Mortality Predictors Of Pre-variant SARS-CoV-2 Infected ARDS Patients Receiving Favipiravir and Tocilizumab

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Research Article

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Abstract

Objective

In this study, viral clearance (oronasopharyngeal swab RT-PCR negativity) and intensive care outcomes and risk factors affecting mortality of critically ill patients with COVID-19-related acute respiratory distress syndrome (ARDS) who received tocilizumab and favipiravir treatments together before vaccination were investigated.

Material-Methods

The data of patients who were followed up and treated between 1 July 2020 and 5 October 2020 were retrospectively analyzed. Demographic data of the patients (age, gender), oro-nasopharyngeal swab RT-PCR and classification of ARDS, respiratory support treatments, all medical treatments, and ICU outcomes were recorded.

Results

Totally, 60 patients with a median age of 69.8 [24–87], 25 females and 35 males were included in the study. Mean APACHE II score was 18.9 ± 8.0; and SOFA score was 4.5 ± 2.0. Thirty-four (56.7%) patients were intubated during follow-up. Tocilizumab was given on average of 2.5th day (± 2.0 days). On the day of tocilizumab administration, 1 (1.7%) patient had mild ARDS, 30 (50.0%) had moderate ARDS, 29 (48.3%) had severe ARDS. PaO2/FIO2 on the day of tocilizumab administration was 96.7 ± 36.6 mmHg. Forty (66.7%) patients died, while 20 (33.3%) patients transferred to the service. The mean length of stay in the ICU was 11.4 ± 5.5 days. Advanced age [Hazard ratio (HR) 1.8; 95% confidense interval (CI) 0.88–0.93; $p < 0.001$), higher APACHE II score (HR 0.81, 95% CI 0.74–0.98; $p = 0.001$), higher SOFA score on the day of tocilizumab administration (HR 1.47, 95% CI 0.39–0.79; $p = 0.001$), and lower PaO2/FIO2 ratio (HR 2.54, 95% CI 2.33–3.79; $p < 0.001$) were determined as independent risk factors for mortality.

Conclusion

Patients who were administered tocilizumab and favipiravir together in our intensive care unit were mostly patients with severe ARDS and had higher inflammatory markers. High mortality was attributed to the use of tocilizumab as an add-on treatment, not as a routine treatment.

Introduction

The coronavirus 2019 (COVID-19) pandemic is still a huge threat for global health. As of 28 November 2021, there are more than 259 million cases worldwide with 5,183,003 deaths (1). COVID-19 is a disease characterized by an initial phase of viral replication and a second phase generated by the host response

(immune phase). Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection can lead to acute respiratory distress syndrome (ARDS) by causing an exaggerated immune response in the immune phase, and the primary mortality risk of COVID-19 is attributable to severe pneumonia that leads to ARDS. SARS-CoV-2 associated ARDS is known to have a high reported mortality rate of up to 60.6%. (2–4). Many proinflammatory cytokines are involved in the pathogenesis of COVID-19 related ARDS, however, interleukin-6 (IL-6) seems as the most important cytokine that was found to be a poor prognostic factor in COVID-19 in previous studies (5, 6) Therefore it is reasonable to speculate that IL-6 blockade can be beneficial to prevent poor prognosis, particularly in COVID-19 patients with severe pneumonia by preventing progression to ARDS and intubation. Tocilizumab (Actemra®, Roche Medical, USA) is a humanized monoclonal antibody that can target both membrane-bound and soluble form of the IL-6 receptor. At the beginning of the pandemic, the efficacy of tocilizumab in severe COVID-19 was unknown and only case reports were available. (7, 8). In March 2020, China approved tocilizumab for the treatment of exaggerated inflammation in patients with the coronavirus SARS-CoV-2 (9), and then several studies have evaluated its efficacy in the treatment of severe COVID-19 pneumonia (10–12). In January 2021, the REMAP-CAP trial (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) released preliminary evidence that tocilizumab and sarilumab could prevent fatality among severely ill COVID-19 patients. The drugs were added to the United Kingdom recommended list for COVID-19 treatment (13). The RECOVERY Trial revealed a similar result: 29% of the patients in the tocilizumab group died within 28 days compared with 33% in the usual care group, a statistically significant reduction of the risk of death on top of the reduction already given by dexamethasone. It also reduced the chance of a patient needing to go on a ventilator or dying from 38–33% (14). In June 2021, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization for tocilizumab for the treatment of COVID-19 in hospitalized people aged two years of age and older who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation (MV) or extracorporeal membrane oxygenation (ECMO) (15).

At the beginning of the pandemic, the combination of anti-viral and immunomodulatory drugs theoretically seemed reasonable to prevent disease progression and cytokine storm in COVID-19, however, due to the pandemic circumstances, there were not enough randomized controlled studies and scientific evidence to demonstrate their efficacy. Favipiravir was recommended for patients with severe COVID-19 pneumonia who met the following criteria in the treatment guideline of the Turkish Ministry of Health, COVID-19 dated April 12, 2020: 1. Symptoms such as fever, muscle/joint pains, cough, sore throat and nasal congestion, and tachypnea (≥ 30/minute)) present, with an SpO2 level below 90% in room air, 2. Poor prognostic markers in laboratory studies [lymphocyte count < 800/µl, C-reactive protein (CRP) > 40 mg/l or ferritin > 500ng/ml or D-Dimer > 1000 ng/ml, etc.], 3. Bilateral diffuse pneumonia on chest X-ray or thorax tomography (16). No recommendation was made regarding the use of tocilizumab during this period. Here, in our single center, retrospective study, we reported our treatment experience with tocilizimab and favipiravir in patients who developed SARS-CoV-2 associated ARDS, and discussed the mortality related factors in the lights of current studies.

Material-methods

This study, which examines the efficacy of tocilizumab on viral clearance and clinical improvement in patients with COVID-19-related severe pneumonia and ARDS, included patients COVID-19 intensive care unit (ICU) between 1 July 2020 and 5 October 2020. Sixty patients who received tocilizumab and favipiravir treatment together were included. Demographic data of the patients (age, gender), oro-nasopharyngeal swab RT-PCR and rapid antibody test results, severity of ARDS, type of respiratory support treatments, medical treatments, and ICU outcomes were recorded. Our study was conducted in accordance with the Declaration of Helsinki with the ethics guidelines. This retrospective study was approved by the Instutional Review Board of tertiary hospital (Approval number 101/05, 28/12/2020).

In COVID-19, extremely elevated IL-6 and C-reactive protein (CRP) levels can be an indicator of cytokine storm. In our study, patients were considered for the use of tocilizumab if the following criteria were met:

1. Signs of respiratory compromise consisting of tachypnea (> 30 breaths/minute), dyspnea, use of accessory respiratory muscles.
2. Peripheral capillary oxygen saturation (SpO2) < 90% or increasing oxygen requirement over 24 hours, rapidly desaturation or recently intubated.
3. Two or more of the following laboratory parameters: IL-6 > 40 pg/ml, CRP > 70 mg/L, ferritin > 500 mg/ml, D-dimer > 0.5 µg/ml, LDH > 300 U/L.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics (Version 17.0, SPSS Inc). The normal distribution of the data was tested using the Shapiro-Wilk test. Continuous variables were shown as mean ± standard deviation or median (25th and 75th percentiles) depending on data distribution and compared using Student's t test or Mann-Whitney U test. Categorical variables are expressed as numbers (%) and compared using Chi-square test or Fisher exact test. Multiple regression analysis was performed to determine the independent risk factors affecting mortality.

Results

Sixty patients, with a median age of 69.8 [24–87], 25 (41.7%) female, 35 (58.3%) male, were included in the study. At the time of admission to ICU, the mean APACHE II score was 18.9 ± 9.0, the SOFA score was 4.2 ± 2.2, and the SOFA score on the day of tocilizumab administration was 4.5 ± 2.0. Fifty-two (86.7%) patients had positive oro-nasopharyngeal swab for SARS-CoV-2 by RT-PCR; Although 8 (13.3%) patients had negative results for SARS-CoV-2 by RT-PCR, there was a history of contact with a COVID-19 patient with intense ground glass opacities on thorax computed tomography (CT). Also, 8 patients had positive Ig M/Ig G rapid antibody tests. All patients were started on favipiravir (2x1200 mg tb loading dose, 2x600 mg tb maintenance dose, orally) treatment on the day of admission to the ICU. Mean favipiravir treatment duration was 5.5 ± 1.5 days. Tocilizumab was given on average 2.5 ± 2.0 days after ICU admission. Fifty patients (83.3%) received a single dose of 400 mg IV tocilizumab and 10 patients (16.7%) received two

doses of 400 mg IV tocilizumab. RT-PCR negativity was obtained on day 14 in 13 (65%) of 20 surviving patients. Secondary bacterial infection was encountered in three (5%) patients. Other characteristics of study group were seen in Table 1.

Table 1
General characteristics of patients

Characteristics	**n = 60 (%)**
Age, median (25–75)	69.8 (24–87)
Gender (%)	25 (41.7)
Female	35 (58.3)
Male	
APACHE II score (mean ± SD)	18.9 ± 9.0
SOFA score on the day of tocilizumab administration (mean ± SD)	4.5 ± 2.0
Comorbidities	
Hypertension	36 (60)
Diabetes mellitus	21 (35)
Atherosclerotic heart disease	10 (16.7)
Congestive heart failure	4 (6.7)
History of cerebrovascular event	2 (3.3)
Cancer	5 (8.3)
Previous lung disease	19 (31.6)
Time from symptom onset to ICU admission [median (25–75)]	2.5 (1–5)
ARDS Severity at the time of ICU admission (%)	30 (50.0)
Moderate ARDS	30 (50.0)
Severe ARDS	
Organ failures in ICU admission (%)	
Acute hypoxic respiratory failure	54 (90)
Acute hypoxic/hypercapnic respiratory failure	6 (10)
Acute coronary syndrome/cardiogenic shock	5 (8.3)
Acute kidney failure	20 (33.3)
Respiratory Support Treatments in ICU	
Simple facemask	5 (8.3)

APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment Score, SD: Standart deviation, CVE:Cerebrovascular event, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit

Characteristics	n = 60 (%)
Reservuar mask	7 (11.7)
High flow nasal oxygen	21 (35)
Non-invasive mechanical ventilation	24 (40)
Invasive mechanical ventilation	3 (5)
Other medical treatments	
Methylprednisolone	51 (85)
Dexamethasone	6 (10)
Hydroxychloroquine	6 (10)
Additional interventions	
Convalescent plasma	10 (16.7)
Plasmapheresis	2 (3.3)
ICU Outcome	
Exitus	40 (66.7)
Transfer to service	20 (33.3)
The duration of ICU stay (day) (mean ± SD)	11.4 ± 5.5

APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment Score, SD: Standart deviation, CVE:Cerebrovascular event, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit

Forty patients (66.6%) died, patients who died were older (71.5 vs 60.0 years; p = 0.025). The severity of the disease and the number of organ failures were higher at admission to the ICU in patients who died. Patients who died had higher APACHE score (21.0 ± 8.1 vs 15.1 ± 6.4; p = 0.009) and SOFA score (5.1 ± 2.1 vs 3.6 ± 1.6; p = 0.014) on the day of tocilizumab administration. All died patients had severe ARDS on the day of tocilizumab administration and their PaO2/FIO2 ratio were 94.8 ± 98.2 (Table 2). Patients who died had higher incidence of tachycardia (107.3 ± 25.2 vs 92.1 ± 19.8 beats/min; p = 0.028), and hypotension (systolic blood pressure 118.4 ± 16.4 vs 129.2 ± 19.1 mmHg; p = 0.031) on admission to the ICU. There was no significant difference in the uptake patterns on thorax CT and arterial blood gas values at ICU admission. In laboratory values, Na (139.8 ± 6.7 vs 136.5 ± 4.5 mEq/L; p = 0.052) and ferritin (1281 ± 1000 vs 746.0 ± 53.5 µg/L; p = 0.035) levels were higher (Table 3).

Table 2
Comparison of the characteristics of the patients who died and survived

Parameters	Patients who died (n = 40)	Patients who survived (n = 20)	p
Age (median) (25–75) (year)	71.5 (37–87)	60 (24–84)	**0.025**
Gender (%)	16 (40)	9 (45)	0.461
Female	24 (60)	11 (55)	
Male			
APACHE II score (mean ± SD)	21.0 ± 8.1	15.1 ± 6.4	**0.009**
SOFA Score at the time of tocilizumab given (mean ± SD)	5.1 ± 2.1	3.6 ± 1.6	**0.014**
Comorbidities	25 (62.5)	11 (55.0)	0.344
Hypertension	15 (37.5)	8 (40.0)	0.564
Diabetes Mellitus	6 (15.0)	4 (20.0)	0.457
Atherosclerotic heart disease	2 (5.0)	2 (10.0)	0.418
Congestive heart failure	2 (5.0)	0	0.279
History of cerebrovascular event	3 (7.5)	2 (10.0)	0.556
Cancer	10 (25.0)	6 (30.0)	0.498
Obstructive lung disease			
Organ failures in ICU admission	36 (90.0)	20 (100.0)	0.643
Acute hypoxic respiratory failure	4 (10.0)	0	0.452
Acute hypoxic/hypercapnic respiratory failure	3 (7.5)	2 (10.0)	0.556
Acute coronary syndrome/cardiogenic shock	16 (40.0)	4 (20.0)	0.047
Acute kidney failure	3 (7.5)	0	0.281
Acute cerebrovascular event			
$PaO_2/FİO_2$ during ICU stay (mmHg) (mean ± SD)	110.1 ± 37.3	106.6 ± 40.6	0.746
PaO_2/FiO_2 at the day of tocilizumab given (mmHg) (mean ± SD)	94.8 ± 98.2	100.5 ± 34.0	0.575

APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, SD:Standart deviation, ARDS: Acute Respiratory Distress Syndrome.

Parameters	Patients who died (n = 40)	Patients who survived (n = 20)	p
ARDS classification	17 (42.5)	10 (50.0)	0.423
Moderate ARDS	23 (57.5)	10 (50.0)	
Severe ARDS			

APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, SD:Standart deviation, ARDS: Acute Respiratory Distress Syndrome.

Table 3
Comparison of clinical, radiological and laboratory findings of patient groups at the time of intensive care unit admission

Parameters	Patients who died (n = 40)	Patients who survived (n = 20)	p
Vital signs at the time of admission to ICU (mean ± SD)			
Body temperature (°C)	36.9 ± 0.8	36.8 ± 0.6	0.618
Heart rate (beat/minute)	107.3 ± 25.2	92.1 ± 19.8	**0.028**
Blood pressure (arterial) (systolic) (mmHg)	118.4 ± 16.4	129.2 ± 19.1	**0.031**
Respiratory rate (breath/minute)	32.1 ± 6.3	29.1 ± 7.1	0.153
Thorax CT findings (N,%)			
Bilateral involvement	34 (85.0)	17 (85.0)	0.683
Peripheral involvement	36 (90.0)	20 (100)	0.540
Ground-glass opacities	40 (100)	20 (100)	-
Alveolar consolidation	19 (47.5)	5 (25.0)	0.094
Air bronchogram	11 (27.5)	4 (20.0)	0.541
Number of lobes involved (mean ± SD)	4.0 ± 1.4	3.7 ± 1.6	0.491
Arterial blood gas findings at intensive care admission (mean ± SD)			
pH	7.41 ± 0.1	7.43 ± 0.1	0.201
PaO_2 (mmHg)	63.2 ± 14.1	67.0 ± 19.3	0.508
PaCO2 (mmHg)	35.4 ± 11.9	35.7 ± 6.7	0.921
Lactate (mmol/L)	2.1 ± 1.3	1.8 ± 0.8	0.520
SpO_2/FiO_2	152.0 ± 66.1	147 ± 55.4	0.776
Laboratory Findings (mean ± SD)			
WBC ($10^3/\mu L$)	13.1 ± 10.1	9.2 ± 4.4	0.138
Hg (gr/dl)	12.9 ± 2.2	11.8 ± 1.9	0.453

ICU:Intensive Care Unit, SD:Standart deviation, CT:Computed tomography, WBC: White blood cell, Hg: hemoglobin, Htc: hematocrit, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CK: creatinine kinase, CK-MB: creatinine kinase myoglobulin, LDH: lactate dehydrogenase, CRP: C-reactive protein, INR: international normalized ratio, aPTT: activated partial thromboplastin time, PTT: partial thromboplastin time

Parameters	Patients who died (n = 40)	Patients who survived (n = 20)	p
Htc (%)	39.4 ± 6.5	36.1 ± 5.2	0.257
Platelet (10^3/μL)	241.0 ± 106.0	268.8 ± 129.2	0.368
Neutrophil count (10^3/μL)	10.4 ± 7.5	7.1 ± 4.2	0.071
Lymphocyte count (10^3/μL)	0.8 ± 0.7	1.1 ± 0.7	0.486
Urea (mg/dl)	67.2 ± 35.8	52.0 ± 27.1	0.099
Creatinine (mg/dl)	1.2 ± 0.5	1.02 ± 0.6	0.272
AST (U/L)	67.3 ± 22.8	41.8 ± 15.5	0.179
ALT (U/L)	44.8 ± 15.6	38.3 ± 22.1	0.599
CK (U/L)	517.9 ± 110	365 ± 78.2	0.581
CK-MB (U/L)	35.3 ± 20.3	28.9 ± 20.1	0.264
Na (mEq/L)	139.8 ± 6.7	136.5 ± 4.5	**0.052**
K (mEq/L)	4.2 ± 0.7	4.3 ± 0.4	0.513
Cl (mEq/L)	101.9 ± 7.1	99.1 ± 4.2	0.110
LDH (U/L)	616.0 ± 436.3	467.1 ± 164.7	0.157
D-Dimer (μg/ml) (median) (25–75)	1220 (380–3110)	970 (300–4005)	0.998
Fibrinogen (mg/dl) (median) (25–75)	530 (484–672)	536 (450–668)	0.994
Ferritin (μg/l)	1281 ± 1000	746.0 ± 535.0	**0.035**
CRP (mg/L) (median) (25–75)	146 (86–195)	94 (41–195)	0.107
Procalcitonin (μg/l) (median) (25–75)	0.53 (0.2–5.1)	0.18 (0.09–0.6)	0.072
INR	1.4 ± 0.8	1.2 ± 0.2	0.265
aPTT (sn)	41.1 ± 1.6	36.0 ± 8.5	0.136
PTT (sn)	12.9 ± 9.3	28.9 ± 20.6	0.306

ICU:Intensive Care Unit, SD:Standart deviation, CT:Computed tomography, WBC: White blood cell, Hg: hemoglobin, Htc: hematocrit, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CK: creatinine kinase, CK-MB: creatinine kinase myoglobulin, LDH: lactate dehydrogenase, CRP: C-reactive protein, INR: international normalized ratio, aPTT: activated partial thromboplastin time, PTT: partial thromboplastin time

There was no difference in type of respiratory support treatments received by deceased and surviving patients at the time of admission to the ICU. Patients who survived in the ICU received longer HFNO treatment (7.9 ± 6.4 vs 4.2 ± 3.2 days, p = 0.015). The rate of receiving methylprednisolone, dexamethasone, and other treatments were similar between two groups. A higher rate of C vitamin therapy was observed in surviving patients (35% vs 10%; p = 0.030). Patients who survived stayed longer in the ICU (13.0 ± 5.0 vs 9.2 ± 4.5; p = 0.06) (Table 4).

Table 4
Comparison of respiratory and medical treatments of patients during intensive care follow-up

Parameters	**Patients who died (n = 40)**	**Patients who survived (n = 20)**	**p**
Respiratory support treatments (n,%)			
Low flow oxygen therapies	9 (22.5)	3 (15.0)	0.44
High flow nasal oxygen therapy	13 (32.5)	8 (40.0)	0.46
Noninvasive mechanical ventilation	15 (37.5)	9 (45.0)	0.44
Invasive mechanical ventilation	3 (7.5)	0 (0)	0.27
The duration of respiratory support treatment (mean ± SD)			
High flow nasal oxygen therapy	4.2 ± 3.2	7.9 ± 6.4	0.015
Noninvasive mechanical ventilation	4.2 ± 3.6	5.7 ± 5.4	0.177
Other medical treatments (%)			
Steroid therapy	37 (92.5)	20 (100.0)	0.441
Methylprednisolone	35 (87.5)	16 (80.0)	
Dexamethasone	2 (5.0)	4 (20.0)	
Convalescent plasma	4 (10.0)	7 (35.0)	0.030
N-Acetyl cysteine	13 (32.5)	6 (30.0)	0.519
C-Vitamin IV	13 (32.5)	6 (30.0)	0.519
Plasmapheresis	1 (2.5)	1 (5.0)	0.575
The duration of ICU stay (day) (mean ± SD)	9.2 ± 4.5	13.0 ± 5.0	0.006

ICU:Intensive Care Unit, SD:Standart deviation.

Estimated hazard ratios for the variables as mentioned before are investigated in Table 5. Results indicated that older age (HR 1.8 per 10-year increase in age, 95% CI 0.88 to 0.98, p < 0.001), APACHE II score over 21 (HR 0.81, 95% CI 0.74–0.98, p = 0.001) and SOFA (HR 1.47 per doubling, 95% CI 0.39–0.79,

p < 0.001), lower PaO2/FiO2 (HR 2.54 per doubling, 95% CI 2.33– 3.79, p < 0.001) increased the hazard of mortality and these factor indepently related with mortality (Table 5).

Table 5
Multivariate analysis on the risk of secondary infections of any type in patients hospitalized with coronavirus disease 2019 (COVID-19) associated acute respiratory distress syndrome

Baseline characteristics	Hazard ratio	95% confidence interval	p
Age (> 65 years)	1.8	0.88–0.93	**< 0.001**
APACHE II score (> 21 point)	0.81	0.74–0.98	**0.001**
SOFA score on the day of tocilizumab admission	1.47	0.39–0.79	**0.001**
Laktat (> 3 mmol/L)	1.77	1.1–3.35	0.069
Neutrophil count ($15x10^3$/L)	1.86	0.1–7.7	0.125
$PaO_2/FİO_2$ on the day of tocilizumab (< 80 mmHg)	2.54	2.33–3.79	**< 0.001**
Ferritin (> 1000 µg/L)	2.05	0.5–2.03	0.833
Heartbeat (> 90 beat/minute)	3.21	0.8–6.7	0.368
Systolic blood tension (< 90 mmHg)	1.13	0.182–1.366	0.184
Procalcitonin (> 0.5)	0.9	0.358–3.128	0.624

Discussion

In our study, mortality was higher in critical COVID-19-associated ARDS patients given favipiravir and tocilizumab. Patients who died were elderly (> 65 years), had high APACHE II score, high SOFA score on the day of tocilizumab administration and low PaO2/FIO2 ratio. Also they were mostly severe ARDS patients and had high inflammatory markers. High mortality was attributed to the use of tocilizumab as a salvage treatment, not as a routine treatment.

SARS-CoV-2 infection might cause a hyperimmune response associated with acute respiratory distress (ARDS), the latteris a leading cause of death for severe COVID-19 (17). Uncontrolled immune activation would result in cytokine storm, also known as cytokine release syndrome (CRS), appearing as overproduction of pro-inflammatory cytokines and chemokines (18). Severe COVID-19 patients always present elevated inflammatory markers, among which the elevation of IL-6 is associated with severity of COVID-19. The upregulated expression of IL-6 receptor (IL-6R) was also detected in COVID-19 patients (19). Therefore, IL-6/IL6R might serve as a messenger not only for transmitting inflammatory signals throughout the lung and other organs but also by activating cellular signal pathway, thus causing ARDS

and multiple organ dysfunction. It is reasonable to speculate that IL-6 blockade is beneficial for avoiding poor prognosis.

In more than one year, a relatively high number of different types of trials have evaluated the effects of tocilizumab. So far, the growing body of studies assessing the efficacy and safety of tocilizumab for treatment of SARS-CoV-2-associated hyperinflammation, severe pneumonia, and ARDS has yielded mixed results.

Jordan et al. (20) used a single dose of 400 mg tocilizumab IV in 27 patients at the beginning of the pandemic (13 March 2020-11 April 2020). Twenty-one patients were in MV upon admission to the ICU, and six patients were receiving nasal oxygen therapy; Tocilizumab was administered while 22 patients were on MV. All patients received azithromycin and hydroxychloroquine. While the median PaO2/FIO2 ratio on the day of tocilizumab administration was 161 mmHg, it was 201–300 mmHg in 6 (29%) patients, 101–200 mmHg in 9 (43%) patients, and < 100 mmHg in 3 (14%) patients. Among 21 intubated patients, 15 were extubated after a median of 8 days after tocilizumab administration, 9 were discharged from the hospital within a median of 14 days, and 2 patients died. In this study, where the mean IL-6 level was 356.07 ± 616 pg/ml, only 1 of the 6 non-intubated patients had respiratory deterioration and became intubated(20). Inhibition of IL-6/IL-6R blockade by tocilizumab detected by measuring CRP. We tought that a single 400 mg dose of tocilizumab does not uniformly block all cellular IL-6Rα, particularly if there is a large amount of circulating IL6Rα/IL6 complexes. Since our patients had high IL-6 levels, two doses of 400 mg tocilizumab were applied to most of our patients.

Zhao et al. (21) compiled studies investigating the use of tocilizumab in severe COVID-19 patients. They analyzed 10 studies, which included a total of 1675 patients, and found that only one study was a randomized controlled trial, while the others were retrospective observational studies. In that randomized controlled trial, total of 675 patients received tocilizumab, while 1000 patients received standard care. ? Mortality was significantly lower in the tocilizumab group [(132/675) 19.5%] vs [(283/1000), 28.3% (OR 0.47; 95% CI 0.36–0.60; p < 0) ,00001). However, a high level of heterogeneity was detected (I2 = 0.74, p < 0.0001). In the standard care group, hydroxychloroquine, lopinavir/ritonavir, remdesivir, azithromycin, low molecular weight heparin (LMWH) and/or methylprednisolone were administered (21). In our study, all patients received standard methylprednisolone, LMWH and favipiravir treatments in addition to tocilizumab, therefore a homogeneous treatment regimen was applied too all patients.

In the study of Somers et al. (22) in which they investigated the use of tocilizumab in COVID-19 patients with MV, 78 of 154 patients were given tocilizumab, while 76 patients did not. Median follow-up was 47 days (28–67 days), and the tocilizumab group was younger (mean age 55 vs. 60 years), had less chronic lung disease (10 vs 28%). The hazard of death was found as 45% decreased by inverse probability weighting (IPTW) analysis [hazard ratio 0.55 (95% CI 0.33–0.90)] for patients who received tocilizumab. However, the superinfection rate (54% vs 26%, p < 0.001) increased in the tocilizumab group. In this study, the PaO2/FIO2 ratio of the tocilizumab group was lower (median 155 vs 198; p = 0.001). Tocilizumab was associated with a lower hazard of death after adjusting for demographics (HR 0.54 95% CI O.29 − 1). In

this observational controlled study, tocilizumab reduced the risk of death in COVID-19 patients who needed MV. Although it increased the risk of secondary bacterial pneumonia, this was not a factor which increased mortality (22). In our study, the median age of the patients was 69.8 (24–71), and the median age of the patients who died was 71.5 (37–87), our patients were older than the study by Somers et al.. Sixteen (26.7%) of our patients had chronic obstructive pulmonary disease and all of our patients were receiving MV or NIMV. The PaO2/FIO2 of the group who died on the day of tocilizumab administration was very low at 94.8 ± 98.2 mmHg.

Mortality rates for tocilizumab-treated patients with COVID-19 of the seven studies ranged from 3.2–38.6%. This differences most probably based on the quailty of care including surge capacity of the ICU. In a prospective study by Toniati et al. (10) from Italy, 100 COVID-19 ARDS patients who needed MV were evaluated. Tocilizumab was administered in two doses of 8 mg/kg, similar to our study. A third dose was also administered according to the clinical response. The mortality rate was found as 20% (n = 20). In our study, a single dose of 400 mg tocilizumab was administered to 83.3% of the patients, while two doses of 400 mg IV tocilizumab were administered to remaining 16.7%. None of our patients received the third dose. Our high mortality rate (66.6%) was attributed to the severity of our patients and to the use of tocilizumab as a salvage treatment. In another prospective single-arm study, 63 severe COVID-19 patients were given tocilizumab and the mortality was 11%. It has been reported that administration of tocilizumab within the first 6 days of hospital admission increases the probability of survival (HR: 2.2, 95% CL 1.3–6.7; $p < 0.05$) (23). However, none of these studies included COVID-19 associated ARDS patients in the critical ICU, different from our study. In the studies mentioned above, all-cause mortality, the risk of ICU admission and the need for MV were found similar between tocilizumab and control group, similar to our results. Tocilizumab add-on treatment for patients with severe COVID-19 patients was associated with a better treatment outcome compared with those without tocilizumab treatment (23, 24). In our study, we attributed the mortality rate of 66.7% in patients receiving tocilizumab to the fact that we gave tocilizumab treatment as an add-on treatment to our patients receiving favipiravir, that all of our patients had ARDS and most of them had severe ARDS.

In our study, advanced age, high APACHE score and high SOFA score on the day of tocilizumab administration and low PaO2/FIO2 ratio were determined as independent risk factors for mortality. Our patient group was older than previous tocilizumab studies, and all of them were critically ill with severe ARDS and had organ failure.

Our study is the first study in Turkey to examine the use of tocilizumab as an add-on treatment to favipiravir in patients with critical COVID-19-associated ARDS. However, our study has some limitations. First, it is a retrospective and single-center study. All patients received favipiravir and tocilizumab, all surviving patients received corticosteroid therapy, while not all patients who died received corticosteroid therapy.

In conclusion; our findings addressed the potential role of tocilizumab in critical COVİD-19 patients to prevent intubation. Our study also highlight the need for adequately powered randomized controlled trials

which further evaluates efficacy of tocilizumab in critical COVID-19 ARDS patients.

Declarations

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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None.

Ethics Statement

This study was performed in accordance with the ethical principles in the Good Clinical Practice (GCP) guidelines and Declaration of Helsinki, applicable local regulatory requirements and the protocol were approved by Ethics Committee of tertiary institution.

Data Availability

The research article data used to support the findings of this study are available from the corresponding author upon request.

Authors' contributions

All authors have contributed sufficiently in the conception and design of the study, data collection, and interpretation as well as the preparation of the manuscript. All authors read and approved the final version of the manuscript.

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