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Effects of Tocilizumab Treatment on COVID-19 Patients in Intensive Care: A Retrospective Research

Yoğun Bakımdaki COVID-19 Hastalarında Tocilizumab Tedavisinin Etkileri: Retrospektif Araştırma

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ABSTRACT Objective: Severe acute respiratory syndrome-coronavirus-2, causing the coronavirus disease-2019 (COVID-19) pandemic, has significantly impacted global health. Treatment has mainly involves supportive care, but various pharmaceutical interventions have also been used. These include antimalarials like quinine, antibiotics, antivirals, convalescent plasma, steroids, blood thinners, antibody therapies, drugs targeting interleukin-6 and interleukin-1, and baricitinib. Each treatment aims to manage and treat COVID-19. **Material and Methods:** We retrospectively evaluated 69 COVID-19 patients who received intravenous (iv) tocilizumab (TCZ) in our hospital's intensive care unit (ICU) between January 1-December 31, 2021. Based on symptom severity, patients received a single iv dose of TCZ at either 400 mg or 800 mg. **Results:** The mean duration of TCZ administration was 6.59 (SD±3.371) days. Of the patients, 37 (53.6%) were male and 32 (46.4%) were female. Mean age was 55.72 (SD±11.62) years. On days 1, 3, and 7th there were statistically significant differences in white blood cell, lymphocyte, platelet, alanine aminotransferase, ferritin, and C-reactive protein (CRP) values. When the factors affecting the risk of death were evaluated, the probability of death increased with increasing procalcitonin (PCT) levels (p=0.03, z=1.97). The results showed that increasing age increased the likelihood of death (p<0.0001, z=5.069). Patients with longer ICU stay were more likely to die (p<0.0001, z=4.186). **Conclusion:** The COVID-19 pandemic has introduced uncertainty about effective drug treatments. In this study of patients treated with TCZ, it was found that mortality rates were higher in the presence of high PCT levels, advanced age, long hospital stays and chronic disease. TCZ administration was linked to reduced inflammatory markers, including CRP and ferritin.

Keywords: COVID-19; tocilizumab; severe acute respiratory syndrome-coronavirus-2; anti-interleukin-6

ÖZET Amaç: Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] pandemisine neden olan şiddetli akut solunum sendromu-koronavirüs-2 küresel sağlığı önemli ölçüde etkilemiştir. Tedavi esas olarak destekleyici bakımı içermekle birlikte, çeşitli farmasötik müdahaleler de kullanılmıştır. Bunlar arasında kinin gibi antimalaryaller, antibiyotikler, antiviraller, iyileşme plazması, steroidler, kan sulandırıcılar, antikor tedavileri, interlökin-6 ve interlökin-1'i hedefleyen ilaçlar ve baricitinib yer almaktadır. Her bir tedavi COVID-19'u yönetmeyi ve tedavi etmeyi amaçlamaktadır. **Gereç ve Yöntemler:** Hastanemizin yoğun bakım ünitesinde (YBÜ) 1 Ocak-31 Aralık 2021 tarihleri arasında intravenöz (iv) tosilizumab [tocilizumab (TCZ)] alan 69 COVID-19 hastasını retrospektif olarak değerlendirdik. Semptom şiddetine bağlı olarak, hastalar 400 mg veya 800 mg'lık tek bir iv doz TCZ aldı. **Bulgular:** Ortalama TCZ uygulama süresi 6,59 (SD±3,371) gündü. Hastaların 37'si (%53,6) erkek ve 32'si (%46,4) kadındı. Ortalama yaş 55,72 (SS±11,62) yıldı. 1, 3 ve 7. günlerde beyaz kan hücresi, lenfosit, trombosit, alanin aminotransferaz, ferritin ve C-reaktif protein (CRP) değerlerinde istatistiksel olarak anlamlı farklılıklar vardı. Ölüm riskini etkileyen faktörler değerlendirildiğinde, prokalsitonin [procalcitonin (PCT)] düzeyleri arttıkça ölüm olasılığı da artmıştır (p=0,03, z=1,97). Sonuçlar artan yaşın ölüm olasılığını artırdığını göstermiştir (p<0,0001, z=5,069). YBÜ'de kalış süresi daha uzun olan hastaların ölme olasılığı daha yüksekti (p<0,0001, z=4,186). **Sonuç:** COVID-19 pandemisi, etkili ilaç tedavileri konusunda belirsizlik yaratmıştır. TCZ ile tedavi edilen hastalar üzerinde yapılan bu çalışmada; yüksek PCT seviyeleri, ileri yaş, uzun hastanede kalış süreleri ve kronik hastalık varlığında mortalite oranlarının daha yüksek olduğu tespit edilmiştir. TCZ uygulaması, CRP ve ferritin dâhil olmak üzere inflamatuar belirteçlerin azalmasıyla bağlantılıdır.

Anahtar Kelimeler: COVID-19; tocilizumab; şiddetli akut solunum sendromu-koronavirüs-2; anti-interlökin-6

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Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), responsible for the coronavirus diseases-2019 (COVID-19) pandemic, has had a profound impact on human health worldwide. The disease's progression may be exacerbated by hyperinflammation, which increases levels of various pro-inflammatory cytokines, such as C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), D-dimer, and interleukin-6 (IL-6). In response to this global health crisis, researchers have been exploring different drug combinations and dosages to develop effective treatment strategies.[1] Many drug therapies, such as quinine, antibiotic drugs, antiviral drugs, concomitant plasmas, corticosteroids, anticoagulant drugs, monoclonal antibodies, IL-6, Janus kinase 1/Janus kinase 2 inhibitors, and anti- IL-1 drugs, have been used to treat COVID-19.[2] Typically, COVID-19 treatment has focused on providing supportive care. The primary cause of mortality in these cases is respiratory failure resulting from acute respiratory distress syndrome.[3]

Tocilizumab (TCZ) (Actemra, Roche, Basel, Switzerland) is a monoclonal antibody that targets the inflammatory IL-6 receptor. TCZ treats various conditions including rheumatoid arthritis, giant cell arteritis, and juvenile idiopathic arthritis.[4] In COVID-19 patients, the disease triggers a substantial activation of T lymphocytes (LYM) and mononuclear macrophages, leading to the production of cytokines like IL-6. These cytokines attach to IL-6 receptors on target cells, triggering a cytokine storm and severe inflammatory responses in the lungs. TCZ, a medication with a high affinity for the IL-6 receptor, can effectively block this interaction. By preventing IL-6 from binding to its receptor, TCZ inhibits the immune-mediated damage to target cells and helps reduce inflammatory responses.[5] TCZ possesses the capability to bind to both membrane-bound and soluble forms of IL-6 receptor, inhibiting IL-6 from binding to these receptors. This mechanism effectively interrupts IL-6 signaling via both receptor types, while leaving the signaling of other cytokines within the IL-6 family unaffected.[6]

Studies examining the different effects of TCZ on COVID-19 patients have reported different results have been found. We aimed to evaluate the laboratory parameters and survival of intensive care patients treated with TCZ in our hospital and to share our experiences.

MATERIAL AND METHODS

This was a retrospective single-center cross-sectional study. We retrospectively evaluated patients who received intravenous (iv) TCZ treatment for COVID-19 in the intensive care unit of our hospital between January 1-December 31, 2021. The patient data were obtained from computer records, discharge summaries, and outpatient records. When necessary, patients families were interviewed, and their information was obtained. Demographic parameters of the patients, such as age, sex, chronic diseases, number of days of intensive care unit (ICU) stay, intubation status, tocilizumab dose, and the day on which they received tocilizumab will be examined. In addition, white blood cell (WBC) count and neutrophil (NEU), LYM, platelet (PLT), d-dimer, ferritin, procalcitonin (PCT), CRP, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels were recorded on days 1, 3, 5, and 7th of TCZ administration, and statistically significant differences were evaluated. Ethical approval the study protocol was approved by the Scientific Research Ethics Committee of Balıkesir Atatürk City Hospital (date: April 6, 2023; no: 2023/1/3). This study was designed as a retrospective cross-sectional study and was conducted in accordance with the principles of the 2013 Declaration of Helsinki.

The study included adult patients (18 years and older) who were admitted to the ICU with confirmed SARS-CoV-2 infection and received at least one iv dose of TCZ. The administration of TCZ followed the COVID-19 treatment guidelines set by the ministry of health. Patients initially suspected of having COVID-19 but later found negative through qualitative real-time PCR testing were not included in the study. All participants received standard COVID-19 care as outlined in the Ministry of Health protocol. The hospital information management system was used to collect patient data. TCZ dosing adhered to the ministry of health's COVID-19 treatment guidelines.

The entire treatment protocol was planned according to the Turkish Ministry of Health's

"COVID-19 Anticytokine-Antiinflammatory Therapies, Coagulopathy Management". TCZ has been used in patients with signs of macrophage activation syndrome (MAS) or rapidly progressing MAS. Depending on the severity of the patient's symptoms, 400 or 800 mg TCZ was administered intravenously. When the first dose of 400 mg was administered, the dose was repeated as 400 mg within 24 h, taking into account the changes in clinical and laboratory findings.

STATISTICAL ANALYSIS

The study data were analyzed using IBM SPSS version 25 (Chicago, IL, USA) statistical package. Distribution statistics such as frequency, mean and median were used for quantitative data. Compliance with normal distribution was tested before hypothesis tests. Student-t test was used for pairwise comparisons, Friedman analysis was used for dependent groups in repeated measurements, and the risk of death in patients was calculated by logistic regression. The significance level α: 0.05 has been accepted in the interpretation of significance.

RESULTS

The study included 69 patients who received TCZ treatment while being followed up in the ICU with the diagnosis of COVID-19. Of the patients, 37 (53.6%) were male and 32 (46.4%) were female. The mean age was 55.72 (SD±11.62) and the median age was 54.00 years. The mean number of days of ICU hospitalization for all patients was 16.22 (SD±6.485), mean 17.74 (SD±6.681) for deceased patients and 13.77 (SD±5.421) for living patients. The mean duration of TCZ administration was 6.59 (SD±3.371) days, 7.21 (SD±3.468) days in patients who died and 5.63 (SD±3.027) days in patients who lived. Forty patients were treated with methylprednisolone in addition to TCZ. Of these, 28 died. Of the 29 patients treated with dexamethasone (Dekort, Deva Holding A.Ş.), 14 died and 15 survived. The demographic and clinical data of patients are shown in Table 1.

TABLE 1: Demographic and clinical data of patients receiving TCZ treatment

Age	
$\bar{X}$±SD	55.72±11.612
Median	54.00
Minimum-maximum	(33-83)
Sex	
Male, n (%)	37 (53.6%)
Female, n (%)	32 (46.4%)
Number of intubated days (day)	
$\bar{X}$±SD	11.93±5.897
Median	12.00
Minimum-maximum	1-27
Days of ICU (day)	
$\bar{X}$±SD	16.22±6.485
Median	15.00
Minimum-maximum	4-36
Dead (n)	42
Alive (n)	27
TCZ dosage(n)	
1	12
2	57
TCZ administration day	
$\bar{X}$±SD	6.59±3.371
Median	6.00
Minimum-maximum	1-15

SD: Standard deviation; ICU: Intensive care unit; TCZ: Tocilizumab

TABLE 2: Results of the Friedman test statistics for laboratory values

	Friedman test (chi-square)	p value
WBC-0, WBC-1, WBC-3, WBC-7	14.600	**0.002**
NEU-0, NEU-1, NEU-3, NEU-7	6.554	0.088
LYM-0, LYM-1, LYM-3, LYM-7	10.151	**0.017**
PLT-0, PLT-1, PLT-3, PLT-7	24.076	**0.000**
HGB-0, HGB-1, HGB-3, HGB-7	2.267	0.519
D-dimer-0, D-dimer-1, D-dimer-3, D-dimer-7	6.286	0.099
Ferritin-0, Ferritin-1, Ferritin-3, Ferritin-7	18.385	**0.000**
AST-0, AST-1, AST-3, AST-7	2.277	0.517
ALT-0, ALT-1, ALT-3,ALT-7	9.546	**0.023**
CRP-0, CRP-1, CRP-3, CRP-7	66.689	**0.000**
PCT-0, PCT1, PCT-3, PCT-7	3.902	0.272

WBC: White blood cell; NEU: Neutrophil; LYM: Lymphocyte; PLT: Platelet; HGB: Hemoglobin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C- reactive protein; PCT: Procalcitonin

When the values of WBC, NEU, LYM, PLT, hemoglobin, D-dimer, AST, ALT, CRP, PCT, and ferritin were compared on the day of drug administration and days 1, 3, and 7th there were statistically significant differences in WBC, LYM, PLT, ALT, ferritin, and CRP levels. Pairwise comparisons of these laboratory parameters according to the day are given in Table 2.

When CRP values were analyzed, a decrease in CRP levels was observed between the day of drug administration and day 7th. In the comparison of CRP levels on days 0, 1, 3, and 7th there was no significant difference between days 0-1, but there was a significant difference compared to the other days (Table 3). ALT levels of the patients showed a regular increase on the 1st day. Although significant differences were observed in the platelet values of patients, they generally remained within the normal range.

Ferritin levels significantly decreased from day 0-7th day after drug administration. There was a significant difference between ferritin levels on the 7th day and other days. In the pairwise comparison of WBC levels, except for day 0 and days 1, 3, and 7th there was a significant difference between all other comparisons, and the values were just above the normal value. There was a significant difference between days 0-7 and 1-7 (Table 3).

Daily changes of some laboratory values are shown in Figure 1.

When the factors affecting the risk of death were evaluated, the probability of death increased with increasing PCT levels (p=0.03, z=1.97). The results showed that increasing age increased the likelihood of death (p<0.0001, z=5.069) and each additional increase in age increased the risk of death by 2.23%. Patients with a longer ICU stay were more likely to die (p<0.0001, z=4.186), and each additional day increased the probability of death by 2.96%.

The presence of chronic diseases increased the likelihood of death (32%) (p=0.0055, z=2.777), and the risk of death was 14% higher in those with high blood pressure. The likelihood of death did not change according to sex. The risk of death did not differ between the day TCZ was administered to patients and between 2 doses of TCZ treatment and a single dose of TCZ was administered. Methylprednisolone use was associated with a 36% higher risk of death than dexamethasone use.

TABLE 3: Comparison of significant values from the Friedman test statistic

	Test statistic	SE	Std. test statistic	p value
WBC-1, WBC-0	0.206	0.230	0.897	0.370
WBC-1, WBC-3	-0.683	0.230	-2.967	**0.003***
WBC-1, WBC-7	-0.730	0.230	-3.174	**0.002***
WBC-0, WBC-3	-0.476	0.230	-2.070	**0.038***
WBC-0, WBC-7	-0.524	0.230	-2.277	**0.023***
WBC-3, WBC-7	-0.048	0.230	-0.207	0.836
LYM-1, LYM-0	0.175	0.230	0.759	0.448
LYM-1, LYM-3	-0.333	0.230	-1.449	0.147
LYM-1, LYM-7	-0.698	0.230	-3.036	**0.002***
LYM-0, LYM-3	-0.159	0.230	-0.690	0.490
LYM-0, LYM-7	-0.524	0.230	-2.277	**0.023***
LYM-3, LYM-7	-0.365	0.230	-1.587	0.112
PLT-7, PLT-0	0.286	0.230	1.242	0.214
PLT-7, PLT-1	0.698	0.230	3.036	**0.002***
PLT-7, PLT-3	1.048	0.230	4.554	**0.000***
PLT-0, PLT-1	-0.413	0.230	-1.794	0.073
PLT-0, PLT-3	-0.762	0.230	-3.312	**0.001***
PLT-1, PLT-3	-0.349	0.230	-1.518	0.129
Ferritin-7, Ferritin-3	0.640	0.278	2.297	**0.022***
Ferritin-7, Ferritin-0	0.872	0.278	3.132	**0.002***
Ferritin-7, Ferritin-1	1.140	0.278	4.093	**0.000***
Ferritin-3, Ferritin-0	0.233	0.278	0.835	0.404
Ferritin-3, Ferritin-1	0.500	0.278	1.796	**0.073***
Ferritin-0, Ferritin-1	-0.267	0.278	-0.961	0.337
CRP-7, CRP-3	0.739	0.269	2.746	**0.006***
CRP-7, CRP-0	1.772	0.269	6.582	**0.000***
CRP-7, CRP-1	1.880	0.269	6.986	**0.000***
CRP-3, CRP-0	1.033	0.269	3.836	**0.000***
CRP-3, CRP-1	1.141	0.269	4.240	**0.000***
CRP-0, CRP-1	-0.109	0.269	-0.404	0.686
ALT-1, ALT-3	-0.153	0.232	-0.661	0.509
ALT-1, ALT-0	0.266	0.232	1.148	0.251
ALT-1, ALT-7	-0.677	0.232	-2.922	**0.003***
ALT-3, ALT-0	0.113	0.232	0.487	0.626
ALT-3, ALT-7	-0.524	0.232	-2.261	**0.024***
ALT-0, ALT-7	-0.411	0.232	-1.774	0.076

*Statistically significant
WBC: White blood cell; LYM: Lymphocyte; PLT: Platelet; ALT: Alanine aminotransferase; CRP: C-reactive protein; SE: Standard error; Std: Standard

DISCUSSION

This study assessed the impact of TCZ therapy on various laboratory parameters in COVID-19 patients admitted to the ICU and examined factors associated with mortality. The results indicate that TCZ treatment is significantly effective, particularly on the inflammatory markers CRP and ferritin, while it induces limited alterations in coagulation and hematological parameters.

TCZ, a monoclonal antibody that inhibits IL-6 receptors, is employed in the treatment of COVID-

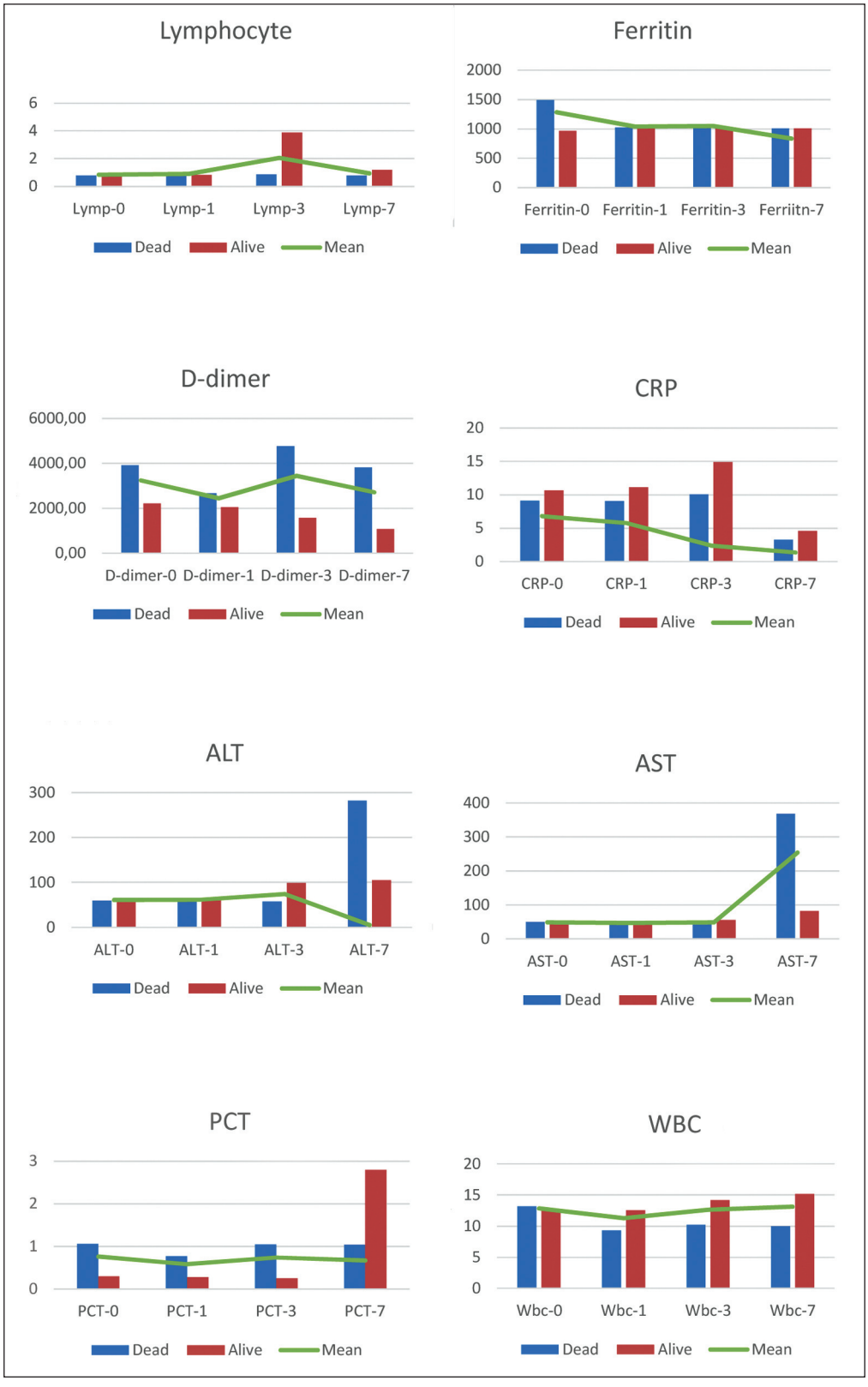

FIGURE 1: Daily variation of laboratory values in dead and alive patients
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PCT: Procalcitonin; WBC: White blood cell

19, particularly for patients experiencing cytokine storms, to mitigate inflammation. Numerous studies have demonstrated that TCZ therapy induces significant changes in laboratory parameters among COVID-19 patients. The administration of TCZ results in notable alterations in inflammatory markers and certain hematologic parameters in these patients. Evaluating these effects is essential for determining the treatment's efficacy and potential adverse effects. TCZ treatment has been associated with significant reductions in inflammatory markers such as CRP, D-dimer, ferritin, and PCT.[7,8]

The combination of TCZ and corticosteroids has shown promising results in treating severe COVID-19 cases, particularly when single therapies have failed. A meta-analysis involving 18,702 patients from 13 randomized controlled trials and 24 case-control studies found that TCZ and dexamethasone contributed to mortality reduction in severe COVID-19 patients.[9] The TCZ-methylprednisolone combination also showed efficacy in reducing mortality in case-control studies. Additionally, a meta-analysis of 5 studies demonstrated that the risk of death in COVID-19 patients treated with corticosteroids and TCZ was 26% lower than TCZ alone and 52% lower than the control group.[10]

Interestingly, while the combination therapy shows promise, individual treatments have yielded mixed results. Corticosteroids alone were not recommended for non-severe COVID-19 patients, as they prolonged hospitalization and delayed viral clearing.[11] The combination of TCZ and corticosteroids appears to be more effective than single therapies in treating severe COVID-19 cases. This synergistic effect may be due to the complementary mechanisms of action of these drugs in modulating the inflammatory response. However, careful consideration of patient condition and disease severity is crucial when deciding on treatment options.[12]

The observed substantial reduction in CRP levels substantiates the hypothesis that TCZ mitigates the inflammatory response by inhibiting IL-6 receptors, thereby significantly diminishing systemic inflammation. While no notable change in CRP levels was detected on the 1st day, significant reductions were evident on the 3rd and 7th days, suggesting that the drug's effect manifests over time. This observation aligns with the delayed CRP response reported in previous studies.[13]

The use of TCZ in COVID-19 patients has been associated with several effects on CRP levels.[14] Some studies have shown that TCZ treatment leads to a rapid decrease in serum CRP levels.[15] In a study comparing the efficacy of TCZ in COVID-19 patients, a decrease in CRP levels, a decrease in ferritin levels only in survivors, and an increase in lymphocyte values were found after TCZ administration.[16] Observational studies have shown administration of TCZ to patients with SARS-CoV-2-associated pneumonia is associated with significant clinical improvement, including higher survival rates and improvements in laboratory parameters such as CRP.

In one study, deceased patients receiving TCZ had higher LDH, troponin I, CRP, and neutrophil levels and lower platelet and lymphocyte levels than discharged patients.[17] Conrozier et al. in successfully treated COVID-19 patients with pneumonia, biomarkers of inflammation (CRP, ferritin, fibrinogen) decreased after TCZ administration as early as day 4 after TCZ injection.[18] Lakatos et al. In their study on the prediction of mortality by laboratory parameters in COVID-19 patients treated with TCZ, they found that the levels of inflammatory markers (CRP, IL-6, ferritin) and LDH were significantly lower in survivors on day 7th after TCZ administration.[19]

Desai et al. reported that the mortality of patients with blood D-dimer concentrations >5,000 ng was higher and that they did not respond to TCZ treatment.[20] In our study, although D-dimer levels were not above 5,000 ng, the mean D-dimer levels were higher in patients who died.

The elevation in ALT levels observed within the first 24 hours post-treatment may indicate a potential hepatotoxic effect of TCZ or the impact of the underlying disease on hepatic function. The literature has documented increases in hepatic transaminases

associated with TCZ administration. A meta-analysis showed a significant reduction in AST levels after TCZ administration, whereas ALT levels remained unchanged.[15] In the long-term use of TCZ in patients with rheumatoid arthritis, an increase in AST values was found.[21] While AST levels were higher in deceased patients in 2 different studies, Lohse et al. found this elevation to be significant, while Al Qaaneh et al. found, this elevation to be not statistically significant.[22,23]

Nevertheless, research conducted in Türkiye revealed that the mortality group exhibited notably elevated levels of CRP, WBC, and neutrophils, along with decreased lymphocyte counts on the 1, 3, and 5th days following TCZ administration. This suggests that the progression of inflammatory markers post-treatment may be associated with patient mortality.[24] Kardos et al. found that TCZ treatment significantly improved absolute lymphocyte and platelet counts and decreased CRP and ferritin levels compared with pretreatment.[25] The total WBC count, absolute neutrophil count, and D-dimer levels remained unchanged. Compared to standard therapy, corticosteroid therapy alone, and corticosteroid and TCZ administration, an increase in WBCs, neutrophils, and lymphocytes was observed after steroid and TCZ treatment.[26] Sarabia De Ardanaz et al. it has been pointed out that a low platelet count is associated with mortality and that there may be an increase in platelet count on the 3rd and 6th days after TCZ administration, but this is misleading.[17] In our study, the platelet count initially increased and then decreased after TCZ administration.

Some studies have examined the role of laboratory parameters as potential markers of death on certain days after TCZ administration. According to these studies, AST, D-dimer, ferritin, WBC, PLT count, LDH, lymphocyte, and CRP levels have been identified as predictors of poor outcomes in COVID-19 patients treated with tocilizumab.[17,19,20,22,27-30] Masotti et al. They reported that PCT level was associated with mortality.[31]

LIMITATIONS

Several limitations should be considered when evaluating the findings of this research. The results must be interpreted with these constraints in mind. This study has a retrospective design and reflects a single-center experience. Therefore, the results cannot be generalized. In addition, we did not have the chance to compare TCZ administration with different treatment modalities, which is a shortcoming in terms of comparing the efficacy of TCZ.

CONCLUSION

During the COVID-19 pandemic, there has been uncertainty about which drugs will be used as treatment. Different drug modalities have been tried to find the most appropriate treatment. In this study, in which we evaluated patients who underwent TCZ, elevated PCT, advanced age, increased number of hospitalization days and presence of chronic diseases were also found to be associated with mortality. TCZ treatment was associated with a decrease in inflammatory markers such as CRP and ferritin. It is extremely important to know the effects of TCZ treatment on clinical and laboratory parameters, both in COVID-19 patients and for future TCZ application areas.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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