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BIOCHEMICAL AND CLINICAL ANALYSIS OF THE EFFECT OF TOCILIZUMAB TREATMENT APPLIED IN THE EMERGENCY DEPARTMENT ON THE MORTALITY OF COVID-19 PATIENTS

ACİL SERVİSTE UYGULANAN TOCİLİZUMAB TEDAVİSİNİN COVİD- 19 HASTALARININ MORTALİTESİNE ETKİSİNİN BİYOKİMYASAL VE KLİNİK ANALİZİ

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Anahtar Sözcükler: Tosilizumab, COVID-19, mortalite, C-Reaktif Protein, acil servis
Keywords: Tocilizumab, COVID-19, mortality, C-Reactive Protein, emergency department

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SUMMARY

Introduction: *The efficacy of tocilizumab (TCZ) treatment in Covid-19 patients in the emergency department is unknown. The aim of the study is to evaluate the effect of Tocilizumab treatment applied in the emergency department on COVID-19 mortality from a biochemical and clinical point of view.*

Material and Method: *Severe COVID-19 patients followed in the emergency critical intensive care unit between September 2020 and September 2021 were included in the study. A study group (patients receiving Tocilizumab treatment) and a control group (patients receiving standard treatment) were formed for this study.Biochemical markers (CRP, LDH, Ferritin, and D-dimer) in these groups and clinical outcomes for the study group were compared.*

Results: *A total of 94 patients, 47 from the study group and 47 from the control group, were included in the study. The survival rate in the study group was 19.1%. The CRP values of post-tocilizumab treatment in the study group were found to be statistically significantly lower than both the pre-treatment and control groups (p = 0.001, p = 0.001, respectively). While there was a statistically significant difference between the survivors and non-survivors in the study group in terms of CRP values only after tocilizumab treatment, the CRP values of the patients who survived post-TCZ treatment were found to be statistically lower than those in the control group (p = 0.020, p = 0.001, respectively). In ROC analysis,for a CRP value of 9 mg/dl after TCZ Treatment, the area under the curve for predicting mortality was 0.75 (95% CI 0.60 -0.86) (p = 0.001).*

Conclusion*: Our study showed that the effect of tocilizumab treatment applied in the emergency department on the mortality of COVID-19 patients is limited, the reduction in CRP with tocilizumab treatment improves survival and CRP is a suitable biomarker for monitoring the response to tocilizumab treatment.*

ÖZ

Giriş: *Acil servisteki COVID-19 hastalarında tosilizumab (TCZ) tedavisinin etkinliği bilinmemektedir. Çalışmanın amacı; acil serviste uygulanan tosilizumab tedavisinin COVID-19 mortalitesi üzerine etkisini biyokimyasal ve klinik açıdan değerlendirmektir.*

Gereç ve Yöntem: *Çalışmaya Eylül 2020 ile Eylül 2021 arasında acil kritik yoğun bakım ünitesinde takip edilen ağır COVID-19 hastaları dahil edildi. Bu çalışma için bir çalışma grubu (tosilizumab tedavisi alan hastalar) ve bir*

kontrol grubu (standart tedavi alan hastalar) oluşturuldu. Bu gruplardaki biyokimyasal belirteçler (CRP, LDH, Ferritin ve D-dimer) ve çalışma grubu için klinik sonuçları karşılaştırıldı.

***Bulgular:** Çalışma grubundan 47 ve kontrol grubundan 47 olmak üzere toplam 94 hasta çalışmaya dahil edildi. Çalışma grubunda hayatta kalma oranı %19,1 idi. Çalışma grubunda tosilizumab tedavisi sonrası CRP değerleri hem tedavi öncesi, hem de kontrol grubuna göre istatistiksel olarak anlamlı derecede düşük bulundu (sırasıyla p=0,001, p=0,001). Sadece tosilizumab tedavisi sonrası CRP değerleri açısından çalışma grubunda sağ kalanlar ile yaşamayanlar arasında istatistiksel olarak anlamlı bir fark bulunurken, TCZ tedavisi sonrası hayatta kalan hastaların CRP değerleri kontrol grubuna göre istatistiksel olarak daha düşük bulundu. (sırasıyla p=0.020, p=0.001). ROC analizinde, TCZ Tedavisinden sonra 9 mg/dl'lik bir CRP değeri için mortaliteyi tahmin etmek için eğrinin altında kalan alan 0.75(%95 CI 0.60-0.86) (p=0.001) idi.*

***Sonuç:** Çalışmamız, acil serviste uygulanan tosilizumab tedavisinin COVID-19 hastalarının mortalitesi üzerindeki etkisinin sınırlı olduğunu, tocilizumab tedavisi ile CRP'deki azalmanın sağkalımı artırdığını ve CRP'nin tocilizumab tedavisine yanıtı izlemede uygun bir biyobelirteç olduğunu göstermiştir.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease with high mortality caused by acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus from the betacoronavirus family (1,2).Recent studies have shown that COVID-19 mortality is the result of acute respiratory distress syndrome (ARDS) and multi-organ failure that develops as a result of cytokine storm (3,4).As a result of studies in which patients who died from COVID-19 disease were examined histopathologically, proinflammatory cytokine levels were found to be high in most patients with the severe clinical course (3-5). Therefore, early detection and treatment of cytokine storm is important (5). IL-6, an important cytokine in inflammation and immune response, has been found to play an important role in the damaged hyperimmune response in the COVID-19-induced cytokine storm (4). For this reason, drugs' effects on the IL-6 receptor have recently been studied in the therapy of COVID-19. Although tocilizumab (TCZ) is a drug used in the treatment of rheumatoid arthritis, its use in the treatment of COVID-19 has recently come to the fore. (2). By suppressing the inflammation that is effective in the cytokine storm, TCZ can stop the cytokine storm in the hyper-inflammation phase and reduce the severity of the disease (6,7).

Due to the uncontrolled immune mechanism in COVID-19 disease, elevations in IL-6 and other acute phase reactants and biochemical markers have been detected (8,9). Studies have shown that elevations in biochemical markers such as CRP, D-dimer, ferritin and LDH are effective in COVID-19 mortality (1,8,9). The regression of these biochemical markers after the 5th day as a result of TCZ treatment gave clinicians hope for their use in the treatment of COVID-19 (10). However, there is no conclusive data that TCZ treatment reduces the number of COVID-19 patients and/or deaths. (2). While some studies have stated that TCZ treatment has no benefit on these biochemical markers in surviving and deceased COVID-19 patients, some studies have revealed that TCZ treatment has positive effects on biochemical markers associated with COVID-19 mortality and may also be clinically beneficial (10,11). Therefore, there is no consensus on the effect of TCZ treatment on COVID-19 mortality.

Our study aims to evaluate the effect of TCZ treatment applied in the emergency department on biochemical markers associated with the mortality of COVID-19 disease and to analyze the clinical outcomes of TCZ treatment.

MATERIALS AND METHODS

This study was carried out in the Konya Meram Public Hospital emergency department. Among the severe COVID-19 patients who applied to the emergency department of Konya Meram Public Hospital and were hospitalized in the emergency critical intensive care unit between September 1, 2020, and September 1, 2021, patients who were given TCZ therapy and standard therapy were included in the study. A total of 94 patients, 47 from the study group and 47 from the control group, were included in the study. This study was carried out retrospectively. This study was conducted as a non-randomized blinded case-control study. Our study was approved after the application made to the ethics committee of KTO

Karatay University Faculty of Medicine (Date: 01/03/2022, decision no: 2022/032)

Severe COVID-19 patients (patients with hypoxemia, respiratory rate ≥ 30/min, oxygen saturation ≤ 93%, positive SARS-CoV-2 RT-PCR test, lung involvement > 25% on computed tomography) who were given TCZ therapy and patients who were given standard therapy were included in the study. In both treatment groups, patients who died within the first 5 days, pregnant women, patients under 18 years of age, end-stage renal disease, cirrhosis, HIV, inflammatory bowel disease, chemotherapy, patients with clinically overt bacterial or fungal infections, and drug hypersensitivity were excluded from the study.

A study group and a control group were formed for this study. The control group consisted of patients who received antibiotic therapy, favipiravir or chloroquine antiviral therapy, antiemetic, proton pump inhibitor, vitamin C, steroid, low molecular weight heparin, oxygen therapy (positive pressure ventilation, high flow therapy, intubation if necessary) as a standard treatment and did not survive. The study group consisted of patients who received TCZ treatment in addition to the standard treatment. A total of 800 mg of TCZ treatment was administered as the first dose of 400 mg and a second dose of 400 mg 24 hours later. CRP, LDH, D-dimer, and Ferritin levels, which are acute phase reactants, were evaluated in both groups. The clinical outcome was divided into three groups (transfer to another service/survival, transfer to another service/non-survival, and non-survival patients). The range of biochemical markers required for inclusion in the study was determined those with a CRP value of more than 5 mg/dl, a LDH value of more than 250 U/L, a D-dimer value of more than 1 µg/ml, and a ferritin value of more than 350 ng/mL at the introduction to the emergency department. The study group was formed as the biochemical marker levels of the patients included in the study at the introduction to the emergency department as the 'pre-TCZ treatment group', and the biochemical marker levels 5 days after the TCZ treatment as the 'post-TCZ treatment group'. The control group, on the other hand, was divided into two groups the biochemical marker levels of the patients who were given standard treatment at the introduction to the emergency department, the 'pre-standard treatment group' and the biochemical marker levels of 5 days after the standard treatment, the 'post-standard treatment group'. Sociodemographic characteristics such as age, gender, and clinical outcomes of the patients were recorded by scanning from the hospital registry system. All these data were recorded in the data collection form and statistical analysis was performed using the SPSS program.

Statistical Analysis

Statistical analysis were performed using SPSS 19.0 for Windows. Descriptive criteria; mean and standard deviation, median, and min-max values were presented as percentage distribution. The compliance of the data with the normal distribution was checked with the Kolmogorov-Smirnov test. For the comparison of continuous variables between independent groups, the Mann Whitney-U test was used when the parametric conditions were met when the Student t-test was not met, and the Wilcoxon signed-rank test was used in the dependent groups when the parametric conditions were met and the t-test was not met in the dependent groups. ROC analysis was used to examine the value of post-treatment laboratory results in predicting mortality in those receiving TCZ treatment. The significance level was determined as $p<0.05$.

RESULTS

A total of 94 patients were included in the study. The mean age of the patients was 67.5 ± 11.7 years for the study group and 70.6 ± 9.4 years for the control group. For both groups, 63.8% of the patients were male. Survival for the study group was 19.1%. The characteristics of the patients included in the study are summarized in Table 1.

When the values of the study group before and after TCZ treatment were evaluated; It was determined that the mean CRP values post-TCZ treatment were statistically significantly lower than pre-TCZ treatment ($p = 0.001$) (Table 2A).

As a result of the statistical analysis, it was found that the mean values of ferritin, LDH, and D-dimer in the pre-standard treatment of the control group were statistically lower than the mean

values of the post-standard treatment ($p < 0.05$) (Table 2B).

When the biochemical marker values of the study and control groups were compared; It was determined that the CRP averages of the study group were statistically lower than those of the control group, while the averages of Ferritin, LDH, and D-Dimer were higher ($p < 0.05$) (Table 2C).

As a result of the statistical analysis, it was determined that the CRP averages of the patients who did not survive post-TCZ treatment in the study group were statistically lower than those in the control group, while the averages of Ferritin, LDH, and D-Dimer were higher ($p < 0.05$) (Table 2D).

It was determined that the CRP values of the patients who survived post-TCZ treatment in the study group were statistically lower than those in the control group, and their ferritin values were higher ($p <0.05$) (Table 2E).

A statistically significant difference was found between survivors and non-survivors in the study group in terms of CRP values only post-tocilizumab treatment ($p = 0.020$) (Table 2F).

As a result of the statistical analysis, it was determined that the change in CRP, ferritin, and LDH levels pre-and post-TCZ treatment in the study group were statistically significantly different from the change pre-and post-standard treatment in the control group ($p <0.05$) (Table 3).

In the ROC analysis of CRP value post-TCZ Treatment to predict mortality, the area under the curve (AUC) was 0.75 (95% CI 0.60-0.86). As a result of the statistical analysis, it was determined that the CRP level post-TCZ treatment was statistically significant in predicting mortality ($p = 0.001$) (Figure 1).

Table 1. Patients' Characteristics

	Study Group	Control Group	Total
Age [a]	67.5 ± 11.7	70.6 ± 9.4	69.1 ± 10.7
Gender [b]			
Male	30 (63.8)	30 (63.8)	60(63.8)
Female	17 (36.2)	17 (36.2)	34(36.2)
Clinical outcome[b]			
transfer to another service/survival	9 (19.1)	0 (0)	9 (9.6)
transfer to another service/non-survival	3 (6.4)	0 (0)	3 (3.2)
non-survival	35 (74.5)	47(100)	82 (87.2)

[a] Mean ± standard deviation, [b] number (%)

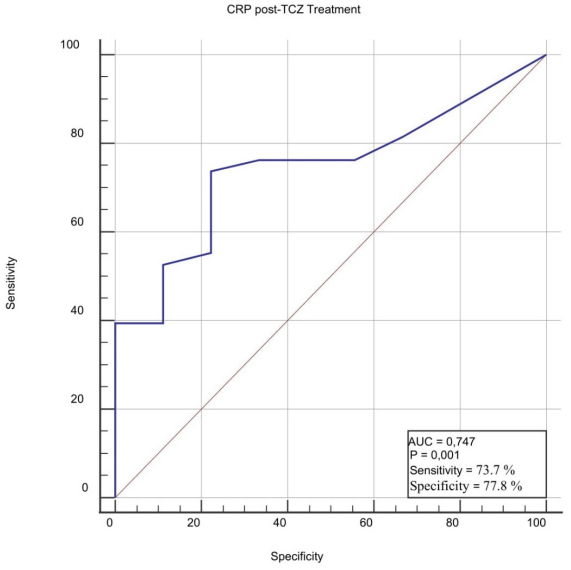

Figure 1. Evaluation of CRP Values Post-TCZ Treatment in Predicting the Presence of Death by ROC Analysis

Table 2. Statistical Analysis of Study Data

A. Comparison of CRP, Ferritin, LDH, and D-Dimer values pre and post-TCZ treatment in the study group		Value [a]	p-value [d]
CRP	pre-TCZ treatment group	149.32 ± 84.03	0.001
	post-TCZ treatment group	39.73 ± 58.98	
Ferritin	pre-TCZ treatment group	1073.09 ± 748.46	0.486
	post-TCZ treatment group	978.49 ± 637.16	
LDH	pre-TCZ treatment group	828.34 ± 1109.38	0.296
	post-TCZ treatment group	664.62 ± 350.14	
D-Dimer	pre-TCZ treatment group	5.84 ± 8.51	0.334
	post-TCZ treatment group	7.10 ± 8.29	
B. Comparison of CRP, Ferritin, LDH, and D-dimer values pre and post-standard treatment in the control group		Value [a]	p-value [d]
CRP	pre-standard treatment group	129.72 ± 75.92	0.205
	post-standard treatment group	112,63 ± 66.78	
Ferritin	pre-standard treatment group	585.94 ± 413.39	0.001
	post-standard treatment group	1078.40 ± 873.51	
LDH	pre-standard treatment group	496.26 ± 203.31	0.001
	post-standard treatment group	673.23 ± 299.06	
D-Dimer	pre-standard treatment group	3.51 ± 5.33	0.005
	post-standard treatment group	7.99 ± 8.78	
C. Comparison of CRP, Ferritin, LDH, and D-Dimer values of the study group and the control group		Value [a]	p-value [e]
CRP	Study group	39.73 ± 58.98	0.001
	Control group	129.72 ± 75.92	
Ferritin	Study group	978.49 ± 637.16	0.001
	Control group	585.94 ± 413.39	
LDH	Study group	664.62 ± 350.14	0.005
	Control group	496.26 ± 203.31	
D-Dimer	Study group	7.10 ± 8.29	0.014
	Control group	3.51 ± 5.33	
D. Comparison of CRP, Ferritin, LDH, and D-Dimer values of patients who did not survive post-TCZ treatment in the study group and those in the control group		Value [a]	p-value [d]
CRP	patients who did not survive post-TCZ treatment in the study group	47.05 ± 63.42	0.001
	Control group	129.72 ± 75.92	
Ferritin	patients who did not survive post-TCZ treatment in the study group	995.68 ± 663.96	0.001
	Control group	585.94 ± 413.39	
LDH	patients who did not survive post-TCZ treatment in the study group	662.34 ± 344.65	0.007
	Control group	496.26 ± 203.31	
D-Dimer	patients who did not survive post-TCZ treatment in the study group	7.84 ± 8.97	0.007
	Control group	3.51 ± 5.33	
E. Comparison of CRP, Ferritin, LDH, and D-Dimer values of patients who survived post-TCZ treatment in the study group and those in the control group		Value [c]	p-value [f]
CRP	patients who survived post-TCZ treatment in the study group	5 [10]	0.001
	Control group	121 [107]	
Ferritin	patients who survived post-TCZ treatment in the study group	738 [1007]	0.028
	Control group	387 [321]	
LDH	patients who survived post-TCZ treatment in the study group	545 [253.5]	0.080
	Control group	435 [255]	
D-Dimer	patients who survived post-TCZ treatment in the study group	2.5 [4.8]	0.359
	Control group	1.9 [3.1]	

Table 2. Continued

F. Comparison of CRP, Ferritin, LDH, and D-Dimer values pre and post- TCZ treatment between survivors and non-survivors in the study group		Value [c]	p-value [f]
CRP	pre-tocilizumab treatment of surviving patients in the study group	153 [87]	0.740
	pre-TCZ treatment of patients who did not survive in the study group	148 [109]	
	post-tocilizumab treatment of surviving patients in the study group	5 [10]	0.020
	post-TCZ treatment of patients who did not survive in the study group	23.4 [56.8]	
Ferritin	pre-tocilizumab treatment of surviving patients in the study group	947 [846.5]	0.968
	pre-TCZ treatment of patients who did not survive in the study group	919 [877.5]	
	post-tocilizumab treatment of surviving patients in the study group	738 [1007]	0.780
	post-TCZ treatment of patients who did not survive in the study group	894 [693]	
LDH	pre-tocilizumab treatment of surviving patients in the study group	736 [497]	0.135
	pre-TCZ treatment of patients who did not survive in the study group	530 [311]	
	post-tocilizumab treatment of surviving patients in the study group	545 [253.5]	0.947
	post-TCZ treatment of patients who did not survive in the study group	548.5 [399.5]	
D-Dimer	pre-tocilizumab treatment of surviving patients in the study group	2.7 [3.6]	0.842
	pre-TCZ treatment of patients who did not survive in the study group	3.1 [2.9]	
	post-tocilizumab treatment of surviving patients in the study group	2.5 [4.8]	0.193
	post-TCZ treatment of patients who did not survive in the study group	4.9 [6.8]	

[a] Mean ± standard deviation, [c] Median [interquartile range], [d] dependent group t-test , [e] Student t-test, [f] Mann Whitney-U test, CRP: C-Reactive Protein, LDH: lactate dehydrogenase, significance level: p value < 0.05

Table 3. Analysis of the Differences Between Pre-and Post-Treatment Values in the Study Group and the Control Group

		Value [c]	p-value [f]
CRP difference	Study group	-108 [111.7]	0.001
	Control group	-13 [117]	
Ferritin difference	Study group	-33 [563]	0.00
	Control group	232 [743]	
LDH difference	Study group	35 [256]	0.002
	Control group	154 [249]	
D-Dimer difference	Study group	1 [5.8]	0.099
	Control group	2 [5.1]	

[c] Median [interquartile range], [f] Mann Whitney U-test, CRP: C-Reactive Protein, LDH: lactate dehydrogenase, significance level: p-value < 0.05

DISCUSSION

The transformation into an epidemic all over the world of the COVID-19 disease has led to occupancy in the services and intensive care units in hospitals, and the length of stay of the patients in the emergency departments (12). This situation has resulted in the introduction of many treatment methods applied in intensive care units in emergency departments. Tocilizumab therapy is an alternative used in severe and critical COVID-19 patients. When the literature was reviewed, we could not find any study investigating the effects of tocilizumab treatment applied in the emergency department on mortality. In our study, we aimed to evaluate the biochemical and clinical evaluation of tocilizumab treatment started in the emergency on COVID-19 mortality.

In our study, we found a survival rate of 19.1% in the group treated with TCZ. In previous studies involving COVID-19 patients and investigating the success of TCZ treatment, the mortality rate of COVID-19 patients treated with tocilizumab was found to be approximately 20-25% (13,14). These randomized studies suggested that advanced age was directly associated with COVID-19 mortality after tocilizumab treatment. The fact that the patients in our study were from the elderly population may be the reason for the high mortality rates. This may be related to the weakening of the immune system in the elderly population and the inadequate response to tocilizumab in the hyperimmune stage, which is impaired during the cytokine storm period, compared to the younger population. In addition,

another reason may be that the patients we included in the study applied in the irreversible stage of the IL-6-centered hyperimmune response responsible for mortality in COVID-19 disease.

In a study conducted by Toniati P. et al. (15), they found that the levels of CRP, fibrinogen, and ferritin, which are the acute phase reactants, were lower and the D-dimer value was higher after TCZ therapy in 100 patients with COVID-19 who did not differentiate between clinical groups. In another study by Hassan M. et al. (16), the data of 120 severe and critical COVID-19 patients after TCZ treatment were evaluated and significant improvement was found in CRP, ALT, ferritin, and D-dimer levels. In our study, we found only a decrease in CRP values after tocilizumab treatment. We did not detect any change in other acute phase reactants. We found lower CRP levels and higher ferritin, ALT, and D-dimer values in patients treated with TCZ compared to the control group. This may be due to the partial effect of tocilizumab treatment on the inflammation cascade. In previous studies, a relationship was found between mortality and increased acute phase reactants (3,5). The high mortality rate after TCZ treatment in our study supports this situation.

In a study examining the inflammatory markers of severe COVID-19 patients who survived and did not survive post-TCZ therapy (11), they said that there was no variability in inflammatory markers between patients who survived and did not survive post-TCZ therapy. On the other hand, many studies have emphasized that CRP is an independent marker for COVID-19 mortality (3,5,17,18). In our study, when we compared the data of patients who survived after TCZ treatment with both the control group and the patients who did not survive after TCZ treatment; We found that the CRP value was lower after treatment in the TCZ treatment group and the living group. In the difference analysis of data pre-and post-TCZ treatment, and pre and post-standard treatment, we found a significant difference in terms of CRP levels. In addition to all these data, we determined that CRP is a significant acute phase reactant in estimating mortality as a result of the ROC analysis. In the light of all these data, this study showed that CRP level is an important parameter in COVID-19 mortality and may be useful in the follow-up of TCZ treatment. This suggests that the main mechanism of action of Tocilizumab therapy in inflammation is CRP-focused.

In our study, we found that lowering the CRP value below 9 mg/dl post-TCZ treatment increased survival. In a study involving severe COVID-19 patients with Cytokine Release Syndrome (19), they said that the response of cytokine absorption therapy and tocilizumab therapy to inflammatory cytokines was similar. In the same study (19), three-day follow-up values were evaluated and they said that although the CRP values in the group receiving tocilizumab were lower than the initial level, they were at the level of 100 mg/dl and the mortality was 50% in the group receiving tocilizumab. Similar to the data in this study, we think that the lack of the desired decrease in CRP level in our study increases mortality and the treatment approach should be planned with a focus on lowering CRP.

There are some limitations to our study. First, the study's being retrospective and the small number of patients are limitations of the study. Second, not evaluating comorbid diseases that may affect mortality is another limitation. Third, another limitation is that we did not analyze the time from the onset of symptoms to admission to the emergency department, which is an important factor in the response to treatment.

CONCLUSION

This study showed that CRP is an acute phase reactant associated with COVID-19 mortality, but the effect of TCZ treatment on mortality is limited, although a decrease in CRP values is achieved with tocilizumab treatment. In addition, we found that CRP is an appropriate biomarker in the follow-up of the response to tocilizumab treatment, and lowering the CRP value below 9 mg/dl post-TCZ treatment increases survival. We think that planning focused on providing an adequate decrease in CRP value should be made in order to reduce COVID-19 mortality. There is a need for multicenter studies with a large population in this regard.

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