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Original Article

Correlation of C-Reactive Protein (CRP) levels with disease activity in chronic urticaria measured by Urticaria Activity Score-7 (UAS7)

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Abstract

Background The Urticaria Activity Score-7 (UAS7) questionnaire is used to assess clinical disease activity in chronic urticaria (CU). The questionnaire is subjective in nature, thus several reports suggest that an objective parameter, such as C-reactive protein (CRP), is needed to support disease activity assessment in CU.

Objective To investigate the relationship between CRP levels and clinical disease activity assessed using UAS7 in patients with CU.

Methods Our study was a quasi-experimental study, using the one group pretest-post test design. We recruited 18 patients aged 18-59 years old with CU who met inclusion and exclusion criteria. We assessed disease activity using the UAS7 questionnaire and measured CRP levels in the first visit. All subjects received an antihistamine (10 mg cetirizine) for 4 weeks and follow-up levels were measured post-treatment. Disease activity was assessed in weekly follow-ups using UAS7. Spearman analysis was used to calculate the correlation between CRP levels and disease activity.

Results We found an increase in CRP levels in more than a third of subjects (median 2.5 mg/L [range 0.1-8.7 mg/L]). Prior to antihistamine treatment, the median UAS7 score was 14 (range 5-32), and the median UAS7 score in the first to fourth week of treatment was 3 (range 0-14), 4 (range 0-14), 3 (range 0-14), and 2 (range 0-12), respectively. The relationship was statistically significant, with a coefficient of correlation of 0.529 (p=0.024).

Conclusion CRP levels were increased in CU patients. CRP levels were significantly correlated with clinical disease activity measured by UAS7. After receiving antihistamines, the proportion of subjects with high CRP levels decreased.

Key words
Biomarker, chronic urticaria, CRP, disease activity, UAS.

Introduction

Urticaria is characterized by localized intracutaneous edema surrounded by erythema and accompanied by itch. The wheals can be various in size and can persist for 30 minutes to 36 hours. Chronic urticaria (CU), which persists over 6 weeks, can be categorized as chronic spontaneous urticaria and chronic inducible urticaria.[1-3] Prevalence of CU is estimated to be around 0.5% to 5% with an incidence of 1.4% per year, and may vary in different regions.[1] Currently, no data is available for the prevalence and incidence of CU in Indonesia. The Allergy-Immunology Division of the Dermatology and

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Venereology Outpatient Clinic, dr. Cipto Mangunkusumo General Hospital, a tertiary referral hospital in Jakarta, Indonesia, had 79 patients with CU in 2019, 28 of them were new patients.[4] The Urticaria Activity Score-7 (UAS7) measures CU signs and symptoms (such as wheals and pruritus) to assess disease activity, quality of life, treatment efficacy, and disease control in CU patients. UAS7 scores are graded as follows: 0–14 (mild), 15–29 (moderate), and 30–42 (severe).[2] Despite being the tool of choice to clinically assess disease activity, the subjective nature of the questionnaire[2] leads to a need for a biomarker as an objective parameter to measure disease activity in addition to UAS7.

C-reactive protein (CRP) is an acute-phase protein produced by hepatocytes as a response to an increase in pro-inflammatory cytokines, especially interleukin-6 (IL-6). Increase in CRP levels can be seen in 24-72 hours after tissue damage or infection. Raised CRP can also be present in malignancies, autoimmune diseases, cardiovascular diseases, and gastrointestinal problems.[6,7] Previous studies have shown CRP can potentially serve as a biomarker for CU. In Indonesia, a study by Wardhana *et al.*[5] showed the total number of urticaria lesions in patients with CU had positive correlation with the increase in CRP levels. Kolkhir *et al.*[8] showed higher CRP levels in CU patients compared with healthy controls. Further studies by the same group[9] showed statistically significant correlations between CRP and disease activity and quality of life in CU patients.

Despite the European Academy of Allergology and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization's (EAACI/GA^{2}LEN/EDF/WAO) guidelines which recommend CRP measurements to be done in all patients with chronic spontaneous urticarial,[3] CRP measurements in CU patients is not yet part of routine laboratory work. Assessing disease activity in CU patients is important to monitor treatment and quality of life, therefore objective markers are needed to supplement subjective questionnaires. We aim to investigate the correlation between CRP levels and CU disease activity (measured with UAS7) to learn whether CRP is a suitable biomarker for CU.

Materials and methods

We performed a quasi-experimental study using a one group pretest-posttest design in the Dermatology and Venereology Outpatient Clinic, dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, in July-November 2020. Subjects were recruited using consecutive sampling. We included CU patients aged 18-59 years old who provided informed consent. Patients who consumed antihistamines in the last 10 days and steroids in the last 12 days before blood draws, consumed medications that may affect CRP levels (NSAIDs, statins, thialozidinedione, estrogen), smoked, consumed alcohol, were pregnant, and showed signs and symptoms of acute infection and inflammation were excluded.

After informed consent was obtained, disease history was taken, as well as physical examination and disease activity assessment using UAS7. Subjects were given treatment according to hospital guidelines (cetirizine 10 mg for 4 weeks), and were instructed to fill out the UAS7 questionnaire every day for 4 weeks. CRP levels were measured before and after the 4-weeks treatment, using the immunoturbidimetry method (Cobas Integra, Roche Diagnostics).

Ethical approval was given by the ethical committee of Universitas Indonesia and Cipto Mangunkusumo General Hospital's Institutional

Table 1 Baseline characteristics of study subjects.

Variable	
Sex	
Female	16
Male	2
Age (years), Mean (SD)	36.39 (2.29)
Disease duration (months), Median (min-max)	24 (2-120)
Education	
Low	0
Middle	6
High	12
Occupation	
Housewife	5
Working	13
Body mass index (BMI), Average (SD)	26.34 (3.61)
BMI classification	
Normal	6
Overweight	8
Obese	4

SD=standard deviation

Review Board.

Results

We included 18 subjects aged 36.39±2.29 years, 16 of which were female. Duration of disease ranged from 2 months to 120 months, with a median of 24 months. Most patients were overweight, with an average body mass index (BMI) of 26.34. Baseline characteristics of study subjects can be seen in **Table 1.**

Clinical characteristics of our study subjects are described in **Table 2**. Satisfactory antihistamine therapy compliance was seen in 14 subjects.

Weekly changes in UAS7 scores are shown in **Figure 1**. Comparisons of CRP levels before and after 4 weeks of treatment is shown in **Table 3** and **Figure 2**. CRP levels were decreased in 10 out of 18 subjects after 4 weeks of treatment.

Using the Spearman's Rank Correlation test, we found moderate positive correlation between plasma CRP levels and CU disease activity measured using the UAS7 questionnaire (r=0.529, p=0.024) (**Figure 3**).

Table 2 Clinical characteristics of study subjects.

Variable	
UAS7 score pre-treatment, Median (min-max)	14 (5-32)
UAS7 classification pre-treatment	
Mild	11
Moderate	6
Severe	1
UAS7 score, first week of treatment, Median (min-max)	3 (0-14)
UAS7 score, second week of treatment, Median (min-max)	4 (0-14)
UAS7 score, third week of treatment, Median (min-max)	3 (0-14)
UAS7 score, fourth week of treatment, Median (min-max)	2 (0-12)
UAS7 classification post-treatment	
Mild	18
CRP level pre-treatment (mg/L), Median (min-max)	2.5 (0.1-8.7)
CRP classification, pre-treatment	
Normal	11
Increased	7
CRP level post-treatment (mg/L), Median (min-max)	3.05 (0.3-6.9)
CRP classification, pre-treatment	
Normal	13
Increased	5
Antihistamine compliance	
Yes	14
No	4

UAS7 = Urticaria Activity Score 7, CRP = C-Reactive Protein

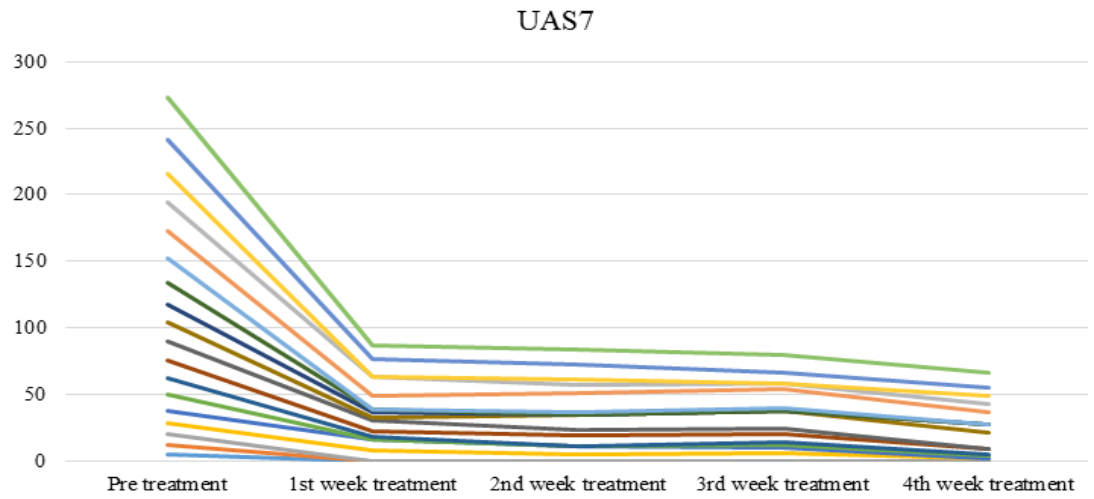

Figure 1 Changes in UAS7 scores pre-treatment and over the course of the 4-weeks treatment in each study subject.

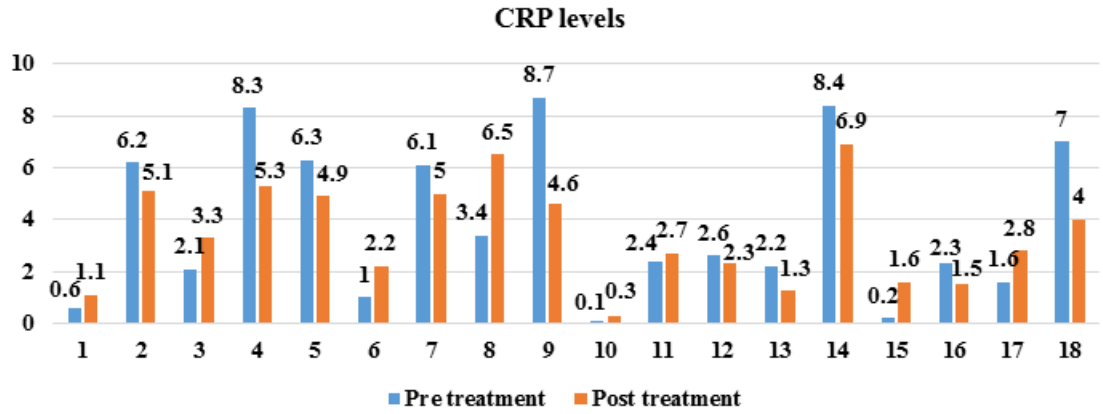

Figure 2 CRP levels pre- and post-antihistamine treatment in each study subject (cut off: 5mg/dl).

Table 3 Comparison of CRP levels pre- and post-treatment with antihistamines for 4 weeks.

Variable	*CRP*		*P**
	Pre-treatment	*Post-treatment*	
CRP levels, median (range)	2.5 (0.1-8.7)	3.05 (0.3-6.9)	0.420

*Wilcoxon's test.

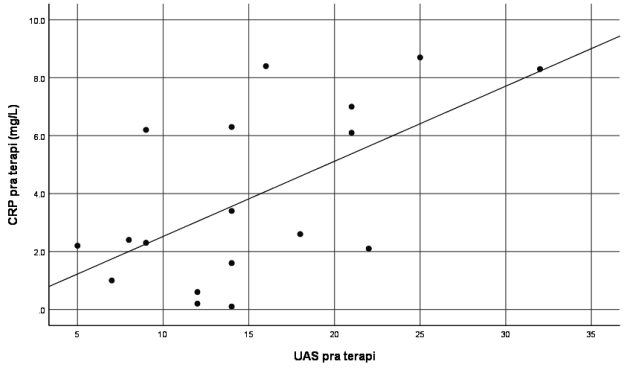

Figure 3 Correlation between pre-treatment CRP levels and chronic urticaria disease activity measured by UAS7.

Discussions

UAS7 is considered the gold standard for assessing clinical disease activity in patients with urticaria. The median of UAS7 score in our study was 14 (mild), with a range of 5 to 32. After classifying the subjects based on their UAS7 scores, we found 11 out of 18 subjects had mild CU. This contradicts findings by Takahagi *et al.*[10] who described a majority of their subjects was classified as severe CU (47 out of 82 subjects). Their study was performed

in an urticaria clinic in a referral hospital, which may explain the dominance of patients with severe symptoms. Although our study was also done in a referral hospital, we had strict inclusion and exclusion criteria, which excluded potential subjects with severe CU who were on antihistamines and did not consent to stop their antihistamines temporarily for the purpose of enrolling in the study.

After receiving 10 mg cetirizine for 4 weeks, we observed a decline in disease activity, shown by decreasing UAS7 scores. This decline was notable since the first week of treatment. After treatment, all subjects were classified as mild CU. The latest guidelines for urticaria management recommends second generation H1-antihistamines as the first line drugs, and the dose can be increased up to 4 times in absence of clinical improvement.[1,3] Cetirizine was chosen in our study due to its wide availability, affordability, and satisfactory safety profile. The prescribed dose remained constant throughout the 4 weeks course because our subjects experienced clinical improvement.

CRP levels in study subjects

CRP measurements were done before and after receiving antihistamines for 4 weeks. Previous studies show CRP levels in patients with CU were significantly lower when the disease was in remission compared to active disease.[10,11] More than one-third of subjects had increased CRP levels in the first measurement, in line with studies by Kolkhir *et al.*[9] and Kasperska-Zajac *et al.*[11] which described 31% and 36.2% of their subjects, respectively, had CRP levels above 5 mg/L.

In the second measurement, only 5 subjects had CRP levels that were higher than normal. This decrease of subjects with high CRP was not statistically significant, and the median post-treatment CRP levels were higher than pre-treatment (3.05 vs 2.5; $p>0.05$). Studies by Takahagi *et al.*[10] and Kasperska-Zajac *et al.*[11] showed CRP levels in CU patients were significantly lower when the disease was in remission compared to active disease. The majority of CRP increase in these previous studies was observed in patients with severe CU that markedly improved with treatment, thus showing significantly lower CRP levels in remission. In our study, only one subject had severe CU; the subject had high CRP levels before treatment and decreased to normal levels after treatment.

In order to find any comorbidities that may exclude any subjects from this study, we performed in-depth interviews and studied the subjects' medical records to look for history of cardiovascular diseases, acute infections, autoimmune diseases, and other confounding variables that may influence CRP levels such as history of smoking, alcohol use, and certain medications. To reduce possible bias, we prescribed antihistamines and measured CRP levels before and after the course of treatment, in order to properly reflect the current state of inflammation.

Correlation of CRP levels with CU disease activity measured with UAS7

We found a moderate positive correlation between CRP levels and CU disease activity. In the last decade, studies on CU have focused on finding objective measures for disease activity and treatment response. One potential biomarker is CRP, as recommended by the (EAACI/ GA^{2}LEN/EDF/WAO) guidelines for uritcaria.[3] An Indonesian study by Wardhana *et al.*[5] investigated the effects of psychological stress on CRP and peripheral blood smears in patients with idiopathic CU. They found psychological stress to be a risk factor of idiopathic CU and

there was a positive correlation between CRP levels and disease severity (assessed by total number of lesions), with R^2=0.041. The study only used the total number of lesions as a proxy for disease severity and did not account for level of pruritus.[5]

Other studies have found positive correlations between CRP and CU disease activity, with various levels of correlations. Kasperska-Zajac *et al.*[11] found strong correlations between CRP levels and CU disease activity (r=0.714, p<0.0001), as well as Kolkhir *et al.*[9] (r=0.759, p<0.01) and Maouia *et al.*[12] (r=0.3, p=0.011). Baek *et al.*[13] did not find a significant correlation between CRP levels and disease activity (r=0.22, p>0.05).

Number of study subjects may influence the level of correlations. Our study only included 18 subjects, a smaller number compared to studies by Kolkhir *et al.*[9] which used retrospective medical records data from 1.253 subjects in Germany and Moscow, and by Kaskperska-Zajac *et al.*[11] whose subjects included 58 CU patients and 30 healthy controls in a cross-sectional study.

Disease severity in the study subjects can contribute to the differing levels of correlations. Previous studies have larger proportions of subjects with severe CU, who had notable CRP decrease after treatment. Our study only had one subject with severe CU.[11]

Limitations

Limitations of this study include the lack of follow-up interviews to ensure no new confounding variables arise in the subjects during the treatment course; one subject had high post-treatment CRP, after re-interview, we discovered that the patient had teeth cavities in the last week, which may explain the increase in CRP. A larger number of study subjects was also needed to establish a stronger correlation.

Conclusions

CRP levels are increased in most patients with chronic urticaria, and decreased after antihistamine treatment. There is a moderate positive correlation between CRP levels and CU disease activity measured with the UAS7 questionnaire.

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