

Title page

Long-term effects of omalizumab on peripheral blood cells and C-reactive protein levels in patients with chronic spontaneous urticaria

Running short title: Omalizumab effects on blood cells and CRP levels

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Abstract

Background: Omalizumab's mechanism of action is not well-understood yet despite its strong therapeutic efficacy in chronic spontaneous urticaria(CSU).

Objective:To determine the overall effect of omalizumab on peripheral blood cell counts and serum C-reactive protein levels(sCRP) during a 1-year follow-up in patients with CSU.

Methods:Data of 74 patients (Male/Female:20/54) were reviewed from medical charts.Leucocyte counts,percentages of peripheral blood cells(lymphocyte,monocyte,neutrophil[PPBN],eosinophil,basophil[PPBB]) and sCRP were recorded at baseline,3rd,6th,12th months of omalizumab treatment.

Results:Although a dramatic increase in the mean PPBB($\pm$ SD) was observed at the 3rdmonth, PPBB(%) gradually decreased after the 3rdmonth (PPBB: 0.38 ± 0.21 [baseline] vs. 0.59 ± 0.3 [3rdmonth], $p=0.002$).However,12thmonth PPBB remained higher than baseline (PPBB: 0.38 ± 0.21 [baseline] vs. 0.46 ± 0.27 [12thmonth], $p=0.03$).A dramatic decrease in the mean PPBN (%) was noticed within the first 3 months (PPBN: 62.85 ± 8.97 [baseline] vs. 58.37 ± 9.07 [3rdmonth], $p=0.04$),and 12thmonth PPBN remained lower than baseline values (PPBN: 62.85 ± 8.97 [baseline] vs. 60.31 ± 8.02 [12thmonth], $p=0.045$).Mean sCRP(mg/dL) decreased rapidly within the first 3 months (sCRP: 1.09 ± 1.53 [baseline] vs. 0.56 ± 0.45 [3rdmonth], $p=0.17$) and 12thmonth sCRP still remained lower than baseline levels (sCRP: 1.09 ± 1.53 [baseline] vs. 0.83 ± 1.06 [12thmonth], $p=0.01$).

Conclusion:Omalizumab substantially increases PPBB,and reduces PPBN accompanied by a reduction in sCRP especially in the first 3 months;however,these effects may continue in the long-term.The alterations in peripheral blood cell ratios and sCRP may contribute to the therapeutic effect of omalizumab in CSU.

Introduction

Chronic spontaneous urticaria (CSU) is a common skin disorder characterized by spontaneous appearance of itchy wheals and/or angioedema lasting for 6 weeks or more that was not triggered by physical and/or environmental stimulus (Zuberbier, 2018). The existing literature comprises of numerous studies on the prevalence of chronic urticaria (CU) which ranges from 0.08 to 1.8 in different studies (Zazzali, 2012; Zuberbier, 2010). Few data are available concerning epidemiology of CSU. However, Lapi et al demonstrated that the annual prevalence of CSU was 0.02% and 0.40% in the years 2002 and 2013, respectively in Italy (Lapi, 2016). Although various etiological factors have been related with the development of CSU, in most cases the exact cause is still not completely known. However, inflammation and coagulation are considered the main factors related with the disease pathogenesis.

Even if CSU is generally not a life-threatening disease, it leads disability, impairment in quality of life, heavy economic burden, and is associated with difficulties in the management of disease despite availability of several therapeutic approaches. Second-generation antihistamines at permitted doses remain the first-line treatment option for the treatment of CSU. Omalizumab is suggested as an add-on third-line therapy option by urticaria guidelines to CSU patients with inadequate response to fourfold doses of second-generation antihistamines (Zuberbier, 2018). Omalizumab is a recombinant humanized IgG1 monoclonal antibody that selectively binds to free IgE, and subsequently decreases serum levels of IgE and the number of high-affinity IgE receptors on mast cells, basophils and dendritic cells (Jackson, 2018). Changes in mast cell degranulation, decrease in serum interleukin-31 levels, reversing basopenia, correction of the basophil IgE receptor functions, alterations in coagulation parameters are proposed effector mechanisms of omalizumab being involved in the pathogenesis of CSU (Kaplan, 2017). A recent study revealed the significant effect of omalizumab on hematological parameters at the 3rd month of treatment compared

with baseline parameters (Acer, 2018). The authors postulated that omalizumab has not only anti IgE effect, but also it may have effects on hematological parameters that may contribute to the therapeutic effect. However, the long-term effects of omalizumab on peripheral blood cell counts and inflammatory markers is not very well-understood.

C-reactive protein (CRP), a sensitive inflammation marker, is shown to be correlated with disease activity, impact, and response to antihistamine therapy in CSU in a recent study (Kolkhir, 2018). Furthermore, guidelines recommend to evaluate serum CRP levels in all patients with CU for diagnosis as well as differential diagnosis (Zuberbier, 2018). Another study has found out the significant lowering effect of omalizumab on serum CRP levels in 106 patients with CSU at the 3rd month of treatment compared with baseline levels (Acer, 2018). However, it is not clarified whether the lowering effect of omalizumab on serum CRP levels persist in patients with CSU in long-term. Thus, the aim of this study was to determine the long-term effect of omalizumab on peripheral blood cells and serum CRP levels during 1-year follow-up.

Materials and Methods

Data of 74 patients who were older than 18 years were reviewed from medical charts. All of the patients were on follow-up for CSU at Hacettepe University hospital between 2016 and 2018. Exclusion criteria consisted of presence of active/chronic infection, malignancy, hematologic disease, autoinflammatory disease, association of other inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, and history of urticarial syndrome or urticarial vasculitis. All patients were treated with 300 mg of subcutaneous omalizumab continuously every 28 days for at least 1 year. Leukocyte count, percentages of peripheral blood cells [lymphocyte, monocyte, neutrophil (PPBN), eosinophil, basophil (PPBB)] and serum CRP levels were evaluated at baseline and at 3rd, 6th and 12th months of omalizumab

treatment. Demographic data, including age, gender, personal and family medical history, and disease duration were reviewed.

Statistical analyses and ethics committee approval

Statistical analysis was performed using IBM SPSS Statistics for Windows v.21.0. (IBM Corp., Armonk, NY). Data is presented as mean $\pm$ standard deviation (SD) or median (range) as appropriate. The Shapiro-Wilk test was used to decide the normality of the distribution of numeric variables. Demographic features of the study population were analyzed using descriptive statistics. Categorical variables were described with frequencies and percentages. Non-parametric tests including the Friedman's test and the Wilcoxon Signed-rank test were used to compare consecutive data including baseline, 3rd, 6th and 12th month leukocyte count, percentage of peripheral blood cells and serum CRP levels. The level of statistical significance was accepted at $p < 0.05$.

The study was approved by the Institutional Ethics Review Board at the Hacettepe University Medical School with the code of GO-17/839-26 on October 24, 2017. All procedures performed in the study were in accordance with the ethical principles of the 1964 Helsinki declaration.

Results

Seventy-four patients (Male/Female: 20/54) were included in this study with a median age of 43.3 years (20–78) and median disease duration of 64.8 months (12–276 mos). Data including mean leucocyte counts, percentage of peripheral blood cells including lymphocyte, monocyte, neutrophil, eosinophil, basophil and serum CRP levels during omalizumab treatment are presented in Table 1. 29.7% of the 74 patients (n=22) exhibited basopenia (mean $\pm$ SD: 0.38 $\pm$ 0.21), while 25.7% (n=19) of the patients had high serum CRP levels (mean $\pm$ SD: 1.09 $\pm$ 1.53) at the beginning of omalizumab treatment. Even though a dramatic increase in the PPBB (mean $\pm$ SD) was observed during the first 3 months of omalizumab therapy (baseline

vs. 3rd mo: 0.38 ± 0.21 vs. 0.59 ± 0.3 , $p=0.002$), PPBB decreased gradually after the 3rd month until the end of 1 year follow-up. However, PPBB (mean $\pm$ SD) still remained higher than baseline values at 12th month (baseline vs. 12th mo: 0.38 ± 0.21 vs. 0.46 ± 0.27 , $p=0.03$, Figure 1a). A dramatic decrease in the PPBN (mean $\pm$ SD) was noticed within the first 3 months (baseline vs. 3rd mo: 62.85 ± 8.97 vs. 58.37 ± 9.07 , $p=0.04$), and PPBN values of 12th month still remained lower than baseline values (baseline vs. 12th mo: 62.85 ± 8.97 vs. 60.31 ± 8.02 , $p=0.045$, Figure 1b). Serum CRP levels decreased rapidly within the first 3 months (baseline vs. 3rd mo: 1.09 ± 1.53 vs. 0.56 ± 0.45 , $p=0.17$), and mean CRP levels of the 12th month still remained lower than baseline levels (baseline vs. 12th mo: 1.09 ± 1.53 vs. 0.83 ± 1.06 , $p=0.01$, Figure 2) (Table 1). No significant correlation was found between serum CRP levels and PPBN ($p=0.33$).

Discussion

Omalizumab is a recombinant humanized monoclonal antibody against IgE used as an add-on therapy for patients with CSU refractory to high doses of oral antihistamine therapy. It was originally accepted for the treatment of allergic asthma refractory to conventional treatments (Xolair US prescribing information, 2018). In CSU, omalizumab prevents angioedema development, enhances quality of life, and is proposed as a favorable drug for long-term use even after discontinuation (Zuberbier, 2018). However, its mechanism of action in CSU is not very well-known yet. Omalizumab can bind to free IgE and subsequently inhibits IgE binding to Fc ϵ RI on basophils, mast cells as well as dendritic cells which may cause down-regulation of mast cell pool, IgE pool, and a decrease in amplification of mast cells (Chang, 2015). Additionally, the drug can decrease Fc ϵ R2 on B cells and may lead a reduction in the formation of IgE-secreting plasma cells. Thus, the overall effect of omalizumab is the inhibition of allergens to activate basophils, mast cells, and their subsequent release of

proinflammatory cytokines, and eventually it depletes the overall inflammatory state in the body (Chang, 2015).

Recent studies have shown that patients with CSU have basopenia reflecting the role of basophils in the pathogenesis of CSU. Metz et al revealed that mean levels of basophils are low in untreated CSU patients, and omalizumab increases peripheral blood basophil numbers compared with placebo early in the first 2 weeks although basophil levels returned almost near to patients' baseline values by 20 week-follow-up (Metz, 2017). Saini et al postulated that circulating blood basophils increased in response to treatment with omalizumab 300 mg, and the authors added that the clinical improvement detected with omalizumab treatment may be linked to its effect on basophils (Saini, 2017). Grattan CE stated that circulating basophils may be recruited from blood into urticarial wheals during disease activity and those with the most severe symptoms have the lowest count of basophils (Grattan, 2003). In the present study, the authors demonstrated that almost one-third of patients had apparent basopenia, and mean PPBB was near to the lower limits of normal ranges of PPBBs at the beginning of omalizumab therapy. In accordance with the literature, this study showed the obvious booster effect of omalizumab in PPBBs early in the first months. Although fluctuations in the PPBB was noticed after the 3rd month, a significant increase in PPBBs was observed at the end of 12th month compared to baseline values. This observation supports the reversing effect of omalizumab on basopenia in patients with CSU even in the late periods.

Numerous studies have established that patients with CSU may have elevated serum CRP levels, and CRP has been proposed to be a possible marker of disease activity, severity and response to treatments particularly oral antihistamines in CSU (Kolkhir, 2018). A study from Tunisia demonstrated a linear positive correlation between serum CRP levels and urticaria activity scores, and the authors revealed that the anti-inflammatory effects of desloratadine was correlated with serum CRP levels in CSU patients (Maouia, 2017). Ohtsuka

T found out that the elevated high sensitivity-CRP levels showed good response to oral cyclosporine therapy in CSU (Ohtsuka, 2010). Kolkhir et al found that elevation of serum CRP levels is associated with more active disease, low quality of life and lack of response to standard doses of levocetirizine in CSU (Kolkhir, 2017). A recent study from Turkey pointed a significant decrease in serum CRP levels with omalizumab in the 3rd month compared with baseline values (Acer, 2018). However, the long-term effect of omalizumab on serum CRP levels is not studied in patients with CSU. To the best of our knowledge, this is the first to assess the set of serum CRP levels in CSU patients treated with omalizumab in a long-term period. In the present study, almost one quarter of study patients had elevated serum CRP levels, and mean serum CRP levels of all patients was slightly higher than normal limits at the beginning of treatment. A dramatic decline in the serum CRP levels was noticed during the first 3 months of omalizumab therapy in this study. Although mean serum CRP levels increased slightly after the 3rd month, the mean levels remained significantly lower at the 12th months of omalizumab therapy compared with the baseline values. Omalizumab exerted anti-inflammatory effects on CSU patients revealed by serum CRP levels. The assessment of CRP levels may help to optimize the management of CSU patients with omalizumab. Although the most obvious reducing effect of the drug is seen in the 3rd month, this effect continues until the end of 1 year according to the relevant study findings.

Even though the anti-inflammatory role of omalizumab on inflammatory cells including mast cells, basophils and dendritic cells is discussed until now, the impact of the drug on neutrophils is an enigma. However, the infiltration of urticaria lesions by neutrophils mainly in the early lesions has already been shown (Kaplan, 2009). Furthermore, ‘neutrophilic urticaria’ is a term used to define a few of urticarial lesions showing predominantly neutrophilic infiltrate on histological examination which reflects a pathway that may be less dependent on mast-cell degranulation contrarily to classical urticaria (Winkelmann, 1988).

Ong revealed the priming effect of repeated allergen challenge on infiltration of neutrophil in asthmatic bronchial biopsies in patients on placebo that was abrogated in those receiving omalizumab (Ong, 2005). Yalcin found out the diminishing effect of omalizumab on peripheral blood neutrophils, eosinophils, macrophages, serum IgE, and IL-4 levels in 10 patients with asthma–chronic obstructive pulmonary disease overlap syndrome in 12 months of treatment reflecting the possible role of omalizumab on neutrophilic inflammation as well as its efficacy against Th2-mediated eosinophilic asthma (Yalcin, 2016). However, the effects of omalizumab on peripheral blood and tissue neutrophil number in CSU is not elucidated yet. A study found out the diminishing effect of omalizumab on peripheral blood neutrophil count in CSU patients on the 3rd month; but long-term outcome is not assessed. The present study assessed the one-year outcome of omalizumab in CSU patients reflecting a reduction in the PPBN at the end of one-year follow-up. Omalizumab may reduce recruitment and activation of neutrophils, and probably other inflammatory cells via inhibiting T-helper cells type-2 immune response and may be used to decrease urticaria activity in CSU patients by this way. However, the lack of tissue sampling from urticarial lesions in order to characterize the distribution of neutrophils, basophils, eosinophils is a limitation of this study.

The main limitations of this study are its retrospective design and the absence of tissue sampling for histopathological examination in order to compare results with blood counts. The determination of treatment response according to the relevant parameters and the inadequate data concerning demographical features, medical and family history are other issues. Since the study was performed at a single centre, generalization of the study results to the entire population might be a challenge. Whether the altered values may return to the baseline values after the cessation of omalizumab therapy is also problematic.

In conclusion, there is now a strong body of evidence indicating that omalizumab inhibits and changes multiple key components of the allergic inflammatory cascade in CSU.

Omalizumab substantially increases the ratio of peripheral blood basophils, and reduces the ratio of peripheral blood neutrophils accompanied by a reduction in serum CRP levels. Although the remarkable effects of omalizumab was detected early in the first 3 months, these effects may persist in long-term even in one-year follow-up. Perhaps, the decreased ratio of blood neutrophil in counter may lead to a shift in the direction of increase in the ratio of blood basophil. Although no correlation was found between serum CRP levels and PPBN at 3rd month of omalizumab therapy both of which decreased prominently, different studies should be done to clarify the relationship between serum CRP and PPBN, and the factors affecting them. The alterations in peripheral blood cell ratios and serum CRP levels may contribute to the therapeutic effect of omalizumab in CSU. Prospective studies are needed to test CRP, and peripheral blood basophil and neutrophil ratio for their use as a biomarker in the management of CSU patients with omalizumab.

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Table 1. Mean peripheral blood cell numbers and ratios, and serum CRP levels at baseline, 3rd, 6th and 12th months of omalizumab treatment.

Laboratory parameters	Baseline	3 rd month	6 th month	12 th month	Normal range
Leukocyte count (/μL)	7844 ± 2257	7178 ± 1708	7416 ± 2400	7337 ± 1896	4300–10300
Lym (%)	27.78 ± 7.44	31.87 ± 9.01	32.47 ± 7.25	29.70 ± 9.67	19.4–49.4
Mon (%)	7.12 ± 2.44	7.29 ± 1.6	7.36 ± 1.91	6.99 ± 1.62	5.1–10.9
Neu (%)	62.85 ± 8.97	58.37 ± 9.07 [*]	58.11 ± 8.93	60.31 ± 8.02 [‡]	41–73
Eos (%)	1.88 ± 1.89	1.85 ± 1.54	1.63 ± 1.2	1.67 ± 1.30	0.9–6
Bas (%)	0.38 ± 0.21	0.59 ± 0.3 ^μ	0.49 ± 0.25 ^α	0.46 ± 0.27 ^β	0.3–1.5
CRP(mg/dL)	1.09 ± 1.53	0.56 ± 0.45	0.66 ± 0.5	0.83 ± 1.06[£]	0–0.8

Lym=Lymphocyte; Mon=Monocyte; Neu=Neutrophil; Eos=Eosinophil; Bas=Basophil;

CRP=C-reactive protein.

p<0.05 is defined statistically significant. Data outside the normal range are shown in bold.

^{*}Significant difference from baseline, p=0.04

[‡]Significant difference from baseline, p=0.045

^μSignificant difference from baseline, p=0.002

^αSignificant difference from baseline, p=0.04

^βSignificant difference from baseline, p=0.03

[£]Significant difference from baseline, p=0.01

Figure Legends

Figure 1. 1a: Diagram showing the change of mean percentages of peripheral blood basophils during omalizumab treatment. **1b:** Diagram showing the alteration of mean percentages of peripheral blood neutrophils during omalizumab therapy.

Figure 2. Change in serum CRP levels during omalizumab treatment is shown.



