

ORIGINAL PAPER

Dermatology

Plasma matrix metalloproteinase-9 level change with omalizumab treatment in chronic spontaneous urticaria

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Abstract

Background: Matrix metalloproteinase-9 (MMP-9) is an enzyme that contributes to inflammation and tissue remodelling. In chronic urticaria, increased plasma levels of MMP-9 and its correlation with disease severity have been shown in several studies, suggesting that MMP-9 could be used to evaluate the effects of new treatments. We aimed to compare MMP-9 levels in chronic urticaria patients with those of healthy patients. Then we planned to investigate the changes in plasma MMP-9 levels with chronic urticaria treatment, the role of this enzyme in demonstrating the efficacy of treatment, and its correlation with C-reactive protein (CRP).

Methods: Forty-one patients with chronic urticaria who were scheduled for omalizumab treatment and 41 sex- and age-matched healthy volunteers were included in the study. In the patient group, before treatment and at the end of the 12th week, the urticaria activity score used for 7 consecutive days (UAS7) was calculated, and the MMP-9 and CRP levels were measured. Plasma MMP-9 levels were measured from venous blood in the control group.

Results: The plasma MMP-9 levels of the patients before treatment were significantly higher than those of the control group ($P < .01$). In the patient group, there was no significant relationship between the UAS7 score and the MMP-9 and CRP levels before treatment. The UAS7 values were 28 ± 7 before omalizumab treatment and 5 ± 6 at the end of the 12th week ($P < .0001$). The post-treatment MMP-9 levels (1818 ± 297 pg/mL) were higher compared with the pre-treatment values (1617 ± 380) ($P < .05$). The post-treatment CRP levels of the patients (2.41 ± 2.17 mg/L) were lower than their pre-treatment CRP levels (8.20 ± 19.70) ($P < .05$).

Conclusion: MMP-9 levels were not associated with the severity of disease, and MMP-9 levels were not decreased with treatment response. Therefore, MMP-9 cannot be used as a parameter of disease activity in chronic urticaria or to evaluate the efficacy of new treatments.

1 | INTRODUCTION

Chronic urticaria is a persistent inflammatory disease characterised by perivascular mixed-type inflammatory cell infiltration, as well as mast cell activation and degranulation.¹ Today, the diagnosis of

chronic urticaria is based on the patients' medical history, physical examination findings and questionnaires to measure the severity of the disease. The diagnosis is purely clinical, and some biomarkers objectively evaluating disease activity have been investigated. The newly developing treatment methods for chronic urticaria aim

to provide the most appropriate treatment and maximum effect for patients. However, the search for a reliable biomarker that can objectively evaluate and predict the outcome of treatment continues.

In chronic urticaria, inflammatory mediators, such as C-reactive protein (CRP) and interleukin-6 (IL-6), are promising candidates as biomarkers because of their correlation with inflammation and clinical severity.² Although biomarkers such as D-dimer and IL-31 appear to be promising in the assessment of post-treatment efficiency, further research is needed to confirm their role.³⁻⁵

Matrix metalloproteinases (MMPs) are a family of zinc-dependent, matrix-destructive endopeptidase enzymes involved in various physiological and pathological processes, such as cell proliferation, migration and differentiation; extracellular matrix remodeling; tissue invasion; and vascularisation. Matrix metalloproteinase-9 (MMP-9) is thought to play a role in inflammation and inflammatory cell trafficking by destroying type IV collagen, the main component of the basement membrane.⁶

There are clinical studies suggesting that MMP-9 plays a role in the pathogenesis of chronic spontaneous urticaria (CSU) and is correlated with disease activation. The association of MMP-9 with disease activity indicates that it might be a good option to evaluate the efficacy of both existing and new therapies. In contrast, there are also studies that advocate that it will not be a good parameter to show disease severity. However, as far as we know, the plasma alteration of MMP-9 after any treatment has not yet been explored. In this study, we compared the levels of MMP-9 of healthy volunteers and patients with CSU. We also investigated the changes in MMP-9 after the treatment of CSU with omalizumab (a recombinant monoclonal antibody developed against immunoglobulin E), determined the correlation of MMP-9 with CRP, and assessed the reliability of this enzyme in evaluating treatment efficacy.

2 | MATERIALS AND METHODS

This research, planned as an analytical cross-sectional study, was conducted between 1 August 2018 and 1 August 2019 in the Department of Dermatology and Medical Biochemistry of Sultan 2. Abdulhamid Han Training and Research Hospital. The study was approved by the local ethics committee (decision no: 2018/0228) and was actualised according to the rules expressed in the Declaration of Helsinki.

The diagnosis of urticaria was based on the European Academy of Allergy and Clinical Immunology guidelines.⁷ In all patients, known potential causes of chronic urticaria were excluded through appropriate laboratory tests. Patients whose potential causes of chronic urticaria had been defined (except autoimmunity) were excluded.

The patients were all resistant to treatment despite the fact that the standard dose of second-generation H1 antihistamines recommended for chronic urticaria was quadrupled. A total of 41 patients with CSU who were planned to receive omalizumab treatment were included in the study. Forty-one sex- and age-matched healthy volunteers were included in the study as the control group. The control

What's known

- The diagnosis of chronic urticaria is purely clinical, and some biomarkers objectively evaluating disease activity have been investigated.
- There are clinical studies suggesting that MMP-9 plays a role in the pathogenesis of chronic spontaneous urticaria and is correlated with disease activation. In contrast, there are also studies that indicate that it would not be a good parameter to show disease severity.

What's new

- MMP-9 was not correlated with disease severity or CRP in patients with chronic urticaria, and its levels in plasma did not decrease after treatment.
- MMP-9 is not a suitable parameter for measuring treatment response and could not be used as a biomarker for the evaluation of new treatments.

group was selected from patients who presented to the dermatology outpatient clinic, had no inflammatory disease and fulfilled the inclusion criteria. Written consent was obtained from all patients who agreed to receive the treatment and from all the healthy volunteers.

2.1 | Inclusion and exclusion criteria

Patients aged between 18 and 70 years who had urticarial symptoms for at least 6 weeks and were scheduled to receive omalizumab treatment because of antihistamine resistance were included in the study. Patients who had previously undergone omalizumab treatment; those with known major cardiovascular history, malignancies, active/chronic infections, concomitant inflammatory diseases (eg, rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel disease) or autoinflammatory diseases; those with physical/inducible urticaria; those who had received corticosteroid or immunosuppressive treatment for chronic urticaria within the last month; and those who had received antihistamine treatment within the last week were excluded from the study. Patients with a disease that would affect plasma MMP-9 levels, including concomitantly diagnosed asthma, allergic rhinitis or atopic dermatitis, were excluded from the study.

2.2 | Study design

The patients were treated with subcutaneous omalizumab at a standard dose of 300 mg every 4 weeks. The urticaria severity of the patients before treatment and at the end of the 12th week was evaluated using urticaria activity scores for the last 7 consecutive days (UAS7). Considering the number of urticarial plaques and

the severity of pruritus reported by the patients, scoring was performed as follows. Number of wheals: 0 = no wheals, 1 = mild (<20 wheals/24 hours), 2 = moderate (21-50 wheals/24 hours) and 3 = intense (>50 wheals/24 hours or large confluent areas of wheals); pruritus: 0 = none, 1 = mild, 2 = moderate and 3 = intense. UAS7 was obtained by adding the wheal and pruritus scores of the last 7 days.⁷ The severity of the disease was evaluated as mild if the UAS7 score was 0-14, moderate if 15-29 and severe if 30-42.

Before treatment from both the patients and the control group and at the end of the 12th week only from the patients receiving treatment, venous blood was obtained after 10-12 hours of fasting and placed in heparinised tubes. The samples were centrifuged at 1500 *g* for 15 minutes at +4°C to separate the serum. The sera obtained were stored at -80°C until required for the assay. On the day of the assay, the serum samples were thawed at room temperature, and the appropriate kit protocol was used.

2.3 | Biochemical analysis of the MMP-9 and CRP parameters

Before omalizumab treatment, MMP-9 levels were measured in the sera of the patients and control groups. At the 12th week of treatment, the serum MMP-9 levels of the patients were re-evaluated. The serum CRP levels of the patients were measured before and after omalizumab treatment. The MMP-9 measurements (Elabscience human MMP-9 ELISA kit, Elabscience Biotechnology Inc, Houston, Texas, USA) were performed using enzyme-linked immunosorbent assay (ELISA) with a BioTek Epoch microplate spectrophotometer. The CRP measurements were undertaken using turbidimetry (CRP WR Turbidimetric, Archem Diagnostic Ind. Ltd.) with a c16000 automated biochemistry analyser.

2.3.1 | MMP-9

This test method uses ELISA, based on biotin double-antibody sandwich technology. The serum is added to wells pre-coated with human monoclonal antibodies specific for MMP-9. After a period of incubation, the monoclonal antibodies bind to the MMP-9 in serum. Anti-MMP-9 antibodies are then added to bind with the biotin-labelled avidin-horseradish peroxidase forming the immune complex. After incubation, washing is performed to remove unbound enzymes. Antibody-bound peroxidase in the wells reacts with the chromogen substrate added to the wells and turns the solution blue in a short time. The colour tone of the solution has a positive correlation with human MMP-9 concentrations at 450 nm. The sensitivity of the MMP-9 test is 18.75 pg/mL, and the coefficient of variation is <10% (detection range: 31.25-2000 pg/mL). The maximum value of our standard was 2000 pg/mL. Serial dilutions were made according to this value. Our values were determined according to the results of this series diffusion absorbance. A microplate strip washer was used as the washer in ELISA measurements.

TABLE 1 Statistical comparison of the control group and patients' pre-treatment MMP-9 levels

	Control (0)	Pre-treatment (I)	P
n (F/M)	41 (30/11)	41 (31/10)	.848 ^a
Age, year ^c	42 ± 12	42 ± 14	.927 ^b
MMP-9, pg/ mL ^{c,d}	319 ± 174 260 (150-950)	1617 ± 380 1672 (833-2390)	<.001 ^a

Abbreviations: F/M, female/male; MMP-9, matrix metalloproteinase-9; n, number of participants; SD: standard deviation.

^aP-value Mann-Whitney U test;

^bunpaired t-test;

^cMean ± SD;

^dMedian (minimum-maximum).

2.3.2 | CRP

This is an immunoturbidimetric method. The CRP antigens in the sample react with and bind to the specific antiserum. The level of turbidity that is proportional to the CRP concentration is measured at 340 nm.

2.4 | Statistical analysis

The Statistical Package for the Social Sciences v. 25 (IBM Corp., Chicago, USA) and InStat3 GraphPad software were used for all statistical analyses. In the evaluation of dependent groups where the number of repeated measurements was two, the paired t-test was used for data that showed Gaussian distribution, and the Wilcoxon matched-pairs test for data without Gaussian distribution. The unpaired t-test was used for those with Gaussian distribution, and the Mann-Whitney U test was used for those without Gaussian distribution, both in the analysis of independent groups with two groups and in the comparison of MMP-9 data of the control and patient groups before treatment. A correlation analysis was undertaken to test the relationship between the UAS7, CRP and MMP-9 parameters of all participants before and after treatment. The correlations between these parameters were determined using Pearson's correlation analysis for parametric data and Spearman's correlation analysis for non-parametric data. The results were evaluated at the 95% confidence interval and *P* < .05 significance levels.

3 | RESULTS

The mean age of the 41 patients (31 females and 10 males) with chronic urticaria was 42.12 ± 14.25 (range, 21-67) years. The mean age of the control group (30 females and 11 males) was 42 ± 12 years. There was no statistical difference between the mean ages and sexes of both groups (*P* > .05) (Table 1). The mean disease duration was 24.56 ± 23.45 (range, 4-120) months. In 12 patients, the findings were accompanied by angioedema. Sixteen patients had severe and

25 had moderate urticaria. Before the monthly 300 mg omalizumab treatment, the mean UAS7 score was calculated as 28 ± 7 , the mean MMP-9 level was measured as 1617 ± 380 pg/mL, and the mean CRP level was 8.20 ± 19.70 mg/L (Table 2). The plasma MMP-9 level of the control group was measured as 319 ± 174 pg/mL. This value was significantly lower than in the patient group ($P < .01$) (Table 1).

No significant relationship was observed between disease duration and the UAS7, CRP and MMP-9 values in patients before treatment. There was also no statistically significant relationship between the UAS7 score indicating the severity of disease before treatment and MMP-9 ($P = .062$) and CRP levels ($P = .813$). The UAS7, MMP-9 and CRP values did not significantly differ between the patients with and without angioedema. There was also no significant relationship between MMP-9 and CRP levels at the beginning of treatment ($P = .46$).

At the end of the 12th week, 21 of the 41 patients included in the study had a complete response and 19 had a partial response to omalizumab treatment; one patient did not respond adequately. Complete response was defined as a $>90\%$ decrease, partial response as a 30%-90% decrease, and non-response as a $<30\%$ decrease in the UAS7 score after treatment.⁸ The mean UAS7 score after treatment was 5 ± 6 (Table 2). The post-treatment urticaria activity score was significantly lower compared with the baseline score ($P < .001$) (Figure 1).

When the MMP-9 levels of the patients before and after treatment were examined (Table 2), it was determined that the post-treatment MMP-9 levels were statistically significantly higher compared with the pre-treatment values ($P = .005$) (Figure 2). On the contrary, the post-treatment CRP levels of the patients were significantly lower than their pre-treatment values ($P = .002$) (Figure 3).

According to the results of the correlation matrix analysis, the MMP-9 levels had a weak but significant inverse correlation with UAS7 (Spearman's $r = -0.267$, $P = .015$); however, no significant correlation was found between the MMP-9 and CRP levels (Spearman's

$r = 0.043$, $P = .704$) (Figure 4). There was also no statistically significant correlation between the UAS7 and CRP levels (Spearman's $r = 0.099$, $P = .376$).

4 | DISCUSSION

MMP-9 is a type IV collagenase produced by a wide variety of cells, such as epithelial cells, fibroblasts, keratinocytes, osteoblasts, dendritic cells, macrophages, granulocytes, mast cells and T cells.^{6,9} MMP-9 levels are reported to be high in patients with chronic urticaria, and some studies have shown that these levels are correlated with disease severity. This correlation between disease severity and MMP-9 level was considered to be related to cutaneous mast cell degranulation.¹⁰

Currently, the EAACI/GA²LEN/EDF/WAO guideline recommends up to a four-fold increase in H1 antihistamines, the first step in the treatment of chronic urticaria, in selected cases. Omalizumab treatment has been approved in severe antihistaminic-resistant cases and has been shown to be effective in 70%-80% of patients.¹¹ Omalizumab is a monoclonal antibody against IgE. It acts by reducing mast cell function and binding free IgE. Thus, it reduces receptor expression, mast cell degranulation and secretion of inflammatory mediators.^{12,13} In our study, the omalizumab treatment was administered to patients with CSU, and a significant decrease was observed in the severity of urticaria after treatment. However, as the severity of the disease decreased, the plasma MMP-9 levels increased rather than decreased. This situation made us think that elevated plasma MMP-9 level in CSU could not be solely attributed to IgE-mediated mast cell degranulation.

It has been shown in previous studies that mast cells are involved in the activation and production of MMPs. Tumour necrosis factor- α (TNF- α) release is induced by IgE-mediated activation from mast cells, and the released TNF- α causes MMP-9 production with autocrine effect. Also, proMMP-9 is converted to its active form after IgE-mediated mast cell activation.⁹ Nonetheless, it appears that mast cell degranulation does not occur merely through IgE-mediated activation. It has been shown that mast cells are located close to T cells in allergic tissues. It has now been demonstrated that mast cells degranulate and produce TNF- α in response to direct contact with T cells. TNF- α secretion is responsible for the upregulation of some mast cell genes, including MMP-9. This direct stimulation is an alternative, independent mechanism of mast cell degranulation.^{14,15} The mast cell subtype MC_T (mast cells that are tryptase-positive but chymase-negative), which is especially associated with allergic diseases and is closely located with lymphocytes, is increased in lesioned skin in patients with CSU.¹⁶ Although direct activation of mast cells by T cells has not yet been demonstrated for cutaneous mast cells, it is considered that active T cells located close to cutaneous mast cells may cause mast cell degranulation and MMP-9 secretion.¹⁰

Omalizumab inhibits IgE-mediated mast cell degranulation, but MMP-9 release may continue after treatment because degranulation

TABLE 2 Statistical comparisons of the UAS7, MMP-9 and CRP values before and after treatment

	Pre-treatment (I)	Post-treatment (II)	P
n (F/M)	41 (31/10)	41 (31/10)	–
UAS7	28 ± 7	5 ± 6	$<.001^a$
MMP-9, pg/mL ^c	1617 ± 380	1818 ± 297	$.005^a$
CRP, mg/L ^{c,d}	8.20 ± 19.70 2.0 (0.8-118.6)	2.41 ± 2.17 1.8 (0.8-12.6)	$.002^b$

Abbreviations: CRP: C-reactive protein; F/M: female/male; MMP-9: matrix metalloproteinase-9; n: number of participants; SD: standard deviation; UAS: urticaria activity score of 7 days.

^aP-value obtained using the paired t-test;

^bP-value obtained using the Wilcoxon matched-pairs test (non-parametric);

^cMean $\pm$ SD;

^dMedian (minimum-maximum).

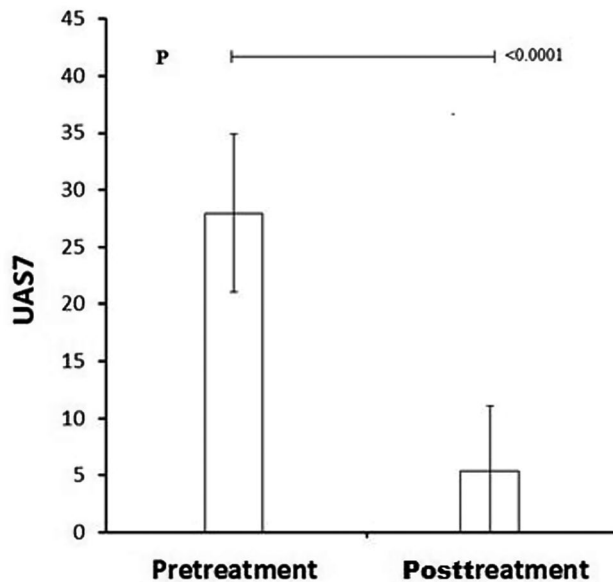


FIGURE 1 Comparison of UAS7 scores before and after omalizumab treatment

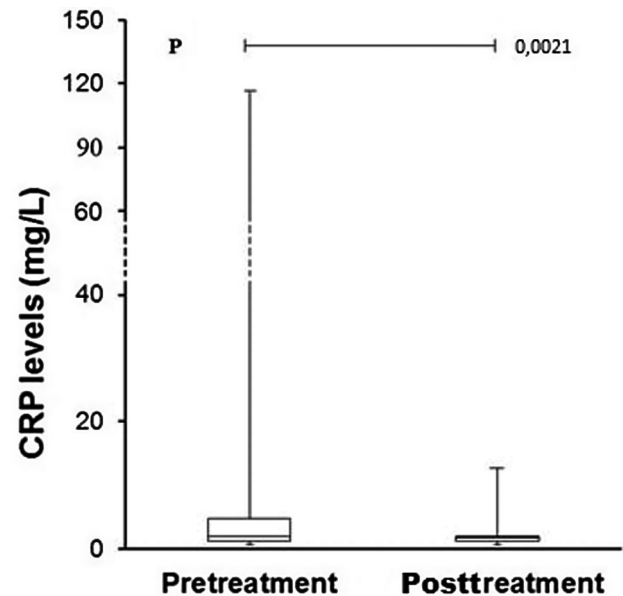


FIGURE 3 Comparison of CRP levels before and after omalizumab treatment

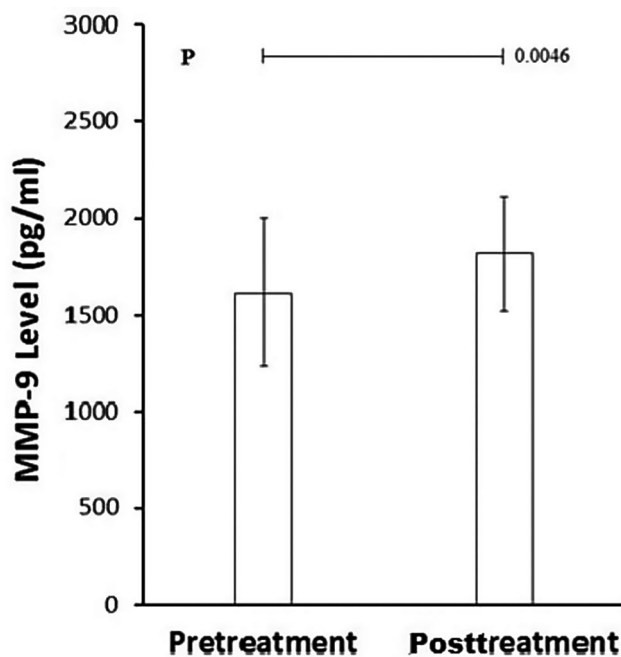


FIGURE 2 Comparison of MMP-9 levels before and after omalizumab treatment

by the alternative route cannot be prevented. The fact that the plasma level of MMP-9 does not decrease after anti-IgE treatment may indicate that T cells directly cause mast cell degranulation and maintain MMP-9 secretion.

It is also likely that CD4+ T cells involved in the pathogenesis of chronic urticaria produce MMP-9 to disrupt the extracellular matrix during their migration to the skin.¹⁰ In addition, MMP-9 may also be an acute-phase reactant that is stimulated by TNF- α or other cytokines. Similar to CRP, it may be high in the systemic circulation

instead of being produced in the skin.¹ All of these will be answered in further studies by demonstrating the true source of plasma MMP-9 in chronic urticaria.

The studies that showed high levels of MMP-9 in patients with chronic urticaria and its association with disease activation suggested the use of MMP-9 as a marker of disease activation. Tedeschi et al found that MMP-9 levels were high in patients with chronic urticaria and that the MMP-9 level was positively correlated with disease severity.¹⁷ Dilek et al demonstrated that MMP-9 levels were higher in children with chronic urticaria than in healthy volunteers.¹⁸ Except for one study that argued MMP-9 was only elevated in patients with chronic autoimmune urticaria,¹⁹ researchers reported increased MMP-9 levels in all cases, regardless of autoimmunity.^{17,20}

Altrichter et al found high levels of MMP-9 in patients with chronic urticaria but did not indicate an association between this parameter and disease activity. Those authors considered that high MMP-9 levels in patients with psoriasis, as well as those with chronic urticaria, resulted from the general inflammatory condition. They argued that MMP-9 did not specifically reflect disease activity, and thus it was not suitable for the assessment of disease activity.²⁰ In the present study, we found that MMP-9 levels were higher in patients with CSU, in line with other studies. Accordant with the study of Altrichter et al, we also found that MMP-9 level was not correlated with disease severity before treatment in patients with CSU. There is no study showing the changes in these levels after treatment. In the current study, we investigated plasma MMP-9 levels after omalizumab treatment, which is an effective option in chronic urticaria. We found that the post-treatment MMP-9 levels were higher compared with pre-treatment values.

The high levels of MMP-9 in the plasma of patients with chronic urticaria have been attributed to its assistance in the destruction

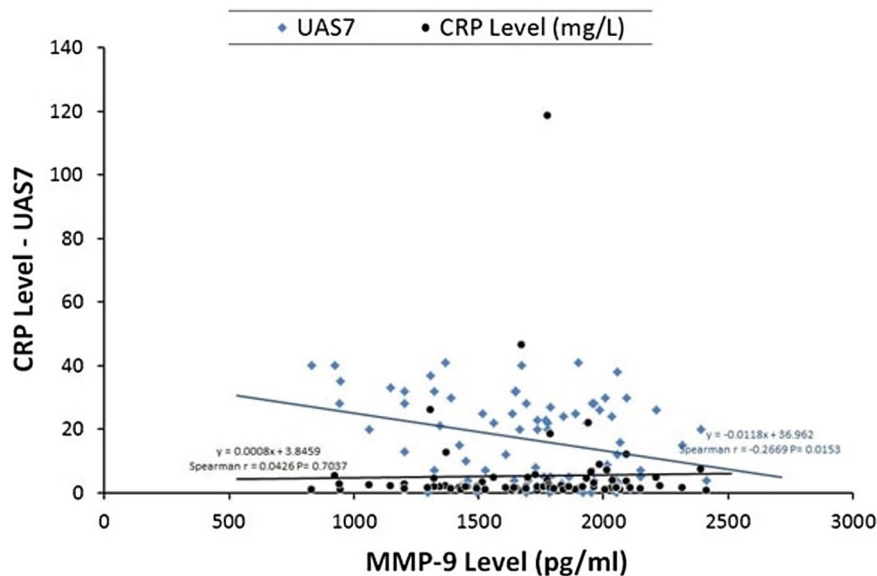


FIGURE 4 Correlation results of the changes in the CRP, MMP-9 and UAS7 values with omalizumab treatment

of type IV collagen in the basement membrane and its involvement in the transportation of inflammatory cells to the inflammation site. Wheals owing to the increased vascular permeability are characteristic in chronic urticaria. There is also evidence that MMPs cause increased vascular permeability by primarily disrupting tight junction proteins.²¹ Furthermore, MMPs strongly induce leukocyte migration.²² It is also considered that MMP-9 regulates the function of pro-inflammatory chemokines by separating them, thus contributing to the inflammatory process.²³ All these factors may explain how MMP-9 contributes to the inflammatory process in CSU. However, it should be borne in mind that MMPs have both pro-inflammatory and anti-inflammatory properties. MMPs can activate, inactivate or antagonise the biologic functions of cytokines and chemokines through a proteolytic process, thereby triggering or suppressing inflammation.²⁴

The N-terminal proteolytic process of CXCL-8 (CXC motif ligand 8 = IL-8), a chemotactic factor for neutrophils, basophils and T cells, results in the production of more potent chemoattractants. The processing of CXCL-8 by MMP-9 enhances the chemotactic activity of IL-8. In contrast, MMP-9 processes and inactivates other inflammatory chemokines, such as CXCL-5 and CXCL-6.²⁵

MMP-9 is considered to play a regulatory role in reducing allergen-induced airway inflammation. It decreases the transepithelial chemokine gradient and disrupts the leukocyte flow to the region. MMP-9 also processes neutrophil- and macrophage-specific chemoattractant proteins (S100A8 and S100A9) and Ym1, an eosinophil chemotactic molecule, in the bronchoalveolar fluid of asthmatic mice. Thus, it is thought to contribute to the clearance of the inflammatory cells of the lungs by establishing the chemotactic balance.^{26,27}

MMP-9 also plays a dual role in the processing of IL-1 β . It converts the IL-1 precursor beta to a more stable and active IL-1 β form. In addition, various MMPs, including MMP-9, break down and inactivate the active IL-1 beta and control its biologic activity, thus preventing the progression of inflammation.^{28,29} Furthermore, MMP-9

indirectly increases the activity of neutrophil elastase by inactivating alpha-1 antitrypsin, an inhibitor of neutrophil elastase. It also contributes to the inflammation process in this manner.³⁰

In mice with MMP-9 deficiency, it was shown that the production of IL-10, which is a down-regulator of delayed-type hypersensitivity, was not induced, and the response to contact hypersensitisation was exaggerated and prolonged. It is considered that Th2 cells require MMP-9 for entry into the antigen region, and MMP-9 directly stimulates IL-10 production from keratinocytes or macrophages.³¹

As indicated by the findings reported in the literature, MMP-9 plays a dual role in disease processes, such as most other MMPs, contributing to disease severity in the early stages, while trying to protect the organism against further damage in later stages. MMPs are enzymes that keep the organism in balance. The high plasma level of MMP-9 in patients with chronic urticaria can be explained by its contribution to inflammation. However, in the current study, the MMP-9 levels did not decrease even though the patients greatly benefited from omalizumab treatment. It was even observed that MMP-9 increased in response to treatment and recovery. It is hard to predict the exact mechanism by which MMP-9 increases after treatment in chronic urticaria. The possible benefits of this condition may be the anti-inflammatory effects of MMP-9, which may have prevented the destructive effects of chronic inflammation. It seems that omalizumab accelerates the repair of the damaged body by stimulating the synthesis of MMP-9. However, it should be taken into consideration that levels of MMP-9 that increase beyond the body's tolerance may have adverse effects.

CRP stands out as a sensitive inflammatory marker shown to be correlated with disease activity and treatment response in chronic urticaria in previous studies.^{32,33} On the other hand, even in patients with severe activity, the CRP level remains within the limits of normal laboratory values, yet it can be measured above the upper limit in mild disease. This situation limits its use as a biomarker in disease activity.² In the current study, CRP was not associated with disease severity at an individual level. However, consistent with the study of

Acer et al, we observed that CRP values were significantly reduced in the blood of patients with chronic urticaria after omalizumab treatment.³⁴

Some studies found that increased plasma MMP was correlated with CRP.^{17,20} In our study, the MMP-9 and CRP levels were not correlated. In addition, their levels were not correlated with disease severity, and CRP significantly decreased, whereas MMP-9 significantly increased following treatment. The decline in CRP was not correlated with the decrease in the UAS7 score, which suggests that CRP does not specifically reflect the severity of the disease; rather, it indicates the overall inflammatory state.

In this study, we aimed to determine the changes in blood MMP-9 after treatment and investigate whether MMP-9 could be used as a good biomarker for demonstrating disease activity, which is a controversial issue in the literature. The limitation of the study is that we did not follow the MMP-9 change during the omalizumab treatment and after the drug was discontinued. However, we evaluated the levels at the end of the 12th week when the high treatment efficiency of omalizumab was indicated. Further research is needed to provide an understanding of the changes in MMP-9 levels with spontaneous remission and long-term therapy.

In conclusion, MMP-9 was not correlated with disease severity or CRP in patients with chronic urticaria, and its plasma levels did not decrease after treatment. Therefore, we consider that MMP-9 is not a good biomarker in the assessment of disease activity. MMP-9 is not a suitable parameter for measuring treatment response and cannot be used as a biomarker for the evaluation of new treatments.

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DISCLOSURES

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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Plasma matrix metalloproteinase-9 level change with omalizumab treatment in chronic spontaneous urticaria

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MMP-9 was not correlated with disease severity or CRP in patients with chronic urticaria, and its plasma levels did not decrease after treatment. Therefore, we consider that MMP-9 is not a good biomarker in the assessment of disease activity. MMP-9 is not a suitable parameter for measuring treatment response and cannot be used as a biomarker for the evaluation of new treatments.

