg has been suggested to result in a faster, stronger, and longer-lasting response [6, 7]. However, the efficacy of omalizumab varies from patient to patient, and there are variations in the rate of recurrence following treatment, despite it being the sole and first known biological agent. Therefore, it is important to remember that patient-based illness and treatment management should serve as the foundation [2]. A study examining 84 publications revealed that approximately 60% of the published research on the use of omalizumab had a starting dose of 300 mg. In approximately 35% of studies, the initial dose was 150 mg. These findings confirm that omalizumab, when administered at the prescribed dosage, is both safe and effective [8]. In our study, we observed that all patients were treated with 300 mg every four weeks, as recommended in the literature.

A recent study by Wang et al. [9] examined 235 patients with CSU treated with omalizumab at a dosage of either 150 or 300 mg. The study found that approximately 96% of patients (n=226) experienced a rapid response to treatment within the first month. Furthermore, approximately 75% (n=180) of patients achieved a complete response to treatment. By the end of the third month, approximately 99% of the patients (n=232) had responded to the treatment. Notably, all age groups showed a positive response to treatment. The study also observed a significant improvement in UAS7 and the DQLI scores upon starting treatment (both $p<0.001$). Only six patients experienced side effects, including injection site reactions (n=3), weight gain (n=2), increased hair loss (n=2), and arthralgia (n=1). In our study, we observed a remarkably high response rate among patients. Specifically, 98.4% of the patients demonstrated a moderate or higher response. Approximately half of the patients experienced a good response, whereas a quarter achieved a complete response. When evaluating treatment response, we noticed a significant difference in the UAS7, UCT, and DLQI scores before and after omalizumab treatment ($p<0.001$ for all three scores) during the last visit. However, unlike this study, the most common side effect observed in patients was myalgia, which occurred in three patients (3.1%).

In 2023, Hide et al. [10] published a study that examined the data of 280 patients who received omalizumab for CSU. Of these patients, 274 were administered a dose of 300 mg, while six received a lower dose. The average duration of omalizumab treatment was 195 days and the mean follow-up period was 330 days. The study observed that over 90% of the patients responded positively to treatment, but approximately 23% experienced relapse after treatment discontinuation. Approximately 4% (n=11) of patients reported drug-related side effects, although none of these events were deemed serious. The patients in this study had an average duration of omalizumab use of 23.6 months, and the average follow-up period was 27.0 months, which was longer than the duration reported in the present study. No significant drug-related adverse effects were observed.

Recommended approaches to treatment during follow-up include reducing the dose and increasing the interval of drug use after patients respond well to treatment with 300 mg every four weeks. It is argued that this treatment management contributes to patients' spontaneous remission in the early period and is cost-effective [11]. This study revealed that 15 individuals experienced

changes in both dosage and duration of treatment during the follow-up period. Almost half of the patients required a longer dosage interval, whereas the rest required an increased dosage. However, no dose reductions were required during the follow-up period.

While guidelines are available for treating chronic urticaria, there is still a lack of clear information about the ongoing use of omalizumab therapy and antihistamines. Currently, there is no consensus on the most effective way to administer antihistamine treatment with omalizumab, including determining the appropriate dosage, duration of treatment, and discontinuation of treatment [12, 13].

A multicenter study conducted in patients undergoing omalizumab treatment suggested that second-generation antihistamines (sgAHs) could be a good choice for symptom management. This study demonstrated that sgAHs were effective in reducing symptoms in patients who responded well to treatment, but were not completely responsive [12]. In our study, we administered sgAH in combination with omalizumab to all the patients. Approximately 40% of patients received the lowest dose of sgAH, whereas approximately 35% received the highest dose of sgAH with omalizumab. However, we found no significant correlation between the AH dosage and treatment response.

Another multicenter study published in 2022 included 298 CSU patients treated with omalizumab. The study found that CSU patients without inducible urticaria who responded well to omalizumab could maintain control of their symptoms even without antihistamines [13]. Another study reported that omalizumab treatment resulted in a rapid response in patients. However, there was no difference in treatment response between omalizumab alone and in combination with antihistamines. Additionally, it has also been suggested that immunomodulatory agents, such as dapsone and colchicine, can be used in certain patients [14]. In our study, we found that dapsone was added to the treatment regimen of two patients who had already received omalizumab and sgAH.

In a study investigating the effects of CSU on patients' mental health, it was found that approximately 41% of the patients exhibited depressive symptoms. Furthermore, those who responded to omalizumab treatment experienced a significant decrease in depression assessment scores [15]. To evaluate the impact of CSU treatment on patients' lives, we used the DLQI. The results indicated a significant difference ($p<0.001$) in the DLQI scores before and after omalizumab treatment, suggesting a positive effect on patients' lives.

The limitations of our study include the relatively small number of patients from a single center, insufficient data on relapse, and lack of detailed comparison data for each visit, except for the first visit before omalizumab treatment and the last visit after omalizumab treatment. We believe that further studies on the use of antihistamines in combination with omalizumab treatment could have a positive impact on reducing the required dose of omalizumab over time and extending the interval between treatments. This could be a significant factor in making the drug more accessible and cost effective for patients.

Conclusion

Our study showed that omalizumab is a reliable and beneficial therapeutic agent for combination therapy with antihistamines for the treatment of CSU.

Ethics Committee Approval: The Ankara Etlik City Hospital Ethics Committee granted approval for this study (date: 26.04.2023, number: AESH-EK1-2023-050).

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