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ORIGINAL ARTICLE



The effect of omalizumab on hematological and inflammatory parameters in patients with chronic spontaneous urticaria

Ersoy Acer , Hilal Kaya Erdogan , Nihan Yüksel Çanakçı  and Zeynep Nurhan Saracoglu 

Department of Dermatology, Eskişehir Osmangazi University, Eskişehir, Turkey

ABSTRACT

Purpose: The mechanism of action of omalizumab in chronic spontaneous urticaria (CSU) is not exactly known. In previous studies, D-dimer which is a fibrin-degradation product and interleukin-31 which has a role in inflammation were found to be decreased in patients with chronic urticaria treated with omalizumab. However, to our knowledge, there is no study on the effects of omalizumab on the ratio of neutrophil to lymphocyte (NLR) and the ratio of platelet to lymphocyte (PLR) which are inflammatory parameters in patients with CSU in the PubMed database. In this study, we aimed to evaluate the effects of omalizumab on hematological and inflammatory parameters in patients with CSU.

Materials and Methods: One hundred six CSU patients treated with omalizumab were evaluated retrospectively. Complete blood count (CBC) and C-reactive protein (CRP) levels before treatment and at the third month of treatment were recorded. NLR and PLR were calculated from the CBC results. CBC parameters, CRP levels, NLR and PLR of the patients before treatment and at the end of third month of treatment were compared.

Results: There was a significant decrease in white blood cell count, platelet count, neutrophil count, CRP level, NLR and PLR and a significant increase in mean platelet volume and eosinophil count with omalizumab treatment in CSU patients ($p < 0.05$). Basophil count increased; but there was no statistically significant difference ($p = 0.293$).

Conclusion: This study shows that omalizumab has not only anti Ig E effect, but also it may have inhibitory effects on inflammation and coagulation in patients with CSU.

Further prospective studies are warranted in order to evaluate the effect of omalizumab on hematological and inflammatory parameters and correlation between omalizumab response rate and these inflammatory parameters in patients with CSU.

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Introduction

Urticaria is a common group of diseases characterized by pruritic wheals and/or angioedema. If the symptoms last more than 6 weeks, it is called as chronic urticaria¹. CU is divided into two groups: chronic inducible urticaria and chronic spontaneous urticaria (CSU)^{1–3}. Pathogenesis of CU is not exactly elucidated; but various mechanisms such as autoimmunity, inflammation and coagulation may play roles⁴.

C-reactive protein (CRP) is a sensitive systemic marker of inflammation. It was high in patients with CU and correlation with disease activity was reported in previous studies^{5–9}. The platelet count, mean platelet volume (MPV), the ratio of neutrophil to lymphocyte (NLR) and the ratio of platelet to lymphocyte (PLR) can be obtained from the complete blood count (CBC), which is cheap and easily accessible. Activation of coagulation cascade in patients with CU has been reported. There is a close relationship between coagulation and inflammation^{2,4}. MPV is an important marker of platelet reactivity and is an indicator of inflammation¹⁰. In the literature, platelet count and MPV have been evaluated in patients with urticaria and there are conflicting results^{10–14}. In recent

years, NLR and PLR have been used as inflammatory markers in many diseases such as rheumatoid arthritis, familial Mediterranean fever, psoriasis and as prognostic factor in oncological diseases^{15–19}. To our knowledge, there is no study evaluating these inflammatory markers in patients with urticaria in the PubMed database.

Omalizumab is used as a second-line therapy in the anti-histamine-resistant CSU^{1,2}. The mechanism of action of omalizumab in CSU is not exactly known²⁰. A decrease in D-dimer levels, which is a fibrin-degradation product, and in interleukin-31 (IL-31) levels, which have a role in inflammation, in CU patients treated with omalizumab have been reported^{21,22}. To our knowledge, our study is the first study on the effect of omalizumab on NLR and PLR in patients with CSU.

In this study, we aimed to evaluate the effect of omalizumab on hematological and inflammatory parameters in patients with CSU.

Materials and methods

Local ethics committee approved the study protocol. A total of 252 CSU patients treated with omalizumab in our

dermatology department between 2013 and 2017 were evaluated retrospectively.

A total of 106 patients, 76 women and 30 men, who received at least three doses of 300 mg/month subcutaneous omalizumab and had available CBC before treatment and at the end of third month of treatment (before taking the fourth dose of omalizumab) were included in the study. Patients with active infection, hepatic disease, malignancy, hematologic disease and on immunosuppressive, iron-containing, platelet function affecting and other treatment of urticaria except antihistamines were excluded. CBC parameters [erythrocyte, hemoglobin, leukocyte, platelet, neutrophil, lymphocyte, eosinophil, basophil and monocyte counts, red cell distribution width (RDW), platelet distribution width (PDW), MPV] and CRP levels were recorded. NLR (was calculated as the neutrophil count divided by the lymphocyte count) and PLR (was calculated as the platelet count divided by the lymphocyte count) were obtained from the CBC results. CBC parameters, NLR, PLR and CRP levels of the patients before treatment and at the end of third month of treatment were compared. All patients included in the study had hemogram parameters before treatment and at the end of third month of treatment, whereas 39 had CRP levels before treatment, 26 of them had CRP levels at the end of third month of treatment.

Erythrocyte and platelet counts by impedance method and leukocyte subgroups by laser optics method had been measured on LH 750 analyzer (Beckman Coulter, Brea, CA). The CRP test had been performed on NFL BN-II (Dade Behring, Siemens) device by immunonephelometric method.

IBM SPSS Statistics 21.0 software was used for the data analyses. Continuous data was presented as mean $\pm$ standard deviation and median. Categorical data was presented in percentage. The Shapiro Wilk test was used to search the normal distribution compliance of data. Dependent sample *t* test was used to compare peer groups with normal distribution. The Wilcoxon Signed Ranks Test was used to compare peer groups that were not in compliance with normal distribution. Spearman correlation coefficients were calculated for variables that were not in conformity with normal distribution in determining the direction and size of the relationship (correlation) between variables. $p < 0.05$ value was accepted to be statistically significant.

Results

Seventy-six of 106 patients (71.7%) were females and 30 patients (28.3%) were males. The mean age of the patients was 45.02 ± 12.50 (min: 19 max: 78). There was a statistically significant decrease in WBC count, platelet count, neutrophil count, CRP level, NLR and PLR, and an increase in MPV and eosinophil count with omalizumab treatment in CSU patients ($p < 0.05$). Basophil count increased; but there was not statistically significant difference ($p = 0.293$) (Table 1).

Discussion

The pathogenesis of CU is complex and not exactly elucidated. Various mechanisms such as autoimmunity,

Table 1. Hematological and inflammatory parameters before and at the end of third month of the treatment.

	Pre-treatment	Post-treatment	<i>p</i> *
RBC ($10^6/\mu\text{l}$)	4.84 ± 4.08	4.87 ± 4.25	0.185
Hb (g/dl)	13.81 ± 1.51	13.88 ± 1.47	0.418
WBC ($10^3/\mu\text{l}$)	8.7 ± 2.9	7.5 ± 2.1	<0.001
PLT ($10^3/\mu\text{l}$)	286.2 ± 845.5	267.8 ± 722.5	0.001
MPV (fl)	8.75 ± 0.99	8.89 ± 1.00	0.007
RDW (%)	14.40 ± 2.58	14.18 ± 1.54	0.389
PDW (%)	16.49 ± 0.54	16.54 ± 0.59	0.322
NEU ($10^3/\mu\text{l}$)	5.6 ± 2.6	4.4 ± 1.7	<0.001
LNF ($10^3/\mu\text{l}$)	2.3 ± 0.8	2.3 ± 0.7	0.821
EOS ($10^3/\mu\text{l}$)	0.15 ± 0.17	0.20 ± 0.28	0.016
BAZ ($10^3/\mu\text{l}$)	0.047 ± 0.014	0.052 ± 0.014	0.293
MON ($10^3/\mu\text{l}$)	0.53 ± 0.21	0.51 ± 0.19	0.405
CRP (mg/dl)	1.25 ± 1.22	0.52 ± 0.41	0.036
NLR	2.79 ± 2.24	2.03 ± 0.87	<0.001
PLR	136.39 ± 66.36	122.44 ± 36.80	0.034

RBC: red blood cell; Hb: hemoglobin; PLT: platelet; MPV: mean platelet volume; RDW: red blood cell distribution width; PDW: platelet distribution width; NEU: neutrophil; LNF: lymphocyte; EOS: eosinophil; BAZ: basophil; MON: monocyte; CRP: C-reactive protein; NLR: ratio of neutrophil to lymphocyte; PLR: ratio of platelet to lymphocyte.

*Paired samples *t* test.

Bold values indicate statistically significant results.

inflammation and coagulation are thought to be involved in pathogenesis of CU⁴.

Second generation H1 antihistamines are used as first-line therapy in the CU. Omalizumab is used as a second-line therapy in the antihistamine-resistant CU^{1,2}.

Omalizumab is a recombinant DNA-derived humanized immunoglobulin (Ig) G1K monoclonal antibody that selectively binds to human Ig E. The mechanism of action of omalizumab in CSU is not exactly known. Omalizumab binds free IgE with high affinity and prevents binding of allergen specific Ig E to the low affinity Ig E receptor (FcεRI). It does not bind to Ig E on the cell surface. It reduces free Ig E levels; a decrease in free Ig E levels leads to a decrease in FcεRI receptors on basophils and mast cells. Apart from this mechanism, it is thought that it decreases the activity of Ig G autoantibodies against FcεRI, Ig E and Ig E autoantibodies against autoantigens (thyroperoxidase, ds DNA). Omalizumab also reverses the basopenia, corrects the basophil Ig E receptor function, decreases the abnormal intrinsic Ig E activity and inhibits coagulation that plays a role in the etiopathogenesis of CSU²⁰. Yalcin et al reported that D-dimer levels decreased in CU patients treated with omalizumab²¹. In another study, IL-31 levels that play an important role in the initiation of chronic skin inflammation were decreased in patients with CSU successfully treated with omalizumab²². These studies demonstrate that omalizumab may have inhibitory effects on inflammation and coagulation in CU patients.

Thrombin is a potent agonist of platelets that plays a role in the pathogenesis of urticaria and induces activation of platelets²³. Platelets establish an important link between inflammation, thrombosis and atherosclerosis, and release many mediators that are important for these processes. MPV is an important marker that shows platelet reactivity and is an indicator for inflammation¹⁰. Relationship between high MPV values and increased disease activity in some inflammatory diseases have been reported^{24,25}. However, there are conflicting results in studies evaluating MPV levels in CU patients^{10–14}. In our study, there was a statistically significant

increase in MPV values with omalizumab treatment. The effect of omalizumab on MPV values should be confirmed with further prospective studies.

Alicja Kasperska-Zajac et al. reported that platelet counts were significantly higher in patients with moderate CSU compared with mild CSU and control group, and also platelet counts and CRP levels are correlated¹⁴. It has been suggested that platelets may play a role in pathogenesis of CSU. In our study, we found significant decrease in the platelet counts with omalizumab treatment. Our results support the inhibitory effect of omalizumab on platelets in the treatment of CSU.

CU is associated with the inflammatory response accompanied with mast cell activation. CRP is a sensitive systemic marker of inflammation. It has been shown that CRP levels are high in patients with CU and correlated with activity of CU⁵⁻⁹. In our study, a significant decrease in CRP levels with omalizumab treatment in patients with CSU has been found. Furthermore, we found a significant decrease in WBC and neutrophil counts with omalizumab treatment in our study. NLR and PLR are markers of the systemic inflammatory response and may be used in monitoring inflammation. They can easily be calculated by parameters obtained from CBC. They have been used as inflammatory markers in many diseases and as prognostic factor in various oncologic diseases in recent studies¹⁵⁻¹⁹. To our knowledge, there is no study evaluating NLR and PLR in patients with CU in the PubMed database. In our study, a significant decrease in NLR and PLR with omalizumab treatment has been found. This supports that omalizumab may have anti-inflammatory effects in CSU patients.

Lorenzo et al. reported that eosinophil count was significantly higher in patients with acute urticaria and symptomatic CU than control group²⁶. However, we found an increase in eosinophil counts with omalizumab treatment in patients with CSU. Eosinophil counts may increase reactively with omalizumab treatment. Generally, during active disease period, basopenia is seen in patients with CSU due to basophil migration into skin. Basopenia reverses with treatment or regression of urticarial lesions^{3,27}. Similarly, in our study there was an increase in basophil counts with omalizumab treatment but this increase was not statistically significant.

There are limitations of our study. There were not detailed clinical findings, severity of disease and response to omalizumab treatment of patients due to retrospective design.

In conclusion, there was a significant decrease in WBC count, platelet count, neutrophil count, PLR, NLR and CRP level and a significant increase in MPV and eosinophil count with omalizumab treatment in patients with CSU. Our study shows that omalizumab has not only anti Ig E effect, but it also may have inhibitory effects on inflammation and coagulation in CSU patients. Further prospective studies are warranted in order to evaluate the effect of omalizumab on hematological and inflammatory parameters and correlation between response rate to omalizumab and these parameters in CSU patients. These parameters may be used in monitoring response rate to omalizumab.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Ersoy Acer  <http://orcid.org/0000-0002-6041-6636>
Hilal Kaya Erdogan  <http://orcid.org/0000-0002-8172-1920>
Nihan Yüksel Çanakçı  <http://orcid.org/0000-0002-3299-0876>
Zeynep Nurhan Saracoglu  <http://orcid.org/0000-0002-9116-2288>

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