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Original Research Article

Effect of tocilizumab treatment for COVID-19-induced acute respiratory distress syndrome (ARDS) on renal function of patients

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Abstract

Purpose: *To study the effect of tocilizumab (TCZ) on the renal function of patients with severe coronavirus disease 2019 (COVID-19) induced acute respiratory distress syndrome (ARDS).*
Methods: *The renal functions of patients with severe COVID-19 were determined before and after TCZ administration using the Cockcroft-Gault method, and the results were compared. The patients who were without kidney failure before COVID-19 infection, were given TCZ for treatment of ARDS.*
Results: *Ninety-two patients (mean age = 62.79 ± 12.43 y) comprised of 60 men (65.2 %) and 32 women (34.8 %) were included in the study. Mean values and ranges of glomerular filtration rate (GFR) were 92 (59 - 124.25) before TCZ, 102 (65.25 - 121.75) 5 days after TCZ, and 85.5 (64.25 - 134.25) mL/min/1.73 m^2 at 10 days after TCZ (p = 0.670). Similar to GFR, there were no significant differences in the values of blood urea nitrogen (BUN) or creatinine before and after treatment. Moreover, TCZ had no effect on the GFR of 26 patients with stage 3 or above kidney failure associated with COVID-19 (p = 0.540). However, moderate TCZ-related side-effects were observed in 11 patients (11.9 %), while mortality due to COVID-19 occurred in 32 patients (34.8 %).*
Conclusion: *The TCZ used in the treatment of COVID-19-related ARDS did not exert any ameliorating or exacerbating effect on the renal function of patients.*

Keywords: *Coronavirus disease 2019, Severe acute respiratory syndrome coronavirus 2, Tocilizumab, Renal function*

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INTRODUCTION

The RNA virus coronavirus is widely present in nature. The coronavirus family has caused several global epidemics in previous years, and a new specie resulted in a further outbreak in late December 2019, which spread rapidly across the world due to its uniquely high transmissibility and infectivity. The World Health Organization (WHO) declared this outbreak as a pandemic and named the disease coronavirus disease 2019 (COVID-19). The International Committee on Taxonomy of Viruses gave this novel coronavirus the name: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The clinical manifestations of COVID-19 range from completely asymptomatic presentation, to mild acute respiratory disease, severe pneumonia,

and even acute respiratory distress syndrome (ARDS) [2]. Approximately 14 % of COVID-19 patients develop severe symptoms; 5 % develop critical disease manifesting in respiratory failure, shock and/or multiple-organ failure, while most deaths are attributable to severe COVID-19 [3,4].

Severe COVID-19 disease manifests in the form of immune system dysregulation, which is thought to be triggered by various proinflammatory cytokines and chemokines. Investigation of the immune systems of patients with COVID-19 has revealed that activation of abnormal pathogenic T-cells results in the production of numerous cytokines, particularly interleukin 6 (IL-6), and an inflammatory cytokine storm. High plasma levels of IL-6 and other cytokines are seen in COVID-19 patients. IL-6 plays a major role in this inflammatory storm which may lead to pulmonary fibrosis and organ failure due to impairment of gaseous exchange across the alveolar capillary membrane [5,6].

Tocilizumab (TCZ) is a recombinant humanized, anti-human monoclonal antibody, and a member of the immunoglobulin G1k subclass which acts against soluble and membrane-bound IL-6 receptors [7]. Therefore, TCZ has been used as a therapeutic regimen for COVID-19, and several studies have evaluated its efficacy in the treatment of severe cases [1,8,9].

Studies have shown that SARS-CoV-2 binds to the surface of the host cell through angiotensin-converting enzyme-2 (ACE-2) receptor, thereby enabling the virus to enter the cell and replicate [10]. The ACE-2 receptors are expressed in tissues such as the heart, kidneys, endothelium, and intestine, and particularly in pulmonary tissues [1]. The SARS-CoV-2 incubates in kidney tissue, and the cytokine release syndrome which develops in severe disease impairs renal functions. Multi-organ failure develops with cytokine release syndrome, and acute kidney injury develops in severe cases of COVID-19 [11]. Therefore, it may be hypothesized that TCZ can affect renal functions by reducing concentrations of IL-6 and other inflammatory cytokines. As far as it is known, there have been no previous studies on this subject. The present research investigated the effect of TCZ on renal functions when used in the treatment of ARDS due to severe COVID-19.

METHODS

Following the receipt of ethical approval, data from patients on TCZ due to severe COVID-19 between April 2020 and March 2021 were evaluated retrospectively in the Department of Anesthesiology and Reanimation, Samsun Training and Research Hospital, Samsun, Turkey. This study was approved by the Medical Ethics Committee of the University of Health Sciences (ref no. GOKA/2021/6/10 dated 24.03.2021), and followed international guidelines for human studies. Data analysis was performed in April and May 2021.

Patient selection and evaluation

The patients included in this study were those hospitalized in our intensive care unit who developed ARDS due to severe COVID-19, after being diagnosed with COVID-19 using real-time PCR. Standard treatments were administered in line with the Turkish Ministry of Health Guideline for the diagnosis and treatment protocol for COVID-19. The treatments comprised favipiravir, methylprednisolone, low molecular weight heparin, reliever drugs for other symptoms, and oxygen therapy [12]. Under this protocol, TCZ therapy is usually recommended for patients whose conditions worsen, despite current treatment. Severe COVID-19 was diagnosed in any of the following conditions: (1) respiratory rate ≥ 30 breaths/min, (2) SpO_2 ≤ 90 % while breathing room air, or (3) PaO_2/FiO_2 ≤ 300 mmHg, or widespread bilateral pneumonia at tomography. Critical cases were defined as those meeting any of the following conditions: (1) respiratory failure requiring mechanical ventilation, and (2) shock, in addition to (3) other organ failures requiring admission to the intensive care unit. Patients with stage 2 or higher renal failure prior to COVID-19, or with exitus occurring within 10 days after administration of TCZ, were excluded from the study.

Tocilizumab therapy

The immunotherapy strategy concerning TCZ was adopted under the Turkish Ministry of Health Diagnosis and Treatment Protocol for COVID-19 [12]. The first dose was set at 4 – 8 mg/kg (the recommended dose is 400 mg, diluted to 100 mL with 0.9 % normal saline, and infusion time exceeding 1 h). For patients exhibiting poor initial response, a second application involving the same dose, was performed after 12 h. The number of administrations was restricted to two, and the total maximum single dose did not exceed 800 mg. Tocilizumab was not administered under the following conditions: pregnancy, liver injury or failure, as indicated by serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level > 5 times the upper normal limit, neutropenia < 0.5×10^9/L, platelets

<50 × 10^9/L, immunosuppressive therapy or diagnosis of immunity-related diseases or cancer, allergy to TCZ or any excipients, presence of active hepatitis and tuberculosis associated with specific bacterial and fungal infections, and history of organ transplantation.

Calculation of glomerular filtration rate

Glomerular filtration rate (GFR) was calculated before, and on the 5th and 10th days after TCZ, using the Cockcroft-Gault method [13].

Data collection

Clinical data were retrospectively analyzed by investigating data archived in the Samsun Training and Research Hospital. These data were on gender, age, co-existing diseases, and clinical symptoms. Hemoglobin, % neutrophil, % lymphocytes, platelets, D-dimer, ferritin, C-reactive protein (CRP), procalcitonin, prothrombin time, ALT, AST, blood urea nitrogen (BUN), creatinine, and GFR values were recorded. This study focused on changes in renal function before and after treatment with TCZ.

Statistical analysis

Data analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 25 software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was applied to determine normality of measured data. Descriptive data are expressed as mean ± standard deviation for numerical variables, and as median (interquartile range (IQR): 25th percentile-75th percentile) for non-normally distributed continuous data. One-way repeated ANOVA was applied to evaluate statistically significant difference in normally distributed numerical variables. Values of $p < 0.05$ were regarded as indicative of statistically significant differences. Friedman's test was applied to determine the presence significant differences amongst non-normally distributed numerical variables. Wilcoxon's test and the Bonferroni corrected test were used to identify the sources of significance in variables found to be significant.

RESULTS

Ninety-two patients, 60 men (65.2 %) and 32 women (34.8 %), with a mean age of 62.79 ± 12.43 years, were included in this study. The patients were diagnosed using real-time RT-PCR, and they exhibited signs of severe COVID-19, as was evident in computed tomography (CT). Twenty-two patients (23.9 %) had no chronic medical disease, while the most frequent disease was hypertension in 25 patients (27.2 %). The demographic and clinic characteristics of the patients are presented in Table 1.

Post-TCZ treatment, there were significant differences in values of neutrophils, lymphocytes, platelets, D-dimer, ferritin, CRP, procalcitonin, prothrombin time, and ALT, when compared to pre-treatment levels ($p < 0.005$). However, no significant differences were observed between pre- and post-treatment values of hemoglobin and AST ($p > 0.05$). These results are shown in Table 2.

Evaluation of renal function before TCZ administration, 5 days after TCZ, and 10 days after TCZ revealed BUN values and ranges of 54.5 (39.25 - 76.75), 51.5 (38 - 75.25), and 51 (35 - 74.75) mg/dL, respectively ($p = 0.367$). The corresponding creatinine levels at these time points, and their ranges were 0.9 (0.7 - 1.17), 0.8 (0.7 - 1.17), and 0.9 (0.7 - 1.2) mg/dL, respectively ($p = 0.166$), while the values and ranges for GFR were 92 (59 - 124.25), 102 (65.25 - 121.75), and 85.5 (64.25 - 134.25) mL/min/1.73 m^2, respectively ($p = 0.670$).

Table 1: Patients' demographic and clinical characteristics

Characteristic	Patients (n = 92)
Age (years, mean ± SD)	62.79±12.43
Gender (n, %)	
Male	60 (65.2 %)
Female	32 (34.8 %)
Chronic medical illness (n, %)	
Hypertension	25 (27.2 %)
Diabetes	13 (14.1 %)
Chronic obstructive pulmonary disease	10 (10.9 %)
Coronary heart disease	8 (8.7 %)
Coronary heart disease + hypertension	6 (6.5 %)
Coronary heart disease + diabetes	4 (4.3 %)
Hepatitis	2 (2.2 %)
Other	2 (2.2 %)
None	22 (23.9 %)
Oxygen therapy (n, %)	
Nasal cannula	41 (44.5 %)
Invasive ventilation	51 (55.5 %)
Dialysis	7 (7.6 %)
Hospitalization (days, mean ± SD)	22.33±11.04
≤14	22 (23.9 %)
15–28	54 (58.7 %)
≥29	16 (17.4 %)
Exitus (n, %)	32 (34.8 %)

Table 2: Laboratory tests of before and after TCZ

Variable* (Normal laboratory range)	Before TCZ (n = 92)	Day 5 (n = 92)	Day 10 (n = 92)	*p*
Hemoglobin (g/dL), (11-15)	12.62±1.68	12.81±1.69	12.73±1.73	0.376
NP (%), (40–75)	87.44 (80.32-91.76)	85.46 (73.48-89.95)	76.25 (60.09-88.95)	<0.001
LP (%), (20–40)	6.69 (4.09-12.4)	9.87 (5.02-17.27)	12.94 (4.76-23.02)	<0.001
Platelet count ($\times10^9$/L), (125-350)	234 (183.5-299.7)	263 (181.25-343.25)	206 (140.5-282.5)	0.008
D-dimer (mg/L), (0–0.55)	1.26 (0.57-4.53)	2.18 (0.93-6.06)	1.8 (0.9-5.38)	<0.001
Ferritin (µg/L), (13–150)	721.5 (464.25-1265)	650.5 (320.5-984.5)	478 (246.2-771.2)	<0.001
C-reactive protein (mg/L), (0–5)	124.78 (69.72-163.52)	13.72 (3.24-42.29)	4.53 (2.42-14.97)	<0.001
Procalcitonin (ng/mL), (0–0.5)	0.14 (0.08-0.33)	0.07 (0.04-0.13)	0.04 (0.02-0.14)	<0.001
Prothrombin time, (0.8–1.2)	12.1 (11.4-13)	11.95 (11.1-12.8)	11.7 (11.12-12.77)	0.048
ALT (IU/L), (0-50)	28.5 (19-53.5)	49 (31-81.25)	44.5 (23.25-76)	<0.001
AST (IU/L), (15–40)	37.55 (27-56.75)	40 (27.25-62.5)	38 (26-51)	0.218
BUN (mg/dL), (17–43)	54.5 (39.25-76.75)	51.5 (38-75.25)	51 (35-74.75)	0.367
Creatinine (mg/dL), (0.51–0.95)	0.9 (0.7-1.17)	0.8 (0.7-1.17)	0.9 (0.7-1.2)	0.166
GFR (mL/min/1.73m^2)	92 (59-124.25)	102 (65.25-121.75)	85.5 (64.25-134.25)	0.670

*All data are expressed as median and interquartile range (IQR, 25th - 75th percentile), except for hemoglobin (mean ± SD). ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GFR = glomerular filtration rate; NP = neutrophil percentage; LP = lymphocyte percentage; TCZ = tocilizumab

Table 3: Results of renal function test before and after tocilizumab therapy in patients who developed renal failure after COVID-19

Variable* (Normal laboratory range)	Before TCZ (n = 26)	Day 5 (n = 26)	Day 10 (n = 26)	p
BUN (mg/dL), (17–43)	78 (55.75-91.25)	94 (66-121.5)	78.5 (57.75-154.5)	0.129
Creatinine (mg/dL), (0.51-0.95)	1.3 (1.1-1.7)	1.3 (1-1.52)	1.2 (1-1.62)	0.505
GFR (mL/min/1.73 m^2)	55 (41.75-58)	53.5 (35.75-64.5)	51 (36.25-66.5)	0.540

*All data are expressed as median and interquartile range (IQR, 25th - 75th percentile). BUN = blood urea nitrogen; GFR = glomerular filtration rate

Pre- and post-TCZ treatment renal functions of a subgroup of patients with stage 3 or higher renal failure associated with COVID-19 were compared. Sixteen (61.5 %) of the patients in this subgroup were men, and their BUN values and ranges at pre-TCZ, 5th day post-TCZ and 10th day post-TCZ were 78 (55.75 - 91.25), 94 (66 - 121.5), and 78.5 (57.75 - 154.5) mg/dL, respectively (p = 0.129) (Table 3). The corresponding values for GFR were 55 (41.75 - 58), 53.5 (35.75 - 64.5), and 51 (36.25 - 66.5) mL/min/1.73 m^2 (p = 0.54). Acute kidney injury requiring dialysis was observed in seven (7.6 %) of the patients in this group.

No severe adverse events were reported by any patient in this study. Non-severe adverse events were observed in 11 patients (11.9 %). These events comprised elevated hepatic transaminase (> 5 times above the upper threshold) in 8 patients (8.7 %), and neutropenia in 3 patients (3.2 %). No emerging bacterial, fungal, or viral infections occurred. The mean length of hospital stay was 22.33 ± 11.04 days, while mortality due to COVID-19 occurred in 32 patients (34.8 %).

DISCUSSION

Mild symptoms of COVID-19 include fever, cough, and shortness of breath. However, symptoms worsen rapidly in a substantial proportion of cases, manifesting in the form of tight chest, shortness of breath, and even respiratory failure. ARDS is the most-feared complication of COVID-19. Cases of ARDS generally require oxygen therapy and even assisted ventilation in the intensive care unit. Indeed, ARDS is one of the most severe complications of COVID-19, and it results in high mortality rate. One meta-analysis reported that 15.7 % of COVID-19 cases resulted in development of ARDS [14]. In previous randomized controlled studies, mortality of up to 20 % was reported in COVID-19 patients who developed ARDS [15-17]. Therefore, researchers began seeking alternative treatments for severe COVID-19, leading to the employment of TCZ in

the treatment of cases complicated with ARDS [8,9,15-17].

The present study focused on the effect of TCZ therapy on renal functions of patients with ARDS due to severe COVID-19. Multi-organ failure due to cytokine release syndrome develops in COVID-19. Acute kidney injury develops when the kidneys are affected, and the prevalence of COVID-19-related acute kidney injury is quite high [18-20]. In such a situation, TCZ, an IL-6 inhibitor, may exert a hepato-protective effect. The present study which was based on this hepatoprotection hypothesis, investigated the effects of TCZ on renal functions of patients with no known kidney failure prior to COVID-19, and compared their pre- and post-TCZ therapy levels of creatinine, BUN and GFR. The results showed that TCZ produced no ameliorating or deleterious effect on renal function.

At the same time, this study investigated the effect of TCZ therapy on renal functions in a subgroup consisting of patients without renal failure prior to COVID-19, but who had developed stage 3 or higher renal failure (GFR 60 mL/min/1.73 m^2 or less) due to COVID-19. The results showed that TCZ had no effect on renal function in this subgroup. These findings indicate that TCZ had no effect on renal function of patients who developed COVID-19-linked renal failure.

Previous studies have reported 8 - 49.8 % incidence of renal failure in association with COVID-19 [18-20]. In the present study, advanced (stage 3 or higher) kidney failure associated with COVID-19 was seen in 26 patients (28.26 %), 7 (7.6 %) of whom underwent temporary dialysis. The degree of COVID-19-related acute renal injury in the present study is similar to that in previous studies.

Decreases in lymphocytes serve as significant indicators in diagnosis and severity of COVID-19 [21]. The pre-TCZ lymphocyte level in the present study was 6.69 %. Significant improvement commenced with TCZ therapy, with values rising to 9.87 (5.02 - 17.27) 5 days, and to 12.94 (4.76 - 23.02) 10 days after TCZ administration ($p < 0.001$). These values are consistent with those reported by Xu *et al* [8]. Mild or moderate hepatic transaminase elevation has been reported following TCZ therapy [7]. In the present study, mean ALT and AST values increased 5 days after treatment, but thereafter decreased. On the 10^{th} day, ALT and AST values were still high, when compared to pre-TCZ values, but were lower than the corresponding values on the 5^{th} day.

Since the present study focused on the effect of TCZ on renal function, clinical data such as body temperature, heart rate, and oxygen saturation, pulmonary CT, and Sequential Organ Failure Assessment scores were not considered.

Study limitations

There are several limitations in this study. The first limitation concerns its retrospective nature. Secondly, for technical reasons, patients' IL-6 levels could not be investigated. Moreover, the number of patients was low. Finally, since the research was a single center observational study, the possibility of significant bias cannot be completely ruled out. However, despite these limitations, this research is valuable, being the first study on this subject. Further prospective, multi-center studies involving other laboratories are needed to confirm the present findings.

CONCLUSION

The use of TCZ therapy for COVID-19-related ARDS patients has no effect on renal function. However, TCZ does not qualify as an alternative therapeutic method for COVID-19 associated acute kidney injury.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this manuscript, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Sevda Akdeniz conceived the study and participated in the acquisition of data, literature search, and drafting of the manuscript. Ahmet Sen performed the analysis of data, literature search, and drafting of the manuscript. Both authors read the manuscript and approved the final version of the manuscript for publication.

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