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The Effects of Immunosuppressive Therapy on Mortality in Patients Followed in Intensive Care Units with the Diagnosis of Critical Coronavirus Disease-2019 Pneumonia

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ABSTRACT

Introduction: The efficacy and safety of immunosuppressive therapy in Coronavirus disease-2019 (COVID-19) still controversial. We evaluated the effects of immunosuppressive therapy on mortality in patients followed in the intensive care units (ICU) due to critical COVID-19 pneumonia.

Methods: We compared patients followed up in the ICUs due to severe COVID-19 pneumonia who received immunosuppressive therapy with those who did not in terms of 1-month mortality, retrospectively.

Results: A total of 362 patients followed up in ICUs with a diagnosis of critical COVID-19 pneumonia were included in the study. The patients were divided into two groups as patients who received immunosuppressive therapy [n=249, 165 patients (45.5%) who received only corticosteroids, 25 patients (7%) who received only tocilizumab, and 59 patients (16.5%) who received tocilizumab + corticosteroid] and patients who did not (n=113). One hundred and ninety-two of the patients died (54.1%). There was no statistical difference between the groups in terms of 1-month mortality (p=0.38). Secondary bacterial infection was detected in 25.1% (n=91) n of the patients. The frequency of secondary infections was higher in the patients who received immunosuppressive therapy than in patients who did not receive immunosuppressive therapy (28% vs 17% respectively, p=0.03). The most common secondary bacterial infection was detected in patients who received tocilizumab + corticosteroids (n=25, 42.2%).

Conclusion: In this study, no difference in 1-month mortality was found between patients who received immunosuppressive therapy and those who did not. The frequency of secondary bacterial infections in patients who received immunosuppressive therapy was higher than in patients who did not.

Keywords: COVID-19, immunosuppressive therapy, tocilizumab, corticosteroid, mortality

Introduction

Coronavirus disease-2019 (COVID-19), caused by a new coronavirus [severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)] in December 2019, has turned into a pandemic that affects the whole world. As of the end of November 2021, the number of people infected with SARS-CoV-2 exceeded 200 million, and the number of COVID-19-related deaths exceeded 4.6 million worldwide. Although the vast majority (81%) of people infected with SARS-CoV-2 do not develop any symptoms of the disease or the disease is come around with mild symptoms, intensive care follow-up is required in approximately 5% of the patients (1,2). One of the important reasons for intensive care hospitalization is multiple organ failure caused by the "cytokine storm" caused by SARS-CoV-2. Interleukin-6 (IL-6) receptor antagonists (toculizumab), as well as corticosteroids, are the most commonly used immunosuppressive agents in the prevention and treatment of this cytokine storm.

While the routine use of corticosteroids in the management of cytokine storms in the early stages of the pandemic is not recommended, the use of corticosteroids in severe and critically ill patients is recommended at a strong level of evidence in the recently published guidelines (3,4). The efficacy and use of tocilizumab in the cytokine storm due to COVID-19 is still a matter of debate (5). While the routine use of corticosteroids and tocilizumab in the early period of the pandemic is not recommended in the COVID-19 guideline of the Turkish Ministry of Health, in the current guideline, it is recommended to start 6 mg dexamethasone or equivalent corticosteroid (30-40 mg methylprednisolone, prednisolone or prednisone) treatment per day and apply it for a maximum of 10 days in the patients who develop a need for oxygen and mechanical ventilation. It also approves the use of tocilizumab if procalcitonin is negative in patients who develop the need for oxygen and mechanical ventilation and with persistent fever signs, high or persistently elevated

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C-reactive protein (CRP) findings, evidence of ferritin values (>700 µg/L) that are above the upper limits of normal and continue to increase, and cytokine storm findings such as D-dimer elevation, lymphopenia, thrombocytopenia and neutropenia, deterioration in liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) (6,7).

In this study, we evaluated the effects of immunosuppressive therapy on mortality in patients followed in the intensive care units (ICU) due to critical COVID-19 pneumonia. We compared patients who received immunosuppressive therapy with those who did not, in terms of 1-month mortality.

Methods

Study Design, Population

Retrospectively, 362 patients diagnosed with critical COVID-19 pneumonia in the tertiary ICUs between 10 March 2020 and 1 June 2021 were included in the study. The study was approved by University of Health Sciences Turkey, Ümraniye Training and Research Hospital Clinical Research Ethics Committee (approval number: 45, date: 10.02.2022). Inclusion criteria; a) being older than 18 years old, b) being positive for COVID-19 PCR, c) having new-emergent infiltration compatible with COVID-19 pneumonia on computed tomography, d) having critical-level covid pneumonia findings (the ones with respiratory failure PaO_2/FiO_2 <300 and/or shock, multiple organ failure). Exclusion criteria; a) being younger than 18 years old, b) being pregnant or breastfeeding, c) not having findings compatible with COVID-19 pneumonia on computed tomography, d) not having critical-level covid pneumonia findings (the ones with respiratory failure PaO_2/FiO_2 <300 and/or shock, multiple organ failure). SARS-CoV-2 detection was diagnosed by next-generation sequencing or real time-polymerase chain reaction method. The patients were divided into two groups: patients who received immunosuppressive therapy (patients who received only corticosteroids, patients who received only tocilizumab, and patients who received tocilizumab + corticosteroid) and patients who did not receive immunosuppressive therapy. The groups were compared in terms of clinical outcomes and 1-month mortality.

Corticosteroid Treatment Protocol

The corticosteroid treatment was administered at ≥40 mg/day methylprednisolone for at least 10 days to patients with PaO_2/FiO_2 <300 and/or with COVID-19 pneumonia findings requiring mechanical ventilator or high flow support at the time of admission, in line with the national guideline.

Tocilizumab Treatment Protocol

Tocilizumab treatment was administered at a dose of 800 mg/day immediately or 400 mg/day for two consecutive days in cases where procalcitonin is negative in patients with PaO_2/FiO_2 <300 and/or COVID-19 pneumonia findings requiring mechanical ventilator or high flow support, persistent fever, persistently high or increasing CRP and IL-6, ferritin values that are above the upper limits of normal and continue to increase (>700 µg/L), D-dimer elevation, lymphopenia, thrombocytopenia, and neutropenia with cytokine storm findings such as deterioration in liver function tests (ALT, AST, LDH) at the moment of application in line with the national guide.

Data Collection

The demographic and clinical characteristics, laboratory findings and treatment parameters of the patients were obtained from the hospital information operating system. The Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and Sequential Organ Failure Evaluation Score (SOFA) scores were recorded for all patients in their ICU hospitalizations. Blood, urine, and tracheal aspirate cultures (intubated patients) were taken from all patients with newly developed fever and increased procalcitonin levels. Newly developed fever and/or increase in procalcitonin values and culture positivity were accepted as the presence of secondary infection.

Statistical Analysis

The parametric test was used without a normality test due to the compatibility of the Central Limit Theorem. Non-parametric test statistics were used for laboratory measurement values with high deviations from the mean. Chi-square test and ANOVA-Tukey test were used to compare the means of two groups. Chi-square test statistics were used to evaluate the relationship between categorical variables. The exposure ratio [odds ratio (OR)] of the variables thought to be related to mortality status was given.

Results

A total of 362 patients followed up in ICUs with a diagnosis of critical COVID-19 pneumonia were included in the study. The patients were divided into two groups: patients who received immunosuppressive therapy [n=249, 165 patients (45.5%) who received only corticosteroids, 25 patients (7%) who received only tocilizumab, and 59 patients (16.5%) who received tocilizumab + corticosteroid], and patients who did not receive immunosuppressive therapy such as corticosteroids or tocilizumab (n=113). The mean age of the patients who did not receive immunosuppressive therapy was higher than patients who received immunosuppressive therapy (72.1±15 vs 67.7±13 respectively, p=0.008). The patients who did not receive immunosuppressive therapy had higher SOFA scores than patients who received immunosuppressive therapy (5.92±2 vs 4.3±2 respectively, p<0.0001). No significant difference was found between the two groups in terms of APACHE-II scores, comorbidities, and invasive mechanical ventilation support (p>0.05). ICU length of stay (11.52±9 days vs 7.9±5 days respectively, p<0.0001) and total length of stay (17.4±12 days vs 12±8 days respectively, p<0.0001) were longer in patients who received immunosuppressive therapy. Secondary bacterial infections were detected in 25.1% (n=91) of the patients. The frequency of secondary infections was higher in the patients who received immunosuppressive therapy than patients who did not receive immunosuppressive therapy (28% vs 17% respectively, p=0.03). One hundred and ninety-two of the patients died (54.1%). There was no statistical difference between the groups in terms of 1-month mortality (p=0.38). The demographic and clinical characteristics of the patients are given in Table 1.

Table 1. Demographics and clinical characteristics of the patients

Variables		Total n=362 (%)	Patients who did not receive immunosuppressive therapy n=113 (%)	Patients who received immunosuppressive therapy n=249 (%)	p
Gender	Male	220 (60.8)	68 (60.2)	152 (61)	0.88*
	Female	142 (39.2)	45 (39.8)	97 (39)	
Age (year)	Mean (SD)	69.1±14	72.1±15	67.7±13	**0.008**
APACHE-II	Mean (SD)	53.41±24	51.84±26	54.12±24	0.43
SOFA	Mean (SD)	4.81±2	5.92±2	4.3±2	**<0.0001**
ICU length of stay (day)	Mean (SD)	10.3±8	7.9±5	11.52±9	**<0.0001**
Total length of stay (ICU + clinic) (day)	Mean (SD)	15.7±11	12±8	17.4±12	**<0.0001**
Comorbidities	Yes	316 (87.3)	101 (89.4)	215 (86.3)	0.42
	No	46 (12.7)	12 (10.6)	34 (13.7)	
COPD	Yes	96 (26.5)	29 (25.7)	67 (26.9)	0.8
	No	266 (73.5)	84 (74.3)	182 (73.1)	
CAD	Yes	95 (26.2)	43 (38.1)	52 (20.9)	**0.001**
	No	267 (73.8)	70 (61.9)	197 (79.1)	
DM	Yes	138 (38.1)	47 (41.6)	91 (36.5)	0.36
	No	224 (61.9)	66 (58.4)	158 (63.5)	
CHF	Yes	65 (18)	30 (26.5)	35 (14.1)	0.004
	No	297 (82)	83 (73.5)	214 (85.9)	
CRF	Yes	53 (14.6)	21 (18.6)	32 (12.9)	0.15
	No	309 (85.4)	92 (81.4)	217 (87.1)	
Cancer	Yes	42 (11.6)	14 (12.4)	28 (11.2)	0.75
	No	320 (88.4)	99 (87.6)	221 (88.8)	
HT	Yes	205 (56.6)	63 (55.8)	142 (57)	0.82
	No	157 (43.4)	50 (44.2)	107 (43)	
Neurological disease	Yes	80 (22.1)	33 (29.2)	47 (18.9)	**0.03**
	No	282 (77.9)	80 (70.8)	202 (81.8)	
Arrhythmia	Yes	35 (9.7)	15 (13.3)	20 (8)	0.12
	No	327 (90.3)	98 (86.7)	229 (92)	
Secondary infection	Yes	91 (25.1)	20 (17.7)	71 (28.5)	**0.03**
	No	271 (74.9)	93 (82.3)	178 (71.5)	
IMV support	Yes	173 (47.8)	48 (42.6)	125 (50.2)	0.33
	No	189 (52.2)	65 (57.4)	124 (49.8)	
Death	Yes	196 (54.1)	65 (57.4)	131 (52.6)	0.38
	No	166 (45.9)	48 (42.6)	118 (47.4)	

(*: chi-square test/**: ANOVA-Tukey) p is significant at the level of <0.05. SD: Standard deviation; APACHE-II: Acute physiology and chronic health evaluation, SOFA: Sequential organ failure evaluation, ICU: Intensive care unit, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, CHF: Congestive heart failure, CRF: Chronic renal failure, DM: Diabetes mellitus, HT: Hypertension, IMV: Invasive mechanical ventilation

The subgroup comparison of patients who received only corticosteroids, who received only tocilizumab and who received tocilizumab + corticosteroid with patients who did not receive immunosuppressive therapy is shown in Table 2. The patients who received only tocilizumab had the lowest APACHE-II scores, and the patients who received corticosteroid + tocilizumab had the lowest SOFA scores (p<0.0001). ICU length of stay (day) and total length of stay (ICU + clinic) were the longest in patients who received corticosteroid + tocilizumab and in patients who received only tocilizumab respectively (p<0.0001). The patients who received only tocilizumab had fewer comorbid diseases than the other groups (p=0.02). The most common secondary bacterial infection was detected in patients who received tocilizumab + corticosteroids (n=25, 42.2%). There was no statistical difference between the groups in terms of mortality (p=0.45).

Age (OR) 1.01, 95% confidence interval [(CI: 95%) 1.001-1.03], the presence of comorbid disease (OR: 2.23, 95% CI: 1.18-4.22), the presence of secondary bacterial infection (OR: 3.56, 95% CI: 2.08-6.08), total length

Table 2. Clinical and demographic characteristics of patients according to the type of immunosuppressive therapy they received

Variables		Total (n=362) (%)	Patients who did not receive immunosuppressive therapy (n=113) (%)	Patients who received only corticosteroid (n=165) (%)	Patients who received only tocilizumab (n=25) (%)	Patients who received corticosteroid + tocilizumab (n=59) (%)	p	Difference
Gender	Male	220 (60.8%)	68 (60.2%)	91 (55.2%)	17 (68%)	44 (74.6%)	**0.06***	NA
	Female	142 (39.2%)	45 (39.8%)	74 (44.8%)	8 (32%)	15 (25.4%)		
Age (year)	Mean (SD)	69.1±14	72.1±15	69.7±14	63.5±12	63.9±12	**0.001****	B, c<a d<b
APACHE-II	Mean (SD)	53.41±24	51.84±26	57.65±24	34.45±21	52.57±22	**<0.0001****	c<a d<b
SOFA	Mean (SD)	4.81±2	5.92±2	4.65±2	4.08±1	3.42±1	**<0.0001****	B, d<a
ICU length of stay (day)	Mean (SD)	10.3±8	7.9±5	10.5±7	12.6±15	13.8±8	**<0.0001****	a<b, d b<d
Total length of stay (ICU + clinic) (day)	Mean (SD)	15.7±11	12±8	16.05±9	22.3±24	19.11±10	**<0.0001****	a<b, d b<c
Comorbidities	Yes	316 (87.3)	101 (89.4)	148 (89.7)	17 (68)	50 (84.7)	**0.02***	NA
	No	46 (12.7)	12 (10.6)	17 (10.3)	8 (32)	9 (15.3)		
COPD	Yes	96 (26.5)	29 (25.7)	46 (27.9)	6 (24)	15 (25.4)	0.96	
	No	266 (73.5)	84 (74.3)	119 (72.1)	19 (76)	44 (74.6)		
CAD	Yes	95 (26.2)	43 (38.1)	34 (20.6)	4 (16)	14 (23.7)	**0.006***	
	No	267 (73.8)	70 (61.9)	131 (79.4)	21 (84)	45 (76.3)		
DM	Yes	138 (38.1)	47 (41.6)	61 (37)	9 (36)	21 (35.6)	0.83	
	No	224 (61.9)	66 (58.4)	104 (63)	16 (64)	38 (64.4)		
CHF	Yes	65 (18)	30 (26.5)	30 (18.2)	2 (8)	3 (5.1)	**0.003***	
	No	297 (82)	83 (73.5)	135 (81.8)	23 (92)	56 (94.9)		
CRF	Yes	53 (14.6)	21 (18.6)	25 (15.2)	-	7 (11.9)	0.11	
	No	309 (85.4)	92 (81.4)	140 (84.8)	25 (100)	52 (88.1)		
Cancer	Yes	42 (11.6)	14 (12.4)	26 (15.8)	-	2 (3.4)	**0.02***	
	No	320 (88.4)	99 (87.6)	139 (84.2)	25 (100)	57 (96.6)		
HT	Yes	205 (56.6)	63 (55.8)	97 (58.8)	11 (44)	34 (57.6)	0.57	
	No	157 (43.4)	50 (44.2)	68 (41.2)	14 (56)	25 (42.4)		
Neurological disease	Yes	80 (22.1)	33 (29.2)	40 (24.2)	3 (1.2)	4 (6.8)	**0.004***	
	No	282 (77.9)	80 (70.8)	125 (75.8)	22 (88)	55 (93.2)		
Arrhythmia	Yes	35 (9.7)	15 (13.3)	17 (10.3)	-	3 (5.1)	0.12	
	No	327 (90.3)	98 (86.7)	148 (89.7)	25 (100)	56 (94.9)		
Secondary infection	Yes	91(25.1)	20 (17.7)	42 (25.5)	4 (16)	25 (42.4)	**0.003***	
	No	271(74.9)	93 (82.3)	123 (74.5)	21 (84)	34 (57.6)		
IMV support	Yes	173 (47.8)	48 (42.6)	73 (44.3)	16 (64)	36 (61.1)	**0.04***	
	No	189 (52.2)	65 (57.4)	92 (55.7)	9 (36)	23 (38.9)		
Death	Yes	196 (54.1)	65 (57.4)	88 (53.3)	10 (40)	33 (55.9)	0.45	
	No	166 (45.9)	48 (42.6)	77 (46.7)	15 (60)	26 (44.1)		

(*: chi-square test/**: ANOVA-Tukey), p is significant at the level of <0.05. SD: Standard deviation, APACHE-II: Acute physiology and chronic health evaluation, SOFA: Sequential organ failure evaluation, ICU: Intensive care unit, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, CHF: Congestive heart failure, CRF: Chronic renal failure, DM: Diabetes mellitus, HT: Hypertension, IMV: Invasive mechanical ventilation, NA: Not applicable, a: Patients who did not receive immunosuppressive therapy, b: Patients who received only corticosteroid, c: Patients who received only tocilizumab, d: Patients who received corticosteroid + tocilizumab

of stay (ICU + clinic) (OR: -0.95, 95% CI: 0.93-0.98), APACHE-II scores (OR: 1.02, 95% CI: 1.01-0.03), SOFA scores (OR: 1.36, 95% CI: 1.23-1.5) were statistically associated with increased mortality (p<0.05) (Table 3).

Discussion

The most important finding of our study was that there was no difference in mortality between patients who received immunosuppressive therapy and those who did not, in patients who followed up with the diagnosis

Table 3. Factors related to mortality in all patients

Variables	Odds ratio	Lower (95% CI)	Upper (95% CI)	p
Age	1.01	1.001	1.03	p<0.05
Comorbidities	2.23	1.18	4.22	p<0.05
Secondary infection	3.56	2.08	6.08	p<0.05
Total length of stay (ICU + clinic) (day)	-0.95	0.93	0.98	p<0.05
APACHE-II	1.02	1.01	0.03	p<0.05
SOFA	1.36	1.23	1.5	p<0.05

(Odds ratio) p is significant at the level <0.05. APACHE-II: Acute physiology and chronic health evaluation, SOFA: equential organ failure evaluation, ICU: Intensive care unit, CI: confidence interval

of critical COVID-19 pneumonia in the ICUs. Another important finding was that the frequency of secondary bacterial infections in patients who received immunosuppressive therapy was higher than in patients who did not receive immunosuppressive therapy and this was associated with increased mortality.

Cytokine storm syndrome is a hyperinflammatory condition characterized by increased cytokine levels and multiple organ failure. This hyperinflammatory response is shown as the most important cause of organ failure and mortality in COVID-19 patients and prevention of this hyperinflammatory response is considered one of the most important steps in the treatment (8,9). Corticosteroids, IL-6 and IL-1 inhibitors are the most commonly used agents for treating cytokine storm. However, the efficacy and safety of these drugs in the cytokine storm due to COVID-19 is still a matter of debate. In a meta-analysis involving 15,710 COVID-19 patients, it was shown that corticosteroid use does not have a positive effect on clinical recovery and mortality, and it was reported that one should be careful in terms of side effects (10). In another meta-analysis involving 20,197 COVID-19 patients, it was shown that although corticosteroid use increases the risk of secondary infection, it significantly reduces mortality (11). In the only randomized controlled study on the use of corticosteroids in COVID-19 patients, it was shown that corticosteroid use in severe COVID-19 patients reduces mortality by 35%, but there was no benefit in mild COVID-19 patients (12). In a meta-analysis including 5,776 patients evaluating the efficacy of tocilizumab use in COVID-19 patients, sufficient evidence could not be obtained regarding the clinical efficacy and safety of tocilizumab in COVID-19 patients (13). Similarly, Salvarani et al. (14) found that tocilizumab had no effect on clinical worsening in their randomized controlled study comparing patients treated and untreated with tocilizumab. Hamed et al. (15) showed that the concomitant use of corticosteroids and tocilizumab has no effect on mortality. In our study, we did not find any difference in mortality between the patients followed in the ICUs who received immunosuppressive therapy and the patients who did not receive immunosuppressive therapy. This situation may be related to the severity of the COVID-19 and the excess of comorbid diseases of the patients.

Giacobbe et al. (16) found that the use of tocilizumab and/or steroids in critically ill COVID-19 patients increases the frequency of hospital-acquired infections. van Paassen et al. (11), in their meta-analysis including 20,197 COVID-19 patients, showed that the use of corticosteroids increases the risk of secondary infections and that more antibiotics were needed in these patients. In another meta-analysis, it was reported that the frequency of secondary bacterial infections was higher in patients using tocilizumab, but this was not statistically significant (17). In our study, the frequency of secondary infections was higher in patients who received immunosuppressive therapy in ICUs, and this was associated with increased mortality. The most common secondary infection was in patients who received corticosteroid and tocilizumab together (42%).

Study Limitations

The study strengths are that the number of patients in the groups was sufficient to make an assessment and that the first and second outcomes of the treatments were evaluated on separate arms by evaluating all treatment arms separately. The most important limitation of our study was the retrospective analysis of the cases. For this reason, the groups could not be standardized and the APACHE-II and SOFA scores of the patients at admission to the ICU were different. This situation may affect the generalizability of our results.

Conclusion

In this single-center retrospective study, no difference in mortality was found between patients who received immunosuppressive therapy and those who did not, in patients followed up with critical COVID-19 pneumonia in the ICUs. The frequency of secondary bacterial infections in patients who received immunosuppressive therapy was higher than in patients who did not receive immunosuppressive therapy.

Ethics Committee Approval: The study was approved by University of Health Sciences Turkey, Ümraniye Training and Research Hospital Clinical Research Ethics Committee (approval number: 45, date: 10.02.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - Ö.A., İ.G.E.İ., K.C.; Concept - Ö.A., İ.G.E.İ., K.C., G.K.K., C.Ö., B.Ş.; Design - Ö.A., İ.G.E.İ., K.C., G.K.K., C.Ö., B.Ş.; Data Collection or Processing - Ö.A., İ.G.E.İ., K.C., G.K.K., C.Ö., B.Ş.; Analysis or Interpretation - Ö.A., İ.G.E.İ., K.C., G.K.K., C.Ö., B.Ş.; Literature Search - Ö.A., İ.G.E.İ., K.C., G.K.K., C.Ö., B.Ş.; Writing - Ö.A., İ.G.E.İ.

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