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Evaluation of inflammatory and biochemical markers in COVID-19 patients treated with tocilizumab alone or with the combination of tocilizumab and convalescent plasma transfusion

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Abstract

Aim: Macrophage activation syndrome (MAS) develops due to increased expression of systemic pro-inflammatory cytokines in patients with the 2019 novel coronavirus disease (COVID-19). Immune modulators have been used in anti-cytokine therapy, with the hypothesis that they can ensure cytokine inhibition and treat cytokine storm. The present study aimed to evaluate inflammatory and prognostic biomarkers in severe COVID-19 cases treated with tocilizumab (TCZ) alone or with the combination of tocilizumab and convalescent plasma transfusion (CPT).

Materials and Methods: In this retrospective study, data archives of patients with severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) and who were treated with TCZ alone or the combination of CPT and TCZ were evaluated in line with the literature. The obtained data were statistically evaluated and the alpha significance value was taken as <0.05.

Results: Post-treatment C-reactive protein (CRP) (76.19% in TCZ-administered group; 89.32% in TCZ+CPT-administered group) ($P<0.05$), troponin I (TNI) (25.64% in TCZ-administered group; 90.39% in TCZ+CPT-administered group) ($P<0.05$), and ferritin (FER) (63.63% in the TCZ-administered group; 9.09% in the TCZ+CPT-administered) ($P<0.05$) levels were decreased compared to pre-treatment stage. The mean length of hospital stay was longer in the patients treated with TCZ alone (21.55±8.89 days) than in the patients treated with the combination of TCZ and CPT (27.09±13.66 days) ($P<0.05$).

Conclusion: There was no significant difference between the groups in terms of demographic characteristics. The combination of TCZ and CPT treatment did not decrease the mortality. A significant decrease in CRP and TNI levels was observed in the patients treated with TCZ alone and with the combination of TCZ and CPT. A decrease in FER levels showed the effectiveness of the treatments.

Introduction

The novel coronavirus 2019 (COVID-19), which causes respiratory failure due to severe pneumonia, sepsis, gastrointestinal, hematological, and cardiovascular complications, is known to lead to the neurological complications [1]. Before the introduction of various vaccines [2], consisting of recombinant DNA, mRNA, live attenuated viruses, protein S subunits, virus-like particles, and virus vectors, which have been approved for immediate use, many different pharmacological or non-pharmacological agents have been used in the treatment of COVID-19. Hydroxychloroquine, which has been previously administered to treat malaria and used in the treatment of diseases such as rheumatoid arthritis, lupus, or porphyria cutanea tarda, has been used in the beginning of the pandemic [3]. Furthermore, antivirals such as remdesivir, favipiravir, danoprevir, or lopinavir combined with ritonavir have been used in many clinics for the treatment of COVID-19 also [4]. On the one hand, it has been reported that remdesivir shows some promising results, on the other hand, it has been claimed that hydroxychloroquine or favipiravir can cause harmful effects due to the various toxicities [5]. In so far as preventive vaccines and effective

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antiviral pharmaceuticals were not available at the onset of the pandemic, studies on the therapeutic effects of already existing immunomodulatory agents for COVID-19 have come to the fore [6]. It has been suggested that immune plasma, serum, or immunoglobulin concentrates can be used in the treatment of the SARS-CoV-2 virus when vaccines and/or effective antiviral drugs cannot be obtained as within the case of the Middle East respiratory syndrome coronavirus. Therefore, in many clinics, immunomodulatory molecules such as hyperimmune convalescent plasma transfusion (CPT) have also been tested, considering that the use of immune plasma that contains antibodies against COVID-19 could be effective against the infection [4, 7]. In addition, a clear and extensive response has been sought as to whether sarilumab, tocilizumab (TCZ), and Janus kinase inhibitors, with or without CPT, were effective in treating COVID -19 [7,8]. Together with the use of CPT and TCZ, also known as atlizumab, an interleukin (IL)-6 receptor antagonist immunosuppressive drug [9] used to treat rheumatoid arthritis and systemic juvenile idiopathic arthritis in children, is used in the treatment of severe COVID-19. TCZ has been used in many severe cases of COVID-19, including pregnant women, as an anti-cytokine treatment option for macrophage activation syndrome (MAS), which develops during COVID-19 infection. [10, 11]. Overexpression of the JAK/STAT signalling pathway has been reported to directly contribute to physiological and pathological outcomes in motor neuron diseases and that cytokines such as IL-6 affect autoreactive CD4+ T cells and immune responses in the brain via the JAK/STAT signalling pathway [12]. It has also been suggested that many cases of COVID-19 have a cytokine storm [13] and IL-6 has been reported to play important roles in the immune pathway, cytokine network, and acute inflammation [13, 14]. Having pointed out that overactivation of IL-6 can cause conditions such as respiratory failure, shock, and multi-organ dysfunction [15, 16]. Research, showing that changes in IL levels -6 may indicate inflammatory conditions during viral infection has taken its place in the literature [15]. Research results have revealed that TCZ and CPT treatment reduced IL-6 levels and alleviated inflammation [15-17]. Clinical findings obtained following the use of mentioned drugs have been evaluated in some studies; however, confusing results have been reported [2, 18]. No standard treatment for COVID-19 is present, and it is challenging to interpret the results of the studies including data on drugs applied for treatment [18]. The long-term effects of drugs used against COVID-19 can only be evaluated after several years of clinical experience. Therefore, the efficacy and safety of existing COVID-19 therapeutics should continue to be carefully monitored as a part of post-marketing studies [18]. As is known, C-reactive protein (CRP) and mean platelet volume (MPV) levels may vary in asymptomatic children and/or adults infected with COVID-19 [19-21]. In studies where the ratio of MPV to platelet count has been considered a very important indicator of inflammatory and infectious diseases, elevated MPV has shown to be an independent risk factor for severe pneumonia in patients with COVID-19 [20]. Moreover, high neutrophil-to-lymphocyte ratio levels on hospital admission are associated with severe COVID-19 and mortality [21-23]. In this study, the efficacy of the treatment modalities was investigated in patients with severe COVID-19 who were treated with TCZ alone or TCZ combined with CPT considering the end markers [19-27] that indicate the degree of inflammation such as CRP, D-dimer, FER, lactate dehydrogenase, TNI, white blood cells, neutrophils, lymphocytes, MPV, platelets and albumin.

Materials and Methods

Approval has been obtained from both the hospital management and the local ethics committee of the School of Medicine of Izmir Bakircay University (date: 12.01.2022 no: 467/487) to conduct this retrospective, cross-sectional study.

Inclusion criteria and data collection

47,870 patients' files who were clinically diagnosed with SARS-Cov-2 using a real-time polymerase chain reaction (RT- PCR) and were hospitalized between January 21, 2021, and January 21, 2022, were included in the study. Then, patients who were not treated with TCZ and/or CPT were excluded from the study. Patients with active TB, bacterial, fungal, or viral infections other than SARS-CoV-2 were not also included in the study. Patients with known rheumatological disease, those who received biologics or immunosuppressive therapy for any reason, and patients with a known history of haematological disease or malignancy were excluded from the study. The sample size was determined using "G*Power (3.1.9.4 version) [24, 25]. Reaching the required number of files according to the sample calculation was determined as the primary endpoint of the study. Data obtained from the remaining 61 cases were included in the study. Patients who were treated with TCZ alone and CPT combined with TCZ were divided into moderate, severe, and critical groups according to the COVID-19 treatment guidelines of the Ministry of Health of the Republic of Turkey. The severity of the disease was determined according to the criteria specified in a high-certainty study [16]. Six other patients who did not meet the inclusion criteria were excluded from the study. Medical history, complete blood counts, laboratory results, including serum biochemical tests, and treatments applied of the remaining 55 patients were retrospectively retrieved from the hospital's electronic medical records system. A standard data collection form was created. Data from patients who received TCZ (Actemra 400mg/20ml vial containing concentrated solution for IV infusion), which belongs to the Anatomic Therapeutic Chemical Classification (ATC) class of antineoplastic agents and immunomodulators/immunosuppressants/interleukin inhibitors, were recorded on this form. Next, demographic data, concurrent diseases, data on the intubated patients, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were added. The duration of hospital stays, number of deaths, biochemical lab results, steroids, and/or any other pharmaceutical preparations applied were also recorded.

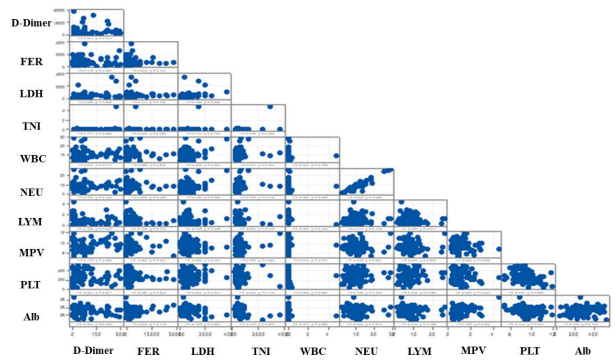

Figure 1. The correlation between categorical variables and the assessment of the severity and direction of the correlation.

Statistical analysis

Statistical analysis was performed by comparing laboratory findings at the time of hospitalization with those obtained at the end of treatment. Minitab Software (version 22) was used to evaluate the data. Estimated power was 0.80, alpha (margin of error): 0.05, effect size was 0.4. Accordingly, the sample size was determined as 50 for the chi-square test. All files (55 files) were included in the study, as the number of files remaining after assessing all the files according to the exclusion criteria. Pearson's correlation test was used to determine whether a relationship existed between categorical variables and, if so, the severity and direction of that relationship. Descriptive statistics were presented as the mean ± standard deviation (M±SD), standard error (SE), and frequency (%). The alpha significance value was accepted as < 0.05.

Results

The mean age of the patients (n=55) was 61.12 ± 12.0 years. The mean age of patients who were treated with TCZ alone was 59.74 ± 12.42 years, while it was 60.08 ± 9.41 years in those who were treated with the combination of CPT and TCZ. Of the patients, 14 (25.45%) were female and 41 (74.54%) were male. Ten of those treated with TCZ alone and four of those treated with the combination of TCZ and CPT were female. There was no concomitant disease in 31 (56.36%) of the patients. There were 9 (16.36%) patients with only type 2 diabetes mellitus (T2DM) and 9 (16.36%) patients with only arterial hypertension (HT). There were six (10.91%) patients with both a diagnosis of T2DM and HT. Prophylactic anticoagulant therapy was also applied to all patients together with empiric antivirals, dexamethasone, and different antibiotics.TCZ was administered to 43 patients (78.18). The combination of CPT and TCZ was administered to 12 patients (21.81%). The mean length of hospital stay was 21.44 ± 8.97 days in the patients treated with TCZ alone. The mean length of hospital stay was 22.41 ± 10.19 days in the patients treated with the combination of CPT and TCZ. Of the patients, 29 patients (52.72%) were intubated. 18 patients (41.86%) treated with TCZ alone were intubated while 11 patients (91.66%) treated with the combination of CPT and TCZ were intubated. Growth of Candida albicans/parapsilosis was observed in urine cultures of three patients due to the use of TCZ. 18 patients (32.72%) died. Of the patients treated with TCZ alone and who died thereafter, two had concomitant T2D (n = 2), six had concomitant HT (n = 6), one had concomitant T2D + HP (n = 1) while three patients had no concomitant disease. Six patients who were administered the combination of CPT and TCZ and subsequently died had no concurrent disease. The mean APACHE II score of the patients treated with TCZ alone and those treated with the combination of CPT and TCZ was 14.69 ± 5.37 and 14.73 ± 5, 93, respectively at the time of the intensive care unit admission. Descriptive statistics of parameters before and after treatment are presented in the tables (Table 1, Table 2). Parameters obtained from the TCZ administered group and the TCZ and CPT- administered groups were compared in terms of fold change before and after treatment (Table 3). The fold- changes were observed in two groups before and after the treatment. Chi-squared revealed that the changes in CRP, FER, and TNI values were statistically significant ($P<0.05$). The changes in other markers were not statistically significant ($P>0.05$). The duration of hospital stay was 21.55 ± 8.89 days in patients who received TCZ alone and 27.09 ± 13.66 days in patients who received CPT combined with TCZ. The results obtained were statistically significant ($P<0.05$). The Pearson's correlation analysis revealed a positive correlation between lactate dehydrogenase (LDH) and CRP (r=0.359; P=0.000); between troponin I (TNI) and CRP (r=0.277; P=0.006); between troponin and LDH (r=0.494; P=0.000); between MPV and CRP (r=0.279; P=0.006); between LDH and FER (r=0.269; P=0.006); between white blood cells (WBC) and FER (r=0.309; P=0.002); between neutrophils and FER (r=0.350; P=0.000); between neutrophils and WBC (r=0.945; P=0.000); between albumin and lymphocytes (r=0.298; P=0.003) and this was statistically significant (Figure 1). A negative correlation was observed between lymphocyte and CRP (r=-0.205; P=0.045); between albumin and CRP (r=-0.262; P=0.01); between albumin and FER (r=-0.268; P=0.007); between albumin and LDH (r=-0.320; P=0.001); between PLT and MPV (r=-0.354; P=0.000); between albumin and MPV (r=-0.233; P=0.022).

Discussion

Since the outbreak of the COVID-19 pandemic, existing pharmaceutical agents have been used or new ones have been tried to prevent or treat the disease. In this context, clinical and scientific communities have also conducted studies on the efficacity and safety of TCZ and/or TCZ combined CPT treatments [28]. In the absence of an effective treatment method, the COVID-19 continues to cause more deaths [29, 30]. Based on limited and largely observational data on the application and use of convalescent plasma in patients with COVID-19, patients benefit clinically from this therapy [31]. However, few randomized and controlled studies have been carried out before [32]. Simonovitch et al. [32] administered CPT to 228 hospitalized patients with severe COVID-19 pneumonia and placebo to 105 patients and assessed their clinical status 30 days after hospital admission. The authors stated that no

Table 1. Descriptive statistical findings obtained before treatment (n=55).

Variable	Group no	Total Count	Mean	SE Mean	StDev
CRP (mg/L)	Only TCZ	44	79.8	10.5	69.8
	TCZ+CPT	11	186.8	28.7	95.2
D-Dimer (ng/mL)	Only TCZ	44	3804	938	6224
	TCZ+CPT	11	3571	1704	5653
FER (µg/L)	Only TCZ	44	841.9	84.8	562.6
	TCZ+CPT	11	698	142	471
LDH (U/L)	Only TCZ	44	498.9	26.0	172.6
	TCZ+CPT	11	701	224	744
TNI (ng/mL)	Only TCZ	44	0.01464	0.00242	0.01608
	TCZ+CPT	11	0.482	0.432	1.433
WBC (10^9/L)	Only TCZ	44	10.107	0.535	3.548
	TCZ+CPT	11	9.65	1.96	6.49
NEU (10^9/L)	Only TCZ	44	8.305	0.471	3.122
	TCZ+CPT	11	8.88	1.94	6.44
LYM (10^9/L)	Only TCZ	44	0.8141	0.0809	0.5364
	TCZ+CPT	11	0.803	0.231	0.766
MPV (fl)	Only TCZ	44	9.184	0.144	0.953
	TCZ+CPT	11	9.609	0.237	0.785
PLT (10^3/µL)	Only TCZ	44	302.4	16.0	105.8
	TCZ+CPT	11	231.7	26.6	88.3
Alb (g/dL)	Only TCZ	44	32.520	0.631	4.182
	TCZ+CPT	11	29.88	1.32	4.37

TCZ: tocilizumab, CPT: convalescent plasma transfusion, CRP: C-reactive protein, FER: ferritin, LDH: lactate dehydrogenase, SE: standard error, StDev: standard deviation, TNI: troponin, WBC: white blood cells, NEU: neutrophils, LYM: lymphocytes MPV: mean platelet volume, PLT: platelet, and Alb: albumin symbolizes.

significant difference was observed between the CPT group and the placebo group in the distribution of clinical outcomes [32]. In an extensive multicenter study by Joyner et al., the clinical status of 20,000 adults who received 200 to 500 mL of CPT was followed up for seven days. Within 4 hours of completion of the COVID-19 convalescent plasma transfusion, 141 transfusion-related serious adverse events and 63 mortality events were reported [33]. Of the cases included in the study, 12 cases treated with TCZ alone, and six cases treated with the combination of TCZ, and CPT died. The study was retrospective; therefore, it could not be provided clear insight into whether the mortalities were related to TCZ administration or CPT transfusion. Wood et al. [34] proposed that CPT of blood donors with antibodies to SARS-Cov-2 may benefit COVID-19 patients by providing immediate passive immunity through transfusion. The authors stated that the optimal product properties, transfusion volume, and timing of administration, including neutralizing antibody titers, remained to be determined. Duan et al. suggested that a single dose of 200 mL CPT taken from a recently recovered patient with an antibody titer ratio of 1:640 is the effective dose to be administered after the onset of symptoms [35]. In the present study, the antibody titer ratio, transfusion volume, and administration time of CPT were compatible with the literature. In a study including 102 confirmed COVID-19 patients, patients were divided into three groups: those receiving CPT alone, TCZ treatment alone, or both treatment [29]. The differences between groups in the proportion of patients recovering and worsening were not significant; however, the within-group difference in the proportion of patients recovering and worsening was statistically significant in the TCZ-treated group [29]. The authors reported that there was a statistically significant difference between the groups in the mean hospital stay, but further randomized studies were needed on the use of CPT and TCZ [29]. In the present study, the mean length of hospitalization of the patients treated with the combination of CPT and TCZ (27.09 ± 13.66 days) was longer than that of the patients treated with TCZ alone (21.55 ± 8.89 days), and these results were statistically significant. ($P<0.05$). However, it may not be concluded that

Table 2. Descriptive statistical findings obtained after treatment (n=55).

Variable	Group no	Total Count	Mean	SE Mean	StDev	Minimum	Maximum
CRP (mg/L)	Only TCZ	44	19.00	6.77	41.74	0.79	245.31
	TCZ+CPT	11	19.95	5.90	11.80	2.62	27.60
D-Dimer (ng/mL)	Only TCZ	44	1944	433	2872	53	15762
	TCZ+CPT	11	5482	2170	7196	345	24500
FER (µg/L)	Only TCZ	44	742	108	694	43	3655
	TCZ+CPT	11	360.7	85.7	191.7	149.6	673.6
LDH (U/L)	Only TCZ	44	570.6	87.0	577.4	148.0	3576.0
	TCZ+CPT	11	537.8	68.9	228.4	202.0	1122.0
TNI (ng/mL)	Only TCZ	44	0.010886	0.000534	0.003545	0.010000	0.032000
	TCZ+CPT	11	0.0463	0.0319	0.0956	0.0100	0.3000
WBC (10^9/L)	Only TCZ	44	10.364	0.877	5.407	3.040	28.750
	TCZ+CPT	11	8.496	0.989	2.212	6.360	11.010
NEU (10^9/L)	Only TCZ	44	8.322	0.905	5.432	2.170	26.200
	TCZ+CPT	11	7.100	0.953	2.130	4.410	9.540
LYM (10^9/L)	Only TCZ	44	1.274	0.137	0.854	0.290	4.410
	TCZ+CPT	11	0.904	0.227	0.509	0.360	1.590
MPV (fl)	Only TCZ	44	9.508	0.154	0.950	7.900	11.900
	TCZ+CPT	11	9.600	0.319	0.638	9.100	10.500
PLT (10^3/µL)	Only TCZ	44	266.6	17.5	116.0	50.0	528.0
	TCZ+CPT	11	222.0	28.1	93.3	38.0	382.0
Alb (g/dL)	Only TCZ	44	32.202	0.866	5.682	19.000	49.200
	TCZ+CPT	11	29.21	1.65	5.46	21.80	36.00

TCZ: tocilizumab, CPT: convalescent plasma transfusion, CRP: C-reactive protein, FER: ferritin, LDH: lactate dehydrogenase, SE: standard error, StDev: standard deviation, TNI: troponin, WBC: white blood cells, NEU: neutrophils, LYM: lymphocytes MPV: mean platelet volume, PLT: platelet, and Alb: albumin symbolizes.

this was related to the administration of CPT only in a retrospective study considering the various accompanying risk factors and the patients' clinical status. There is an important relationship between age and COVID-19. IL-6 levels are markedly higher in COVID-19 patients over the age of 70 years, and those with a body temperature above 37.3℃ [16]. Furthermore, the severity of the disease is reported to be associated with a decrease in SpO2, which might be related to an increase in the level of IL-6 [16]. The course of the disease is much more severe in patients with concomitant diseases such as HT and T2DM [16]. Antwi-Amoabeng et al. reported that the average standard deviation levels of CRP were significantly decreased after treatment 24.6 mg/L compared to baseline 140.4 mg/L [36]. In this study, the CRP value also decreased after treatment compared to before treatment in both patients who were treated with TCZ alone and with CPT combined with TCZ ($P<0.05$). The normal MPV level ranges between 7.5 fL and 11.5 fL. Changes in MPV levels have been considered as a diagnostic and prognostic indicator in diseases such as sepsis, infective endocarditis, pneumonia, brucellosis, cellulitis, and acute pyelonephritis [19]. Platelets with increased MPV levels become more metabolically active and secrete more adhesion and aggregation molecules such as thromboxane A2, serotonin, platelet factor-4, and β-thromboglobulin. Therefore, the increase in MPV shows the risk of cardiovascular disease [38]. This situation may sometimes indicate macrothrombocytopaenia, and sometimes it is attributed to the larger size of the new and young platelets produced in the bone marrow and released into the circulation. In this study, the MPV levels of the patients were within the normal range before and after treatment. The MPV levels of the patients treated with TCZ alone increased by 0.352 fL post-treatment stage compared to the pre-treatment stage, and the MPV levels of those treated with the combination of TCZ and CPT decreased by 0.009 fL post-treatment stage. This was not statistically significant ($P=0.498$). Kevadiya et al. [38] reported that some studies have provided good outcomes in patients with COVID-19 who were treated with TCZ; however, further research is needed to accurately assess the clinical impact of TCZ on COVID-19. The authors stated that dexamethasone is a strong anti-inflammatory corticosteroid, and its nano formulation is

Table 3. Post-treatment findings compared to those of pre-treatment (n=55).

Variable	Ratio	Only TCZ	TCZ Combined CPT	P value
CRP (mg/L)	Increase	13	7	0.036
	Decrease	31	4	
D-Dimer (ng/mL)	Increase	37	8	0.382
	Decrease	7	3	
FER (µg/L)	Increase	16	10	0.001
	Decrease	28	1	
LDH (U/L)	Increase	17	7	0.086
	Decrease	31	4	
TNI (ng/mL)	Increase	3	4	0.009
	Decrease	41	7	
WBC (10^9/L)	Increase	16	7	0.101
	Decrease	28	4	
NEU (10^9/L)	Increase	14	3	0.770
	Decrease	30	8	
LYM (10^9/L)	Increase	34	6	0.130
	Decrease	10	5	
MPV (fl)	Increase	25	5	0.498
	Decrease	19	6	
PLT (10^3/µL)	Increase	17	3	0.483
	Decrease	27	8	
Alb (g/dL)	Increase	18	4	0.783
	Decrease	26	7	

TCZ: tocilizumab, CPT: convalescent plasma transfusion, CRP: C-reactive protein, FER: ferritin, LDH: lactate dehydrogenase, SE: standard error, StDev: standard deviation, TNI: troponin, WBC: white blood cells, NEU: neutrophils, LYM: lymphocytes MPV: mean platelet volume, PLT: platelet, and Alb: albumin symbolizes.

well known for the development of macrophages depot following intravenous and inhalation administration [38]. In that study, the use of dexamethasone was reported to decrease 28-day mortality among patients receiving either invasive mechanical ventilation or oxygen alone, but not in those without respiratory support [38]. In the present study, dexamethasone 6 mg/day was administered. However, the use of dexamethasone could not be associated with mortality and/or morbidity. In a retrospective study including 61 patients with covıd-19 hospitalized and followed up in the intensive care unit with COVID-19, TCZ was administered at a dose of 8 mg/kg [37]. The patients with a mean age of 51 years had an admission APACHE 4 score of 53 and more than one comorbidity (62.3%). 29 patients (47.5%) were ventilated, and 32 patients (52.5%) were given oxygen therapy. No serious adverse effects due to TCZ therapy were observed. However, 12 patients experienced nosocomially acquired infections. The duration of intensive care unit stay was 13 days, and mortality on day-14 was 24.6%. The overall mortality on day-30 was 31.1%. TCZ did not have any effect on the mortality of patients with severe COVID-19 [39]. Salama et al. [40] compared the clinical outcomes of a group of patients, 249 of whom were administered TCZ alone, and 128 of whom were administered a placebo. The authors evaluated the median laboratory values and obtained the following findings in the TCZ-treated group and placebo-treated group respectively; TCZ-treated group: CRP level — mg/liter: 124.50; d-Dimer level — µg/ml: 1.60; FER level pmol/liter: 1404.34; placebo-treated group: CRP:143.40; d-Dimer level:1.21; FER level: 1353.14 [40]. Salvarani et al. [41] reported that no benefit was observed on disease progression compared with standard care in patients with COVID-19 pneumonia and Pao2/Fio2 ratio between 200- and 300-mm Hg who were administered tocilizumab. Yakar et al. [42] reported that up to three doses of TCZ can be applied intravenously or subcutaneously at 400 mg/dose in the cytokine storm and that as the patients' needs for oxygen and mechanical ventilation decrease, so does mortality. They emphasized that TCZ may be useful in the treatment of COVID-19 cases, but that more randomized, large-sample, controlled studies are needed to elucidate the clinical efficacy and safety of TCZ [42]. The mean APACHE II score was 14.69 ± 5.37 in the patients treated with TCZ alone at the admission to the intensive care unit, and that of the patients treated with the combination of TCZ and CPT was 14.73±5.93. In this study, no statistically significant difference was observed between the TCZ-treated group and the CPT combined with TCZ-treated group in terms of all socio-demographic characteristics, mortality, oxygen requirement/intubation. Furthermore, laboratory parameters determinant in COVID-19 infection did not differ significantly between the treatment groups, except for CRP, troponin, and FER values. This study has some limitations. The study has a retrospective design and the results obtained from a small number of cases from the same race were evaluated. This is the first limitation of the study. Some studies [16] have reported that the use of CPT or TCZ alone reduces IL-6 levels. In this study, there were no data on the IL-6 levels of the patients treated with TCZ alone or treated with the combination of TZC and CPT. This is the second limitation of the study.

Conclusion

Significant decreases in CRP, troponin, and FER levels, which are prognostic factors, show the effectiveness of the treatments in cases treated with TCZ alone or the combination with CPT and TCZ. Effective treatment modalities may provide hope for the treatment of severe cases of COVID-19 since many people have died due to COVID-19. However, multicenter, prospective studies with a larger sample size are needed to further elucidate the results obtained in the present study.

Ethics approval

Approval has been obtained from both the hospital management and the local ethics committee of the School of

Medicine of Izmir Bakircay University (date: 12.01.2022 no: 467/487) to conduct this retrospective study.

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