ORIGINAL RESEARCH

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Evaluation of the Efficacy of Tocilizumab in Cytokine Release Syndrome in Patients with COVID-19 (SARS-CoV-2) Pneumonia Followed in the Intensive Care Unit

Yoğun Bakım Ünitesinde Takip Edilen COVID-19 (SARS-CoV-2) Pnömonili Hastalarda Sitokin Release Sendromunda Tociluzimab Kullanımının Etkinliğinin Değerlendirilmesi

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Abstract

Objective: The global severe acute respiratory syndrome-coronavirus-2 pandemic, which emerged in 2019, has resulted in severe complications in approximately 5% of infected individuals, leading to mortality due to respiratory failure, shock, or multiple organ dysfunction. Mortality is primarily attributed to excessive hyperinflammatory response-induced alveolar damage, which subsequently progresses to severe acute respiratory distress syndrome. Tocilizumab, a monoclonal antibody targeting the interleukin-6 receptor, has been utilized in the management of cytokine release syndrome (CRS) and is hypothesized to mitigate alveolar hyperinflammation, thereby reducing disease severity.

Method: This retrospective study analyzed 76 patients diagnosed with coronavirus disease-2019 (COVID-19) pneumonia and developing CRS in the intensive care unit. The patients were divided into two groups: 39 patients who received tocilizumab (Group T) and 37 patients who did not receive tocilizumab (Group C). The primary objective of the study was to assess the effect of tocilizumab on the PaO_2/FiO_2 ratio in critically ill COVID-19 pneumonia patients requiring mechanical ventilatory support. The secondary objective was to evaluate changes in inflammatory and

Öz

Amaç: 2019 yılında tüm dünyada ortaya çıkan şiddetli akut solunum yolu sendromu-koronavirüs-2'ye bağlı pandemi sonrası enfekte bireylerin %5'inde solunum yetmezliği, şok veya multiorgan yetmezliğine bağlı mortalite geliştiği bilinmektedir. Mortalite, çoğunlukla aşırı hiperenflamatuvar yanıta bağlı alveoler hasar ve ardından gelişen ciddi akut solunum sıkıntısı sendromu tablosuna bağlı olarak gelişmektedir. Tocilizumab sitokin salınım sendromunda (CRS) kullanılan bir monoklonal antikordur. Alveoler hiperenflamasyonu azaltarak hastalığın şiddetini azalttığı düşünülmektedir.

Yöntem: Bu çalışmada, yoğun bakım ünitesinde 18-80 yaş arası koronavirüs hastalığı-2019 (COVID-19) pnömonisi tanısı almış hastalar retrospektif olarak incelendi. CRS gelişen toplam 76 hasta çalışmaya dahil edildi; 39 hasta tocilizumab uygulanan Grup T, 37 hasta ise tocilizumabın temin edilemediği dönemin kayıtlarından elde edilen kontrol grubu (Grup C) olmak üzere iki gruba ayrıldı. Bu çalışmanın primer amacı yoğun bakımda mekanik ventilatör desteği altında takip edilen COVID-19 pnömonili, CRS gelişen bireylerde interlökin-6 reseptör blokörü tocilizumabın kullanımının PaO_2/FiO_2 oranı üzerine olan etkisini

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Abstract

coagulation biomarkers between the groups at different time points during intensive care follow-up.

Results: Patients who received tocilizumab demonstrated a significant improvement in the PaO_2/FiO_2 ratio on the seventh day of follow-up. In addition, C-reactive protein (CRP) levels showed a statistically significant reduction on the third and seventh days, while fibrinogen levels significantly decreased on the seventh day. A notable increase in lymphocyte count was also observed on the seventh day.

Conclusion: In critically ill COVID-19 pneumonia patients requiring mechanical ventilatory support, tocilizumab administration was found to be beneficial in attenuating alveolar damage and oxygenation impairment associated with CRS. The significant improvement in the PaO_2/FiO_2 ratio, along with favorable changes in inflammatory and coagulation biomarkers such as CRP, fibrinogen, and lymphocyte count, suggests that tocilizumab may play a therapeutic role in the management of severe COVID-19 cases.

Keywords: COVID-19 pneumonia, cytokine release syndrome, cytokine storm, SARS-CoV-2, tocilizumab

Öz

değerlendirmektir. Sekonder amacı ise, yoğun bakım takibinin 1., 3., 7., 14. ve 28. günlerinde gruplar arasında CRP, fibrinojen ve lenfosit sayısı biyobelirteçlerini karşılaştırmaktır.

Bulgular: Tocilizumab uygulanan hastalarda, 7. günde PaO_2/FiO_2 oranında anlamlı iyileşme; 3. ve 7. günlerde CRP değerlerinde anlamlı düşüş, 7. günde fibrinojen değerlerinde anlamlı düşüş olduğu ve 7. günde lenfosit sayısında anlamlı yükselme olduğu görüldü.

Sonuç: Yoğun bakımda mekanik ventilatör desteği gerektiren şiddetli COVID-19 pnömonili hastalarda, tocilizumab uygulamasının CRS'nin yol açtığı alveoler hasar ve oksijenasyon bozukluğunu düzeltmede yararlı olduğu görülmüştür. PaO_2/FiO_2 oranında anlamlı iyileşmeyle beraber; CRP, fibrinojen, lenfosit sayısı gibi mortalite ile ilişkili biyobelirteçlerin de olumlu yönde değiştiği görüldü.

Anahtar kelimeler: COVID-19 pnömoni, SARS-CoV-2, sitokin fırtınası, sitokin salınım sendromu, tocilizumab

Introduction

The pandemic caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which emerged in December 2019, has led to serious health problems worldwide. Although most individuals infected with SARS-CoV-2 exhibit mild symptoms, approximately 14% of cases progress to severe disease, while 5% develop respiratory failure, shock, or multiorgan failure-related mortality (1).

Difficulties in controlling viral infections and the emergence of mutant viruses continue to pose significant health challenges for millions of people. In most cases, the host immune system effectively activates both innate and adaptive responses, leading to the release of interferons (IFN-α, IFN-β, IFN-γ) and other cytokines, thereby facilitating viral clearance and tissue repair to control the infection (2,3). However, in severe coronavirus disease-2019 (COVID-19) cases, an abnormal host immune response leads to a cytokine storm characterized by the induction of interleukin (IL)-1β, IL-2, IL-6, tumor necrosis factor-α, monocyte chemoattractant protein 1, as well as CD4+ and CD8+ T-cells, and natural killer T-cells (4-7).

In severe COVID-19 patients, cytokine release syndrome (CRS), also referred to as COVID-19 related cytokine storm, is characterized by an excessive and dysregulated immune response. According to modified Temple criteria, CRS can be identified by worsening respiratory symptoms along with typical bilateral lung infiltrates on imaging, elevated inflammatory markers such as C-reactive protein (CRP >4.6 mg/dL) and ferritin (> 250 ng/mL), and a marked increase in IL-6 ≥10 times the upper limit of normal, confirmed on two separate occasions. Furthermore, alternative laboratory-based diagnostic criteria for CRS include ferritin levels exceeding 2000 ng/mL in combination with at least one additional elevated inflammatory marker (e.g., CRP, IL-6, D-dimer), or the presence of abnormalities in at least four inflammatory markers. These combined clinical and laboratory findings support the diagnosis of CRS associated with severe COVID-19 infection (8-10).

The release of IL-6 and IL-1 accelerates the recruitment of neutrophils and cytotoxic-cells to affected tissues, while the production of reactive oxygen species and leukotrienes contributes to acute lung injury and multiple organ damage in severe cases (2). Elevated IL-6 serum levels have been associated with COVID-19 disease severity, SARS-CoV-2 RNA levels, and poorer prognosis (11). In this context, early detection of cytokine storm and identification of immune dysregulation before progression to acute respiratory distress syndrome (ARDS) are crucial in reducing the need for mechanical ventilation. Experience with macrophage activation syndrome and CRS suggests that early interventions in the course of the disease may prevent irreversible tissue damage (12).

Excessive IL-6 production during infections and tissue injury activates the complement and coagulation systems, leading to vascular leakage (13). Additionally, IL-6 activation is considered a key factor in the progression of COVID-19 pneumonia to ARDS and hyperinflammation

(14). Pathological analyses of patients who succumbed to SARS-CoV-2 infection have revealed elevated levels of proinflammatory cytokines (2,7). This phenomenon is believed to contribute to mortality in severe COVID-19 cases by impairing gas exchange due to increased alveolar exudates. In COVID-19 pneumonia, CRS-induced hyperinflammation has been associated with poor prognosis and mortality, as evidenced by elevated IL-6, CRP, ferritin, fibrinogen, D-dimer, lymphopenia, LDH, and renal/liver dysfunction (15,16).

Given the central role of IL-6 in the cytokine storm associated with COVID-19, the humanized monoclonal antibody tocilizumab, which targets the IL-6 receptor, has been utilized to treat patients developing cytokine storm. If left untreated, cytokine storm can progress to respiratory failure, cardiovascular collapse, multiple organ dysfunction, and death.

The aim of this study is to evaluate the effect of tocilizumab on the PaO_2/FiO_2 ratio in patients with COVID-19 pneumonia receiving mechanical ventilatory support in the intensive care unit (ICU), thereby contributing to the advancement of treatment strategies for COVID-19. Additionally, the study aims to assess the clinical and laboratory parameters as well as the impact of IL-6 receptor blockade with tocilizumab on mortality in patients who develop CRS.

Materials and Methods

This study aimed to retrospectively evaluate patients aged 18-80 years who were followed in the ICU between March 23, 2020, and June 1, 2020. The patients had either a confirmed SARS-CoV-2 infection detected by real-time-polymerase chain reaction (RT-PCR) or were PCR-negative but diagnosed with COVID-19 pneumonia based on radiological and clinical findings. They subsequently developed CRS. During this period, 37 patients who developed a cytokine storm but could not receive cilizumab due to its unavailability were compared with 39 patients who received tocilizumab after its procurement by the hospital.

This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital on June 2, 2020 (approval no: 95). Written informed consent was obtained from all patients or their legal representatives before the administration of tocilizumab. This study was conducted in accordance with the Helsinki Declaration.

Patients included in the study were those who were in the ICU within the first 24 hours of follow-up and were experiencing worsening respiratory distress and persistent hypoxia. These patients were receiving invasive or non-invasive mechanical ventilatory support, had peripheral oxygen saturation <94% or a PaO_2/FiO_2 ratio <200 mmHg, with and bilateral pulmonary infiltrations detected on chest radiography. Patients also exhibited elevated levels of inflammatory and coagulation markers, including CRP (mg/L), ferritin (ng/mL), D-dimer (µg/mL), fibrinogen (mg/dL), and lactate dehydrogenase (LDH) (U/L). They had lymphopenia, negative procalcitonin levels, and no signs of secondary infection. Based on these positive laboratory parameters, clinical findings, and radiological evidence, patients diagnosed with CRS were included in the study.

Patients with severe heart failure, advanced chronic obstructive pulmonary disease (COPD), suspected or confirmed pregnancy or secondary bacterial infections, tuberculosis diagnosis or suspicion, gastrointestinal perforation, hematological malignancy, or neutropenia were excluded from the study. Additionally, patients with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding three times the upper laboratory reference limit and those who died within the first 24 hours of ICU admission were not included.

Demographic information, including age, gender, and comorbidities as well as data on invasive or non-invasive mechanical ventilation (NIV) cytokine storm-related inflammatory markers (ferritin, D-dimer, fibrinogen, CRP, AST, ALT, LDH, platelet count, lymphocyte count, and leukocyte count), and oxygenation status (PaO_2/FiO_2 ratio) was retrospectively recorded in an electronic database. These parameters were documented on ICU admission, which was considered day 1, and subsequently on days 3, 7, 14, and 28.

All treatments were administered in accordance with the guidelines of the Turkish Ministry of Health's Scientific Advisory Board. Patients received favipiravir 400 mg twice daily for five days, 400 mg subcutaneous low molecular weight heparin twice daily, and 400 mg of hydroxychloroquine daily. In patients developing cytokine storm, dexamethasone 6 mg was administered intravenously for five days, followed by gradual dose tapering. In cases where procalcitonin levels were elevated later in the ICU stay, the infectious diseases department was consulted, and antimicrobial therapy with piperacillin-tazobactam or meropenem/vancomycin was initiated as needed. Supportive care measures, including high-flow nasal oxygen (HFNO) therapy with a non-rebreather mask,

delivering oxygen at a flow rate of 30-60 L/min and an adjustable inspiratory oxygen fraction to maintain targeted oxygen saturation, non-invasive or invasive mechanical ventilation (IMV), inotropic support, and renal replacement therapy, were provided based on clinical indications.

Tocilizumab became available in the hospital on April 10, 2020, and was administered intravenously to eligible patients. The dose was determined as 8 mg/kg of body weight, with a maximum dose of 800 mg. A second dose of 8 mg/kg was administered 24 hours later if deemed clinically necessary. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug were designated as Group C.

For all patients, CRP, D-dimer, ferritin, fibrinogen, lymphocyte count, leukocyte count, platelet count, AST, ALT, LDH, and PaO_2/FiO_2 values were recorded on ICU admission (day 1) and subsequently on days 3, 7, 14, and 28. The primary objective of this study was to compare changes in the PaO_2/FiO_2 ratio between groups with and without tocilizumab administration, assessing the efficacy of tocilizumab in improving oxygenation by controlling cytokine storm in COVID-19 patients. The secondary objective was to evaluate changes in inflammatory and coagulation biomarkers, including CRP, ferritin, D-dimer, fibrinogen, lymphocyte count, leukocyte count, platelet count, AST, ALT, and LDH, at specific time points during intensive care follow-up on days 1, 3, 7, 14, and 28.

Statistical Analysis

Data analysis was performed using SPSS (version 17.0 for Windows; IBM, Armonk, NY, USA). The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Parametric tests (Student's t-test) were used for normally distributed data, while non-parametric tests (Mann-Whitney U test) were applied for non-normally distributed data. Repeated measurements within groups were analyzed using Repeated Measures ANOVA with Bonferroni post-hoc correction or the Friedman test. Categorical variables were analyzed using the chi-square test. Results were presented as mean ± standard deviation, and a p-value <0.05 was considered statistically significant.

Results

During this period, a total of 318 patients were admitted to the ICU. CRS was suspected in 109 patients. Among these, 33 patients who died within the first 24 hours of ICU admission were excluded from the study. A total of 76 patients who developed CRS were included and analyzed. Of these, 39 patients received tocilizumab (Group T), while 37 patients formed the control group (Group C), which corresponds to the period when tocilizumab was not available.

The demographic characteristics of the patients, including age and gender, are presented in Table 1, with no significant differences observed between the groups. However, comorbidities such as diabetes mellitus, hypertension, COPD, hypothyroidism, and coronary artery disease were found to be more prevalent in the control group (Group C).

Regarding ventilatory support among ICU-admitted patients, in Group T, 16 out of 39 patients received HFNO in combination with NIV, and 26 patients required IMV. In the control group (Group C, n=37), 11 patients received HFNO + NIV, and 23 patients were treated with IMV.

No statistically significant difference was observed in 28-day mortality between the groups (p=0.063).

Regarding inflammatory markers, CRP, mg/L levels were significantly lower in patients who received tocilizumab (Group T) on days 3 and 7, compared to the control group. Due to high mortality rates, statistical analysis could not be performed for days 14 and 28 (Table 2).

No significant difference was found in D-dimer (µg/L) levels between the groups across different time points (Table 3).

When comparing ferritin (ng/mL) levels, a significant difference was observed between the groups on day 3 (Table 3). Fibrinogen (mg/dL) levels showed a statistically significant difference between the groups on days 1 and 7, while intragroup analyses revealed significant changes over time in both groups (Table 3).

In hemogram evaluations, lymphocyte count ($\times 10^3/\mu L$) was significantly higher in Group T on day 7 (Table 4). No significant difference was detected between the groups in white blood cell (white blood cell, $\times 10^3/\mu L$) counts on days 1, 3, and 7 (Table 4). However, platelet count ($\times 10^3/\mu L$) was significantly higher in Group T on days 1 and 3 (Table 4).

Regarding liver enzymes, AST (U/L) and ALT (U/L) levels were significantly higher in Group T on day 7 (Table 5). Additionally, LDH, U/L levels were significantly higher in Group T on days 1 and 3 (Table 5).

When comparing the PaO_2/FiO_2 ratio, used to assess oxygenation, a statistically significant difference was observed between the groups on day 7. In repeated intragroup measurements, the PaO_2/FiO_2 ratio in Group T on day 7 was significantly higher than on days 1 and 3 (Table 6).

Table 1. Comparison of demographic data between groups

	Group T n=39	Group C n=37	p
Age	60.51±11	64.30±10	0.1
Gender (M/F)	29/10	22/15	0.17
Comorbidity (present/absent)	22/17	31/6	**0.009**
Mortality (deceased/discharged)	17/22	24/13	0.063
HFNO/non-invasive mechanical ventilation	16 (41%)	11 (29.7%)	0.30
Invasive mechanical ventilation	23 (59%)	26 (70.3%)	

Values are presented as mean ± standard deviation for continuous variables and as number (percentage) for categorical variables. Between-group comparisons were performed using Student's t-test for continuous variables and the chi-square test for categorical variables. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug but received standard therapy were designated as Group C. HFNO: High flow nazal oxygen. p-value <0.05 was considered statistically significant

Table 2. Comparison of CRP levels between groups

	Group T	Group C	p
CRP day 1	201.17±91.17	188.31±154.87	0.659
CRP day 3	122.95±91.57	208.14±133.05	**0.002**
CRP day 7	34.12±40.64	204.46±144.69	**<0.001**
p (ANOVA)	**<0.001**	0.662	

Values are presented as mean ± standard deviation. Between-group comparisons at each time point were performed using Student's t-test. Repeated measurements within groups were analyzed using repeated measures ANOVA with Bonferroni post-hoc correction. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug and received standard therapy were designated as Group C. CRP: C-reactive protein. The normal range of CRP is <5 mg/L. A p-value <0.05 was considered statistically significant

Table 3. Comparison of D-dimer, ferritin, and fibrinogen levels between groups on days 1, 3, and 7

	Group T	Group C	p
D-dimer day 1	5451.19±16009.52	6778.86±20436.26	0.753
D-dimer day 3	7625.90±19024.20	5034.30±6256.34	0.433
D-dimer day 7	5723.38±9349.69	5728.78±6506.83	0.998
Ferritin day 1	1043.96±864.43	724.02±1632.52	0.287
Ferritin day 3	971.71±696.12	526.23±431.34	**0.001**
Ferritin day 7	821.09±1316.29	590.76±570.25	0.330
Fibrinogen day 1	454.87±116.70	350.97±94.52	**<0.001**
Fibrinogen day 3	380.08±95.09	412.86±97.00	0.141
Fibrinogen day 7	275.92±79.72	451.22±129.92	**<0.001**

Values are presented as mean ± standard deviation. Between-group comparisons at each time point were performed using Student's t-test. Repeated measurements within groups were analyzed using repeated measures ANOVA with Bonferroni post-hoc correction. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug and received standard therapy were designated as Group C. Ranges of the normal values of the parameters (D-dimer <500 µg/L, fibrinogen: 200-400 mg/dL). A p-value <0.05 was considered statistically significant

Table 4. Comparison of lymphocyte, leukocyte, and platelet levels between groups on days 1, 3, and 7

	Group T	Group C	p
Lymphocyte: day 1	866.92±408.20	905.95±585.25	0.736
Lymphocyte: day 3	800.51±440.01	788.65±462.14	0.909
Lymphocyte: day 7	1304.97±886.78	818.11±570.69	**0.006**
Leukocyte day 1	12421.51±15876.93	10326.22±5336.06	0.448
Leukocyte day 3	13025.67±23712.04	10554.59±6268.03	0.541
Leukocyte day 7	11817.18±6323.41	12464.32±6363.09	0.658
Platelet day 1	307051.28±143657.11	207432.43±83616.69	**<0.001**
Platelet day 3	340102.56±143884.62	226081.08±81576.61	**<0.001**
Platelet day 7	304461.54±133274.51	261513.51±85491.59	0.101

Values are presented as mean ± standard deviation. Between-group comparisons at each time point were performed using Student's t-test. Repeated measurements within groups were analyzed using repeated measures ANOVA with Bonferroni post-hoc correction. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug and received standard therapy were designated as Group C. Ranges of the normal values for the parameters are: leukocytes: 4.4000-12.000/µL; lymphocytes: 1.500-5.000/µL; platelets: 150.000-400.000/L. A p-value <0.05 was considered statistically significant

Table 5. Comparison of AST, ALT, and LDH levels between groups on days 1, 3, and 7

	Group T	Group C	p
AST day 1	99.51±256.89	56.43±65.45	0.326
AST day 3	146.77±586.91	43.54±23.93	0.289
AST day 7	79.13±70.12	43.84±21.88	**0.005**
ALT day 1	58.87±84.80	40.16±48.12	0.244
ALT day 3	81.44±199.41	31.65±27.44	0.137
ALT day 7	95.00±76.34	32.57±21.16	**<0.001**
LDH day 1	593.92±197.16	436.11±211.96	**0.001**
LDH day 3	623.82±272.10	448.78±237.97	**0.004**
LDH day 7	550.41±189.97	507.22±311.40	0.465

Values are presented as mean ± standard deviation. Between-group comparisons at each time point were performed using Student's t-test. Repeated measurements within groups were analyzed using repeated measures ANOVA with Bonferroni post-hoc correction. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug and received standard therapy were designated as Group C. Ranges of the normal values of the parameters are AST <50 U/L, ALT <50 U/L, LDH <250 U/L. A p-value <0.05 was considered statistically significant.
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

Table 6. Comparison of P/F ratios between groups on days 1, 3, and 7

	Group T	Group C	p
P/F day 1	137.74±71.09	170.49±92.27	0.086
P/F day 3	171.05±67.82	170.67±78.76	0.982
P/F day 7	223.05±90.83	170.59±86.70	**0.012**
p (ANOVA)	**<0.001**	1.000	

Values are presented as mean ± standard deviation. Between-group comparisons at each time point were performed using Student's t-test. Repeated measurements within groups were analyzed using repeated measures ANOVA with Bonferroni post-hoc correction. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug and received standard therapy were designated as Group C. P/F (PaO_2/FiO_2 ratio), PaO_2 (arterial oxygen pressure in mmHg), and FiO_2 (fraction of inspired oxygen). A p-value <0.05 was considered statistically significant

Discussion

In patients diagnosed with SARS-CoV-2 pneumonia and monitored in the ICU with severe hypoxia, the addition of tocilizumab to standard treatment in cases of CRS, was associated with a significant improvement in the PaO_2/FiO_2 ratio, a notable reduction in acute-phase reactants such as CRP and fibrinogen, and an increase in lymphocyte count compared to patients who received only standard treatment.

The primary cause of mortality in COVID-19 pneumonia is severe respiratory failure due to ARDS (17). Therefore, early identification of CRS through biomarkers and initiation of treatment before the progression of alveolar damage are crucial. The low survival rates in patients requiring mechanical ventilatory support highlight the necessity of early diagnosis and treatment strategies.

IL-6, a multifunctional inflammatory mediator, is believed to contribute to ARDS and interstitial pneumonia observed in severe COVID-19 cases. Blocking the IL-6 receptor is hypothesized to disrupt this cascade, thereby mitigating cytokine storm and preventing disease progression (17-22).

Patients with PCR-negative results who developed cytokine storm, were also included in the study for the diagnosis of COVID-19. Clinical, laboratory, and radiological data were evaluated comprehensively. Although RT-PCR testing is considered the gold standard for COVID-19 diagnosis, the literature reports a false-negative rate ranging from 30% to 70%. Therefore, patients with negative PCR results but clinical symptoms and laboratory findings consistent with COVID-19 (e.g., elevated IL-6, CRP, ferritin, D-dimer) were evaluated in terms of potential CRS. Indeed, a large cohort study conducted at Mount Sinai demonstrated that PCR-negative patients with clinical features compatible with COVID-19 exhibited elevated levels of proinflammatory cytokines and were at risk of developing CRS. These findings indicate that a negative PCR result does not rule out significant immune dysregulation, and that this patient group should also be carefully evaluated for hyperinflammation (23).

In this study, among 39 patients with severe COVID-19 pneumonia and persistent hypoxia who received tocilizumab in addition to standard treatment, 17 (43.6%) died. In the group receiving standard treatment alone, 24 out of 37 patients (70.6%) died. Although the standard treatment group had a higher prevalence of comorbidities, there was no significant difference in the mean age between the two groups. The higher mortality rate in the standard

treatment group may have been influenced by the greater burden of comorbidities. However, in the tocilizumab group, a rapid response and improvement in PaO_2/FiO_2 ratios were observed following treatment. Additionally, acute-phase reactants such as CRP, fibrinogen, and ferritin showed a decline starting from day 3. A significant increase in lymphocyte count was also detected in the tocilizumab group. Due to the unavailability of IL-6 test kits at the hospital where the study was conducted, IL-6 levels could not be measured in the patients, and therefore monitoring could not be used in the diagnosis of CRS.

A total of 56.4% (n=22) of the patients in the tocilizumab group, were discharged from the ICU to the ward, while in the standard treatment group (Group C), only 35% (n=13) were transferred from the ICU to the ward. These findings suggest that tocilizumab plays an active role in the management of CRS in COVID-19 pneumonia.

In the tocilizumab-treated patients, the PaO_2/FiO_2 ratio increased from 137 on day 1 to 223 on day 7. In contrast, no significant change was observed in the standard treatment group. This improvement was attributed to the reduction of cytokines responsible for alveolar exudate accumulation and alveolar damage, following tocilizumab administration. These findings suggest that tocilizumab treatment should be initiated in patients suspected of CRS before significant alveolar damage and exudate formation occur.

A meta-analysis of 3.377 patients with COVID-19 pneumonia demonstrated that IL-10, IL-6, and ferritin levels correlated with disease severity (18). The same study also reported that patients with severe or fatal disease exhibited thrombocytopenia and lymphopenia, along with atypical higher lymphocyte counts when compared to those with moderate disease who eventually recovered (8). Our study findings were consistent with those reported in that meta-analysis.

Mehta et al. (8) emphasized the importance of using inflammatory biomarkers such as erythrocyte sedimentation rate, decreased platelet count, and elevated ferritin levels to identify patients who might benefit from immunomodulatory therapies, including IL-6 inhibitors unlike that study, our findings revealed higher platelet counts. We believe that early identification of disease severity and progression through biomarkers can help guide early treatment strategies (15,16).

Capra et al. (24), in their retrospective study, reported, similarly to our study, that early administration of low-dose tocilizumab reduced hyperinflammation in the lungs and improved survival. However, unlike our study, they administered tocilizumab at an earlier stage. Their mortality rates were significantly lower than ours. In patients admitted to the ICU, inflammatory markers and coagulation parameters were at extremely high levels. Clinically, patients with severe respiratory distress were admitted to intensive care for monitoring. We believe that closer monitoring of patients in the earlier stages of their ICU stay for CRS could lead to better outcomes. In parallel with their findings, we also suggest that tocilizumab should be administered in the early stages and initiating treatment before the need for mechanical ventilation, following an increasing trend in acute-phase reactants, worsening respiratory distress, or a decrease in the PaO_2/FiO_2 ratio, could yield better results.

In recent years, several new drugs and supportive treatment approaches have been developed for the management of COVID-19; however, the effective treatment of severe cases—particularly those involving cytokine storm and associated ARDS—remains a significant clinical challenge. Complementary therapies such as traditional Chinese medicine have been reported to exert modulatory effects on cytokine release and may help prevent the progression to ARDS. Nevertheless, the current evidence in this area is still limited. Therefore, there is a need for more comprehensive, well-designed, and controlled clinical studies to evaluate the efficacy and safety of therapeutic strategies targeting severe hyperinflammatory responses related to COVID-19 (25-27).

Study Limitations

This study has several limitations. A more balanced distribution of comorbidities between the groups could have allowed for a more accurate analysis. The number of patients included was relatively small. Due to high mortality rates, analyses could not be performed on days 14 and 28. A larger study population could provide more meaningful results regarding mortality and other outcomes.

Conclusion

We believe that the use of tocilizumab in COVID-19 pneumonia has a positive impact on the clinical course of the disease. However, we consider it crucial to initiate treatment at an earlier stage, before the need for mechanical ventilatory support arises.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of University

of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital on June 2, 2020 (approval no: 95).

Informed Consent: Written informed consent was obtained from all patients or their legal representatives before tocilizumab administration.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M., Concept: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M., Design: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M., Data Collection or Processing: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M., Analysis or Interpretation: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M., Literature Search: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M., Writing: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M.

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