Original Article

The Effect of Omalizumab Treatment on Hematological Inflammatory Parameters and Immunoglobulin E Levels in Patients with Chronic Spontaneous Urticaria

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Abstract

Objectives: We aimed to evaluate the effect of omalizumab use on hematological parameters, inflammatory markers, and immunoglobulin E (IgE) in patients with chronic spontaneous urticaria and to determine whether there would be any difference between patient and control groups in terms of these values and whether IgE levels before and after omalizumab treatment are correlated with the Urticaria Control Test (UCT). **Materials And Methods:** Forty-five patients with chronic spontaneous urticaria and 45 healthy controls who presented to the dermatology outpatient clinic of Yozgat Bozok University Research and Training Hospital were analyzed retrospectively. Age, gender, neutrophil, lymphocyte, monocyte, eosinophil, basophil, and thrombocyte counts and IgE values before and after 24 weeks of treatment were recorded, and IgE ratios before and after treatment were calculated. The UCT was performed on the patients. The neutrophil/lymphocyte, platelet/lymphocyte, lymphocyte/monocyte, eosinophil/basophil, and eosinophil/lymphocyte ratios were calculated for the control group and the patient group, both before and after treatment. Mean platelet volume (MPV), which is also considered an inflammatory marker, was recorded before treatment, in both the control group and the patient group. **Results:** The patients' median pre-treatment IgE level [189.0 (1.0–1824.0)] was significantly lower than the post-treatment level [561.0 (2.0–4301.0)] (P<0.001). No significant difference was determined in basophil, platelet, eosinophil, monocyte, lymphocyte, and neutrophil counts and neutrophil/lymphocyte, platelet/lymphocyte, lymphocyte/monocyte, eosinophil/basophil, and eosinophil/lymphocyte ratios before and after omalizumab treatment. The mean UCT score of the patients was found to be 11.5 (± 3.9). The mean IgE ratio post-omalizumab treatment/pre-omalizumab treatment was 5.8. No significant difference was found between the patient and control groups regarding neutrophil/lymphocyte, platelet/lymphocyte, lymphocyte/monocyte, eosinophil/basophil, and eosinophil/lymphocyte ratios, as well as MPVs. A significant correlation was found between the patients' UCT scores and IgE levels after omalizumab treatment (r=0.313; P=0.046). **Conclusion:** No changes were observed in hematological inflammatory markers of patients with chronic spontaneous urticaria, compared with healthy controls. Besides, no changes were observed in either inflammatory markers or hematological parameters, following the use of omalizumab in these patients. Hence, it is considered that there is no harm in using omalizumab in diseases such as chronic disease anemia, chronic idiopathic neutropenia, and idiopathic thrombocytopenic purpura. The fact that omalizumab treatment caused a significant increase in IgE levels, in correlation with previous studies, made us think that the methods of reducing the dose or extending the dose interval should be preferred, instead of abruptly interrupting the treatment during the discontinuation period to prevent relapses.

Keywords: Blood cell count, chronic urticaria, immunoglobulin E, inflammation mediators, omalizumab

Introduction

Urticaria is a disease that can be seen in 15–25% of individuals in society at some point in their life and is

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common in the routine of dermatology outpatient clinics. Urticarial lesions can occur anywhere on the body and are characterized by lesions that itch, redden, swell, and disappear as described classically. Lesions lasting less than 6 weeks are called "acute," whereas lasting longer than 6 weeks are called "chronic" urticaria. The chronic urticaria disease is also divided into two: "chronic spontaneous urticaria (CSU)" and "chronic inducible urticaria."[1]

Various mechanisms such as autoimmunity, chronic infections, stress, pseudoallergens, and autoinflammation are emphasized in the pathogenesis of CSU. C-reactive protein (CRP) is a sensitive marker of inflammation and has been found to be high in chronic urticaria.[2] Therewithal, studies have shown that CRP elevation is associated with urticaria disease activity.[2,3] Following these studies, investigations of inflammation markers have gained momentum to elucidate the pathogenesis of CSU. Platelet count, mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), eosinophil/basophil ratio (EBR), eosinophil/lymphocyte ratio (ELR), and platelet/lymphocyte ratio (PLR) are among these inflammatory markers and can be easily obtained from a complete blood count with a low cost. In some of the studies conducted so far, it has been evaluated whether there is a difference in these values between the patient and control groups and whether there is a change before and after treatment with omalizumab, a monoclonal antibody used in the treatment of CSU.[4-7] The results of these studies differ from each other. With the widespread use of omalizumab in the treatment of chronic urticaria, studies have focussed on the fact that pre-treatment immunoglobulin E (IgE) level can be used as a criterion for predicting response to omalizumab treatment, and IgE increased coefficient during treatment may be related to Urticaria Control Test (UCT) scores.[8-10] In recent years, the UCT has been developed, in the evaluation of chronic urticaria activity, as it can both promote patient adherence and can be used practically in the daily outpatient clinic routine.[11] The use of UCT has played a role in guiding the physician and in deciding to continue or alter treatment in follow-up and facilitated the evaluation of disease activity in studies with CSU.

In line with this information, we intend to assess the impact of omalizumab use on hematological parameters, inflammatory markers, and IgE in patients with CSU. However, it was investigated whether there was a difference between the patient and control groups in terms of these values, and the correlation between post-treatment IgE/pre-treatment IgE ratios and UCT.

Materials and methods

The study protocol was approved by the Yozgat Bozok University Ethics Committee [2017-KAEK-189_2021.01.18_10]. Forty-five CSU patients, treated with omalizumab, and 45 controls, age- and gender-matched, examined for routine health check-ups, and had no systemic disease or smoking, were included in the study. The study was performed with the patients who applied to the Yozgat Bozok University Research and Training Hospital Dermatology Outpatient Clinic from June 2016 to December 2020. The data were obtained retrospectively from the hospital registry system. Patients with hemogram values and IgE values, before and after 24 weeks of omalizumab treatment, were included in the study. Patients with missing hospital registration information, any comorbidity of inflammatory systemic disease, and smokers were excluded from the study. Age, gender, neutrophil, lymphocyte, monocyte, eosinophil, basophil, thrombocyte counts, and IgE values before and after 24 weeks of treatment were recorded, and post-treatment IgE/pre-treatment IgE ratios were calculated. UCT was performed on the patients. NLR, PLR, LMR, EBR, and ELR values of the patient group were calculated, before and after the treatment, and also the same values of the control group were calculated. Moreover, pre-treatment values of MPV, which is also considered an inflammatory marker, were recorded in both the control group and the patient group.

Statistical analysis

In summarizing data from the study, descriptive statistics are tabulated for continuous (numeric) variables as mean ± standard deviation or median, minimum, and maximum, depending on the distribution. Categorical variables were outlined as numbers and percentages.

The distribution normality of numerical variables was analyzed via Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson–Darling tests. In the comparison of two independent groups, a *t*-test was used for independent groups when numerical variables conformed to a normal distribution, and the Mann–Whitney *U*-test was used when they did not show normal distribution. In the comparison of some clinical parameters before and after treatment, the *t*-test was used for dependent groups in cases in which the variables were normally distributed, and the Wilcoxon test was used when they did not. Spearman's rho correlation coefficient was used to analyze the correlations between UCT and IgE values, before and after omalizumab treatment. Statistical analyses were performed using the software of the Jamovi project (2020), Jamovi (Version 1.8.1) (Computer Software) (retrieved from https://www.jamovi.org) and JASP (Version 0.14.1.0) (retrieved from https://jasp-stats.org), and the level of significance was considered as 0.05 (*P*-value).

Results

The mean age of the patients was 43.9 (±14.7). Thirty (66.7 %) patients were female, and 15 (33.3 %) were male.

The mean UCT score of the patients was found to be 11.5 (± 3.9). Mean IgE ratios of patients post-omalizumab/pre-omalizumab treatment was 5.8 [Table 1].

The median IgE level of the patients before treatment [189.0 (1.0−1824.0)] was significantly lower when compared with the post-treatment level [561.0 (2.0−4301.0)] (P<0.001). No significant difference was found, between pre-treatment and post-treatment basophil, platelet, eosinophil, monocyte, lymphocyte, neutrophil, NLR, PLR, EBR, LMR, and ELR levels [Table 2 and Figure 1]. No significant difference was determined between the NLR, PLR, EBR, LMR, ELR, and MPV values of the patient and control groups [Table 3].

A significant positive correlation was found between UCT scores of the patients and their IgE levels post-omalizumab treatment (r=0.313; P=0.046). However, no correlation was determined between the UCT scores of the patients and IgE levels pre-omalizumab treatment [Table 4 and Figure 2].

Discussion

CSU is a disease with attacks of itching, redness, swelling, and disappearance. Patients often experience these attacks, that last longer than 1 year, and in a substantial proportion, CSU persists for 5 years or more. These attacks cause problems such as sleep disorders, emotional stress, and loss of work in patients and lead to an increase in the current vicious cycle of the disease and a severe deterioration in the quality of life.[12,13] CSU remains idiopathic, with a high rate of 45% even after 10 years of follow-up; however, various autoimmune diseases, chronic infections, and immune disorders may occur through the duration of the disease in some patients.[13] Therefore, studies on this idiopathic group are still ongoing.

The aim of treatment in CSU is to improve the quality of life and to ensure the continuity of the treatment by preferring treatments with a low adverse effect profile as it is a chronic disease. In up-to-date treatment guidelines, the use of antihistamine medications is recommended as the first-line treatment. Of these agents, non-sedating, second-generation antihistamines should be preferred, and the dose should be increased up to four times a day, depending on the treatment response. Nonetheless, in some patients, the symptoms may not be controlled with the use of high-dose antihistamines. In this situation, the use of omalizumab, an anti-IgE monoclonal antibody, is recommended as an efficient and safe agent.[14] Through binding to free IgE with high affinity, omalizumab prevents allergen-specific IgE from binding to its specific receptor on the mast cell surface. It has no direct impact on mast cells or basophils, as it does not bind directly to cell surface IgE. Thus, it is not expected that omalizumab treatment alters the number or function of blood cells.[6,15,16] The findings of our study are also in line with this expectation. Compared with pre-treatment levels, no difference was determined in the leukocyte, neutrophil, eosinophil, monocyte, basophil, and platelet counts of patients, after 24 weeks of omalizumab treatment. Because omalizumab has no impact on hematological parameters, it can be used safely in the treatment of patients with hematological comorbidities, such as chronic disease anemia, chronic idiopathic neutropenia, and idiopathic thrombocytopenic purpura. Likewise, in the study of Çildağ and Şentürk,[10] no change was observed in eosinophil, lymphocyte, and platelet counts, following 12 weeks of omalizumab treatment. As stated earlier, a compensatory increase in IgE is expected in the patients using this treatment, as omalizumab binds to free IgE with high affinity. In support of this finding, the mean coefficient of IgE increase, before and after 24 weeks of omalizumab treatment, was found to be 5.8 in the present study. This finding clinically indicates that, even if the disease is under control, the decision to discontinue the treatment should be as controlled as possible, because of the fact that free IgE increases with omalizumab treatment. To prevent disease recurrence, it would be a better choice to either extend the dose intervals or reduce the dose. Similar to our review, in the report of Türk *et al.*,[17] although there are no definitive literature data on this subject yet, based on real-life data, it was recommended to gradually discontinue omalizumab treatment by extending the dose intervals.

Numerous studies have scrutinized the validity of serological tests in CSU, to establish the theory of autoimmune disease and to form an autoimmune basis.

Table 1: Sociodemographic characteristics and laboratory values of the patients

	Mean ± SD/*n* (%)	Median [Min.–Max.]
Age	43.9 ± 14.7	43.0 [18.0–76.0]
Sex (%)		
Male	15 (33.3)	15 (33.3)
Female	30 (66.7)	30 (66.7)
Urticaria Control Test	11.5 ± 3.9	12.0 [0.0–16.0]
"Post-treatment/pre-treatment IgE"	5.8 ± 10.6	3.2 [0.7–68.0]

Descriptive statistics were presented as mean ± standard deviation or median [min-max] depending on distribution for numerical variables and number (%) for categorical variables.

Table 2: Comparison of patients' pre-treatment and post-treatment laboratory parameters

	Pre-treatment	Post-treatment	*P*-value
IgE (ng/mL)	189.0 [1.0–1824.0]	561.0 [2.0–4301.0]	<0.001**
Basophil count	0.0 [0.0–2.0]	0.0 [0.0–2.0]	0.134**
Platelet count	277.0 [136.0–417.0]	269.0 [161.0–453.0]	0.901**
Eosinophil count	0.1 [0.0–1.0]	0.1 [0.0–1.2]	0.540**
Monocyte count	0.5 ± 0.2	0.5 ± 0.1	0.768*
Lymphocyte count	2.4 ± 0.6	2.4 ± 0.7	0.803*
Neutrophil count	4.9 ± 1.9	4.8 ± 1.8	0.744*
NLR	2.1 ± 0.8	2.1 ± 0.8	0.792*
PLR	121.2 ± 45.6	123.6 ± 52.9	0.637*
EBR	3.6 [0.0–100.0]	3.5 [0.0–15.2]	0.528**
LMR	4.9 [2.4–8.8]	4.8 [0.6–80.0]	0.657**
ELR	0.1 [0.0–0.6]	0.1 [0.0–0.7]	0.906**

*The *t*-test was used for dependent groups

**The Wilcoxon test was used

The underlined *P*-values were considered significant ($P<0.05$)

Descriptive statistics were presented as mean ± standard deviation or median [min–max], depending on distribution for numerical variables.

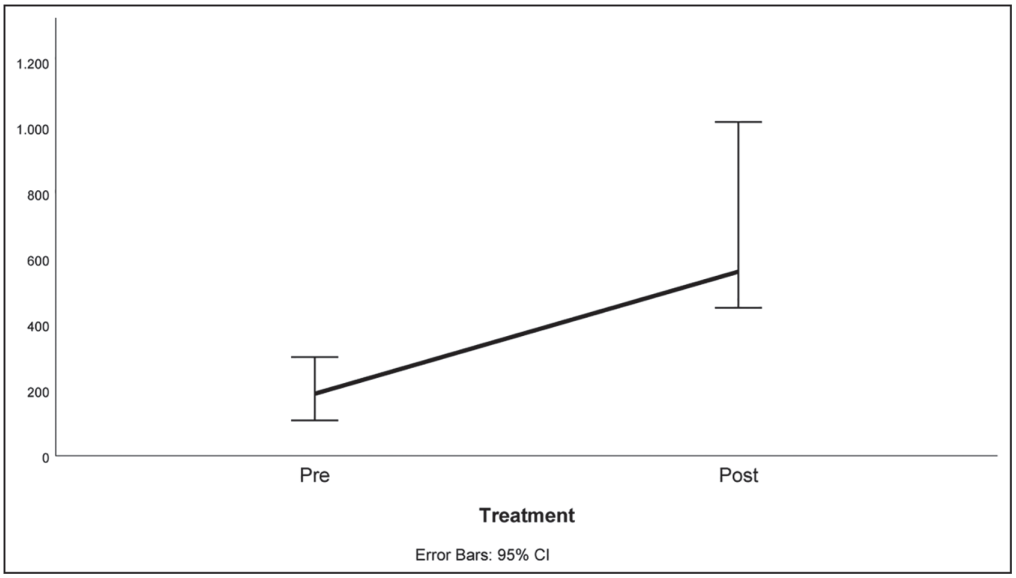

Figure 1: IgE change before and after omalizumab treatment

Immunological changes in the etiopathogenesis of CSU include findings such as increase in the number of T lymphocytes and autoreactive T cells, increase in TNFα, IL-10, MIP-Iα, and RANTES secretion from peripheral blood mononuclear cells, decrease in IL-4 secretion, impaired TLR9-mediated interferon-α production, increased levels of TNF, IL-1β, IL-6, IL-13, IL-12p70, IL-10, IL-31, and B-cell activating factor in serum, as well as increased levels of D-dimer and prothrombin fragments.[18] In the literature, NLR and PLR in various chronic diseases, EBR and ELR in pre-operative and post-operative follow-up in patients with sinonasal polyposis, and LMR in cancer types such as ovarian cancer and gastric cancer as a predictor of poor prognosis have been used. And also LMR has been used as a criterion for response to treatment in the use of some targeted drugs in B-cell lymphoma.[19-24] As the autoimmune hypothesis is emphasized in the pathogenesis of CSU, as mentioned earlier, NLR, PLR, EBR, LMR, and ELR values, which are now considered as inflammatory markers in many diseases, were investigated in the present study. Therefore, the values before and after 24 weeks of omalizumab treatment in the patient group were compared, and it was also assessed whether there was a difference in these values before treatment in the patient group when compared with the control group. The results indicate that there is no difference in hematological inflammatory markers in CSU patients, compared with the control group. This outcome can be interpreted as a supporting finding that the inflammatory process in CSU is mainly dominated by cellular immunity. Moreover, it was observed that the use of omalizumab treatment did not lead to any change in these inflammatory markers. When the other studies in the literature on this subject are reviewed, it

Table 3: Comparison of laboratory values of patient group and control group

	Patient ($n=45$)	Control ($n=45$)	*P*-value
NLR	2.1 ± 0.8	1.9 ± 1.1	0.220
PLR	121.2 ± 45.6	126.7 ± 65.3	0.645
EBR	3.6 [0.0–100.0]	2.5 [0.0–16.5]	0.119
LMR	4.8 ± 1.4	4.5 ± 1.6	0.373
ELR	0.1 [0.0–0.6]	0.0 [0.0–0.2]	0.058
MPV	10.1 ± 0.9	9.9 ± 0.9	0.373

*The *t*-test was used for independent groups

**The Mann–Whitney test was used

Descriptive statistics were presented as mean ± standard deviation or median [min–max], depending on distribution for numerical variables

is noticed that similar to the present study, Ertaş *et al.*[4] found that there was no difference in NLR in the patient group compared with the control group, but unlike our results, NLR decreased after 12 weeks of omalizumab treatment. In the study of Tamer,[6] LMR, PLR, and NLR values were analyzed before and after 12 weeks of omalizumab treatment, and it was revealed that MLR and NLR decreased after treatment, whereas PLR increased; however, this difference was not significant. In the study of Ataseven *et al.*,[25] only NLR and PLR were compared between the patient and control groups regardless of treatment, and similar to our results, no significant difference was detected between them. Besides, in the study of Aktaş Karabay *et al.*,[26] NLR was found to be higher in CSU patients, compared with the control group; other inflammatory markers were not investigated, and their changes after any treatment were not studied. To the best of our knowledge, there is no study in the literature investigating the change in EBR and ELR values before and after treatment in CSU patients or comparing these values with the control group.

In several studies in recent years, similar to hematological inflammatory markers, MPV values were also found to be different in some diseases, compared with control groups, and it was suggested that MPV could be used as an inflammatory marker. For instance, MPV values of patient groups in ankylosing spondylitis, rheumatoid arthritis, and CSU were observed to be lower, compared with the control groups.[4] Contrary to these results, in the present study, no significant difference was determined between patient and control groups in terms of MPV. The difference in studies may be due to the varying number of patients.

When the UCT scores were examined, it was found that the mean score was 11.5, even after a long 24-week treatment period. Yet, if the UCT score is 12 and above, the symptoms of the disease are considered to be under control. This result demonstrates that there are still patients whose symptoms continue, despite using omalizumab treatment. The results of a recent study by Maurer *et al.*[27] support this outcome, and it was found that 27% of CSU patients followed up for 2 years, and using omalizumab treatment,

Table 4: Correlations between pre- and post-treatment UCT and IgE levels of patients

		Spearman's rho	*P*-value
UCT	Pre-treatment—IgE	0.220	0.146
UCT	Post-treatment—IgE	0.313	0.036

Spearman's rho correlation coefficient was used

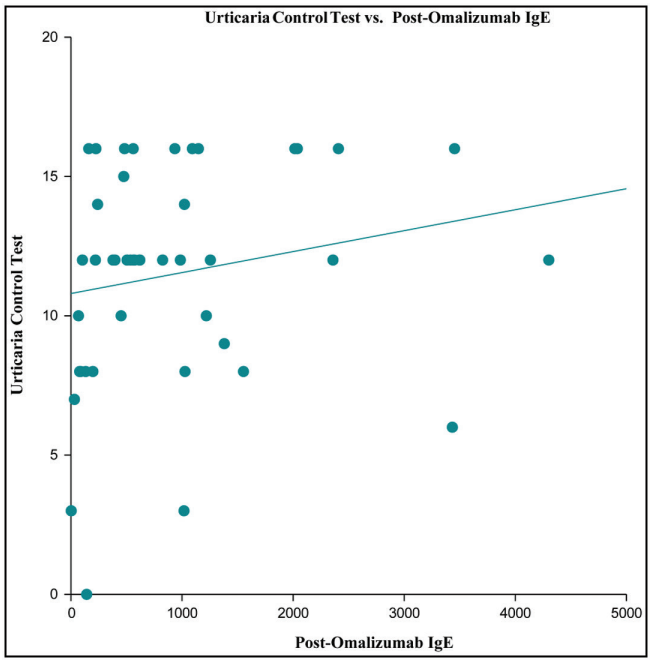

Figure 2: Positive correlation between UCT scores and post-omalizumab treatment IgE levels

had UCT scores below 12 and were "not under adequate treatment." Hence, we should check out the UCT scores, which is a practical measure at each outpatient clinic visit, and consider other treatment options in patients who are not under adequate control. Another remarkable finding in the present study is the positive correlation between UCT and post-omalizumab treatment IgE values. This result reveals that patients with high IgE levels after omalizumab treatment have fewer urticarial symptoms than patients who remain at low IgE levels. Although there is currently no target level related to the IgE level intended to be reached, these data may conduct us in deciding to switch to alternative treatment options more rapidly in a patient who can be mild to moderately controlled with omalizumab treatment. There are numerous studies in the literature that support this finding.[8,9,28] In these studies, therewithal, it has been emphasized that increased total IgE may be associated with higher disease activity, longer disease duration, good response to omalizumab treatment, and rapid relapse after omalizumab treatment discontinued.

Limitations of the study

The study has several limitations. The first of these is that the study was designed retrospectively. For this reason, patients

who did not attend follow-ups or whose blood tests were not performed in some of their follow-ups were excluded from the study, thus the sample size remained small. Consequently, although there is a quantitative difference between the investigated values, this difference may not have been significant. Hence, more valid results can be obtained if a similar study with larger sample size is conducted prospectively. The second limitation is the memory factor that might have occurred due to the computation of the patients' UCT scores at the 24th week of their treatment and the retrospective questioning of the UCT scores before the treatment when attended the follow-up. Thus, the calculation of the current UCT scores of the patients who presented due to CSU at each follow-up would be more helpful in the follow-up of the treatment and would provide more accurate results in terms of scientific studies.

Conclusion

Compared with healthy controls, no changes were observed in hematological inflammatory markers in CSU patients. Moreover, no changes were observed in both inflammatory markers and hematological cell counts due to omalizumab use. Hence, it is considered that there is no harm in using omalizumab in diseases such as chronic disease anemia, chronic idiopathic neutropenia, and idiopathic thrombocytopenic purpura. The fact that omalizumab treatment caused a significant increase in IgE levels, in correlation with previous studies, made us think that the methods of reducing the dose or extending the dose interval should be preferred, instead of abruptly interrupting the treatment during the discontinuation period to prevent relapses. Another remarkable finding in the present study is the positive correlation between UCT and post-omalizumab treatment IgE values. This result reveals that patients with high IgE levels after omalizumab treatment have fewer urticarial symptoms than patients who remain at low IgE levels. Although there is currently no target level related to the IgE level intended to be reached, these data may conduct us in deciding to switch to alternative treatment options more rapidly, in a patient who can be mild to moderately controlled with omalizumab treatment.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

Data are openly available in a public repository that issues datasets with DOIs.

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