ORIGINAL ARTICLE

Comparison of Anakinra and Tocilizumab in Anticytokine Therapy in the Treatment of Coronavirus Disease-2019

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Abstract

Background: It is known that coronavirus disease-2019 (COVID-19) pneumonia causes cytokine storm, and treatment modalities are being developed on inhibition of proinflammatory cytokines. We aimed to investigate the effects of anticytokine therapy on clinical improvement and the differences between anticytokine treatments.

Materials and methods: A total of 90 patients with positive COVID-19 polymerase chain reaction (PCR) test were divided into three groups, group I ($n = 30$) was given anakinra, group II ($n = 30$) was given tocilizumab, and group III ($n = 30$) was given standard treatment. Group I was treated with anakinra for 10 days; tocilizumab, intravenously, was given in group II. Group III patients were selected from those who did not receive any anticytokine treatment other than the standard treatment. Laboratory values, Glasgow coma scale (GCS), and PaO_2/FiO_2 values were analyzed on days 1, 7, and 14.

Results: The seventh-day mortality rates were 6.7% in group II, 23.3% in group I, and 16.7% in group III. In group II, the ferritin levels on the 7th and 14th days were significantly lower ($p = 0.004$), and the lymphocyte levels on the seventh day were significantly higher ($p = 0.018$). Examining the changes between the first intubation days, in the early period (seventh day), group I was found to be 21.7%, group II was 26.9%, and group III was 47.6%.

Conclusion: We observed the positive effects of the use of tocilizumab on clinical improvement in the early period; mechanical ventilation requirement was delayed and at a lower rate. Anakinra treatment did not change mortality and PaO_2/FiO_2 rates. Mechanical ventilation requirements occurred earlier in the patients who were not receiving any anticytokine therapy. Studies with larger patient populations are needed to demonstrate the potential efficacy of anticytokine therapy.

Keywords: Anakinra, Coronavirus disease-2019, Cytokine, Tocilizumab.

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Highlights

- Coronavirus disease-2019 still remains a major problem in the world.
- The efficacy of anticytokine drugs in the treatment is promising.
- We observe that tocilizumab is more effective than anakinra.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19, and is characterized by severe respiratory failure. It shows a clinical course ranging from asymptomatic mild upper respiratory tract disease to severe diseases that require intensive care unit (ICU) support treatments.[1] Such variability in disease severity shows that individual immune responses to SARS-CoV-2 play an important role.

Cytokines are small molecular weight, soluble proteins released by immune system cells and play several roles in the regulation of immune system responses, such as protective immune response against invisible factors, inflammatory response, and tissue healing.[2] It has been shown that interleukin-1 and -6 (IL-1 and IL-6) levels are elevated in the plasma of severely ill patients with COVID-19, and high concentrations of IL-1 and IL-6 increase the risk of mechanical ventilation requirement.[3,4] High fever, high ferritin levels, and high C-reactive protein (CRP) levels can be perceived as cytokine proinflammatory in the peripheral circulation and cause cytokine release syndrome (CRS).[5] Therefore, the blockade of these cytokine storm markers seems to be a new hope in treatment. There are studies showing that the use of anticytokines in COVID-19 pneumonia reduces mortality by preventing respiratory failure and the mechanical ventilation requirement and that it should be an alternative in treatment.[6,7]

Anakinra is a 17 kilo dalton (KD) IL-1 receptor antagonist (IL-1Ra)[8] that inhibits both IL-1α and IL-1β signal transduction. It may be effective in sepsis and macrophage activation syndrome (MAS), and studies have been conducted on this subject.[9] Its clinical similarities with MAS and sepsis in severe patients with COVID-19 suggest that anakinra can be used in the treatment.

Tocilizumab is a monoclonal antibody that inhibits the receptors of IL-6, which rises as an acute phase reactant.[10] The primary stimulator of CRP in the case of inflammation is IL-6 and

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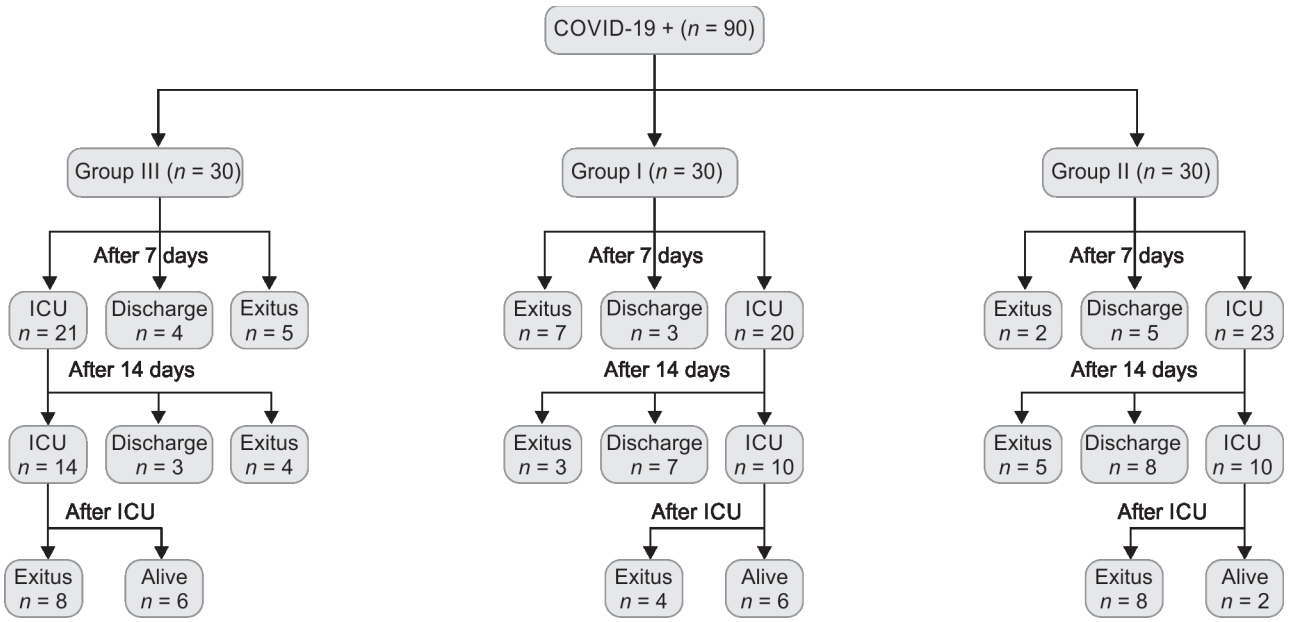
Flowchart 1: Flowchart of the treatment groups



it is shown that blocking this proinflammatory marker is effective in decreasing the progression of inflammation.[11] Therefore, it is believed that there may be an alternative treatment such as anakinra in COVID-19 pneumonia.

The aim of this study is to investigate the effects of anticytokine treatments on mortality, mechanical ventilation requirement, and PaO_2/FiO_2 rates in patients admitted to ICU with COVID-19 pneumonia and to observe the differences between anticytokine treatments.

Materials and Methods

This study was carried out retrospectively in 90 patients in the ICU of Yozgat City Hospital between 1 March 2019 and 10 January 2022; patients were those who tested positive for COVID-19 PCR test, clinical symptoms, and ground glass densities in thorax CT. After the ethical approval of the study (No. 2017-KAEK-189_2022.01.27_02), the data of the patients were analyzed retrospectively. Informed consent, and off-label or foreign drug use permissions were obtained from all patients in all groups receiving anticytokine therapy. The patients who were referred or died within the first 24 hours of hospitalization, younger than 18 years of age, and pregnant patients were excluded from the study. The study had three groups, namely, group III of 30 patients had standard COVID-19 treatment but no anticytokine treatment, group I of 30 patients had anakinra treatment, and group II of 30 patients had tocilizumab treatment in addition to standard treatment (Flowchart 1).

Standard treatment included favipiravir (1,600 mg i.v. on day 1, 1,200 mg i.v. on other days, completed for at least 5 days), glucocorticoid (80 mg/day i.v.), antibiotics, anticoagulants, and supportive fluids.

Group I patients had 600-mg subcutaneous anakinra treatment thrice a day for 10 days in addition to the standard treatment.

Group II patients had 400-mg intravenous tocilizumab treatment once a day for 2 days in addition to the standard treatment.

Glasgow coma scale, PaO_2/FiO_2 ratios, ferritin and lymphocyte values, mechanical ventilation requirement, inotropic support, and chronic diseases were noted on the first day of the treatment. In order to observe the early response, the same parameters were recorded on the seventh day. To evaluate the long-term responses, the same parameters of all patients were examined on the 14th day, and the treatment responses were analyzed according to the days. All patients with acute respiratory failure with GCS <8 or spontaneous respiratory rate above 35/min or below 8/min, PaO_2 <60, $PaCO_2$ >55 were intubated.

Our primary aim is to observe whether anticytokine therapy is effective in COVID-19 disease. Our secondary aim is to contribute to the choice of which anticytokines may be preferred as an alternative treatment in COVID-19 disease. There is not enough evidence in the literature in this area and that our study may contribute to the literature.

Statistical Analysis

Number cruncher statistical system (NCSS) program was used for statistical analysis. The descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used while evaluating the study data. The conformity of the quantitative data to the normal distribution was tested with the Shapiro–Wilk test and graphical examinations. One-way analysis of variance (ANOVA) and binary evaluations with Bonferroni correction were used for comparisons between groups of more than two normally distributed quantitative variables. Kruskal–Wallis test and Dunn–Bonferroni test were used for comparisons between groups of more than two quantitative variables that did not show normal distribution. The Friedman test was used for in-group comparisons of quantitative variables that did not show normal distribution, and the Wilcoxon signed-ranks test with Bonferroni correction was used for the evaluation of pairwise comparisons. Pearson Chi-squared test and Fisher–Freeman–Halton test were used to compare qualitative data. Kaplan Meier Survival

Table 1: Evaluation of descriptive characteristics according to treatment types

	Treatments				
	Anakinra	*Tocilizumab*	*Standard*	*Total*	*p-value*
Age					
Mean ± SD	57, 17 ± 15, 65	58, 27 ± 11, 43	67, 03 ± 12, 61	60, 82 ± 13, 92	[a]0.009**
Median (Min–Max)	58 (24–79)	60 (34–78)	68, 5 (32–87)	63, 5 (24–84)	
Gender					
Female	11 (36, 7)	14 (46, 7)	14 (46, 7)	39 (43, 3)	[b]0.665
Male	19 (63, 3)	16 (53, 3)	16 (53, 3)	51 (56, 7)	
Chronic disease					
–	9 (30, 0)	10 (33, 3)	6 (20, 0)	25 (27, 8)	[b]0.487
+	21 (70, 0)	20 (66, 7)	24 (80, 0)	65 (72, 2)	
Steroids					
–	0 (0, 0)	0 (0, 0)	5 (16, 7)	5 (5, 6)	[c]0.051
250 mg	11 (36,7)	20 (66, 7)	6 (20, 0)	37 (41, 1)	
500 mg	7 (23, 3)	0 (0, 0)	2 (6, 7)	9 (10, 0)	
1,000 mg	12 (40, 0)	10 (33, 3)	17 (56, 7)	39 (43, 3)	
Antiviral treatment					
–	1 (3, 3)	0 (0, 0)	5 (16, 7)	6 (6, 7)	[c]0.044*
+	29 (96, 7)	30 (100, 0)	25 (83, 3)	84 (93, 3)	
Mortality					
Discharged	14 (46, 7)	15 (50, 0)	13 (43, 3)	42 (46, 7)	[b]0.875
Death	16 (53, 3)	15 (50, 0)	17 (56, 7)	48 (53, 3)	
Time					
Mean ± SD	13, 07 ±10, 05	14, 43 ± 9, 98	16, 60 ± 13, 52	14, 70 ± 11, 27	[d]0.641
Median (Min–Max)	10 (4–55)	10 (4–43)	13,5 (3–67)	11 (3–67)	

analysis and log-rank test were used to evaluate the survival. Statistical significance was accepted as $p < 0.05$.

Results

The study was conducted with a total of 90 cases, 43.3% ($n = 39$) female and 56.7% ($n = 51$) male. The ages of the subjects ranged from 24 to 87 years, with an average of 60.82 ± 13.92 years. A statistically significant difference was found between the ages of the cases according to the treatment modalities ($p = 0.009$). According to the results of the pairwise comparison made to determine the difference, the ages of the patients who were treated with standard treatment were found to be significantly higher than those who were treated with anakinra and *Tocilizumab* ($p = 0.025$) (Table 1). There was no statistically significant difference between the groups in terms of the gender distribution of the cases and the presence of chronic disease ($p > 0.05$).

There was no statistically significant difference in the distribution of pulse steroid intake levels between the groups ($p > 0.05$).

The rates of mechanical ventilation requirement on the days 1, 7, and 14 of the cases participating in the study did not show a statistically significant difference between the groups ($p > 0.05$). In the analysis of the changes in intubation status on the seventh day compared to the first day, 21.7% of the new intubated cases were found in group I, 26.9% in group II, and 47.6% in group III, but this was not statistically significant ($p < 0.05$). (Table 2). In group III, the increase in the rate of mechanical ventilation requirement on the 7th day compared to the first day is remarkable.

The rates of inotropic drug requirement on the first, seventh, and fourteenth days of all cases did not show a statistically significant difference in terms of treatment modalities ($p > 0.05$). Considering the changes in the rates of inotropic drug requirement on the seventh day compared to the first day, it was 8.7% in the group I; there were 23.1% cases of new support in group II and 19% in group III, but this was not statistically significant ($p > 0.05$).

Lymphocyte measurements on days 1 and 14 did not show a statistically significant difference between the groups ($p > 0.05$). However, a statistically significant difference was found between the lymphocyte measurements on the seventh day ($p = 0.018$). According to the results of the pairwise comparison made to determine the difference, the seventh-day lymphocyte value of the patients in group II was found to be significantly higher than the other groups ($p = 0.030$) (Table 3).

All groups did not show a significant difference in terms of GCS values ($p > 0.05$). In terms of PaO_2/FiO_2 ratios, there was an increase in the seventh day values compared to the first day in both groups I and II, but it was not found to be statistically significant ($p > 0.05$).

When the ferritin values of the cases were compared, a decrease was observed in groups I and II. While the decrease in group I was not statistically significant ($p > 0.05$), a statistically significant difference was found between the first-, seventh-, and fourteenth-day ferritin measurements of group II patients ($p = 0.004$) (Table 3). When the results of the pairwise comparisons made to determine the difference were analyzed, it was found that the mean decreases of 89.76 ± 298.47 units on the seventh day and 193.55 ± 427.56 units on the fourteenth day according to the ferritin values of the cases on the first day were significant ($p = 0.009$; $p = 0.017$).

Table 2: Evaluation of mechanical ventilation requirement and inotropes usage according to treatment types

	Treatments				
	Anakinra	*Tocilizumab*	*Standard*	*Total*	*p-value*
Inotrope usage					
First day					
–	27 (93, 1)	26 (86, 7)	27 (90, 0)	80 (89, 9)	[c]0.907
+	2 (6, 9)	4 (13, 3)	3 (10, 0)	9 (10, 1)	
Seventh day					
–	20 (87, 0)	18 (69, 2)	16 (76, 2)	54 (77, 1)	[b]0.335
+	3 (13, 0)	8 (30, 8)	5 (23, 8)	16 (22, 9)	
Fourteenth day					
–	4 (40,0)	6 (46,2)	10 (66,7)	20 (52,6)	[b]0.360
+	6 (60,0)	7 (53,8)	5 (33,3)	18 (47,4)	
Early period (first- to seventh-day change) ($n = 70$)					
Continued	21 (91,3)	20 (76,9)	17 (81,0)	58 (82,9)	[c]0.420
Started	2 (8,7)	6 (23,1)	4 (19,0)	12 (17,1)	
Mechanical ventilation					
First day ($n = 90$)					
–	25 (83, 3)	24 (80, 0)	27 (90, 0)	76 (84, 4)	[c]0.666
+	5 (16, 7)	6 (20, 0)	3 (10, 0)	14 (15, 6)	
Seventh day ($n = 70$)					
–	15 (65, 2)	15 (57, 7)	9 (42, 9)	39 (55, 7)	[b]0.318
+	8 (34, 8)	11 (42, 3)	12 (57, 1)	31 (44, 3)	
Fourteenth day ($n = 38$)					
–	1 (10, 0)	4 (30, 8)	7 (46, 7)	12 (31, 6)	[c]0.167
+	9 (90, 0)	9 (69, 2)	8 (53, 3)	26 (68, 4)	
Early period (first- to seventh-day change) ($n = 70$)					
Continued	18 (78, 3)	19 (73, 1)	11 (52, 4)	48 (68, 9)	[c]0.149
Started	5 (21, 7)	7 (26, 9)	10 (47, 6)	22 (31, 4)	

An increase in ferritin values was observed on the seventh day of the patients in Group III, but it was not statistically significant ($p > 0.05$).

When the early period (seventh day) mortality rates were examined, it was found that 23.3% in group A, 6.7% in group II, and 16.7% in group III. Although the percentage of early mortality was low in group II patients, there was no difference between the groups in terms of seventh day mortality ($p > 0.05$). When the mortality rates on the fourteenth day were examined, it was 33.3% in group I, 23.3% in group II, and 30% in group III, and no difference was found ($p > 0.05$) (Table 4).

The survival analyses of all patients were examined; 14 patients (46.7%) out of 30 patients in group I survived, the mean survival time was 21.74 ± 4.33 days; 15 patients (50.0%) out of 30 patients in group II survived, 13 cases (43.3%) out of 30 patients in group III survived, and the mean survival time was 27.26 ± 5.32 days. When the survival rates between the groups were evaluated with the log-rank test, there was no statistically significant difference between the survival rates ($p = 0.555$) (Fig. 1).

Discussion

Many studies have been conducted recently on the fact that cytokine storm and anticytokine therapy are closely related to the course of the disease in COVID-19 pneumonia.[12,13] Based on these studies, we retrospectively compared the patients whose treatment we added tocilizumab and anakinra to those who received standard treatment. We did not find any significant difference in survival and mortality between the groups, but the early mortality rates were lower in the tocilizumab group compared to the other groups. In a similar study, the effects of tocilizumab and standard treatment on 28th day mortality were compared and they reported that there was no statistical difference, but the clinical improvement was observed in the tocilizumab group.[14] In the study of Declercq et al. showed that tocilizumab did not shorten the clinical recovery time or improve the supportive endpoints in the disease course of hypoxic patients with COVID-19 and larger sample groups are needed.[5] In our study, group II patients progressed with low rates of early mortality, but no significant difference was found in survival. We think that this is due to the fact that the clinics of the patients in the ICU are not the same and the response they give to other negative factors such as concomitant infection in the following periods may vary according to the treatments.

Anakinra treatment was associated with a relative reduction of 70% in the incidence of severe respiratory failure.[15] In a retrospective analysis by Cavalli et al., severe COVID-19 patients were treated with high-dose anakinra (5 mg/kg twice daily), and the treatment was associated with a 72% clinical improvement and a significantly higher survival rate.[16] An increase was observed in PaO_2/FiO_2 ratios in group I at early period, but the same increase was not observed in the fourteenth-day results. Considering the increasing number of patients receiving inotropic support in group I, we think that anakinra may trigger organ damage as a result of immunosuppression and septicemia and may be the reason for this

Table 3: Evaluation of lymphocyte, GCS, PaO_2/FiO_2 and ferritin measurements according to treatment types

	Treatments				
	Anakinra	*Tocilizumab*	*Standard*	*Total*	*p-value*
Lymphocyte					
First day					
n	30	30	30	90	[d]0.357
Mean ± SD	0, 42 ± 0, 2	0, 57 ± 0, 84	0, 59 ± 0, 46	0, 53 ± 0, 56	
Median (Min–Max)	0, 4 (0, 2–0, 9)	0, 4 (0, 1–4, 9)	0, 4 (0, 1–2, 1)	0,4 (0, 1–4, 9)	
Seventh day					
n	23	25	21	69	[d]0.018*
Mean ± SD	0, 46 ± 0, 24	0, 89 ± 0, 96	0, 55 ± 0, 61	0, 64 ± 0, 7	
Median (Min–Max)	0, 4 (0, 2–0,9)	0, 6 (0, 2–5)	0, 3 (0, 1–2, 7)	0, 4 (0, 1–5)	
Fourteenth day					
n	10	11	15	36	[d]0.089
Mean ± SD	0, 39 ± 0, 31	0, 76 ± 0, 57	0, 5 ± 0, 36	0, 55 ± 0, 44	
Median (Min–Max)	0, 3 (0, 1–1)	0, 6 (0, 2–2, 2)	0, 3 (0, 2–1, 4)	0, 4 (0, 1–2, 2)	
GCS					
First day					
n	30	30	30	90	[d]0.041*
Mean ± SD	11, 63 ± 1, 65	12, 03 ± 2, 13	12, 27 ± 1, 36	11, 98 ± 1, 74	
Median (Min–Max)	12 (8–14)	13 (5–13)	13 (8–13)	13 (5–14)	
Seventh day					
n	23	24	21	68	[d]0.402
Mean ± SD	12, 3 ± 3, 21	12, 25 ± 3, 35	11, 14 ± 3, 23	11, 93 ± 3, 26	
Median (Min–Max)	15 (8–15)	15 (6–15)	10 (6–15)	13 (6–15)	
Fourteenth day					
n	10	11	15	36	[d]0.376
Mean ± SD	8, 6 ± 2, 99	9, 91 ± 3, 48	10, 93 ± 3, 6	9, 97 ± 3, 44	
Median (Min–Max)	8 (4–15)	8 (6–15)	10 (6–15)	9 (4–15)	
PaO_2/FiO_2					
First day					
n	30	30	30	90	[a]0.567
Mean ± SD	77, 9 ± 15, 52	75, 87 ± 24, 15	74, 17 ± 11, 05	75, 98 ± 17, 63	
Median (Min–Max)	78, 5 (46–110)	74 (35–150)	73 (51–98)	76 (35–150)	
Seventh day					
n	23	25	21	69	[a]0.350
Mean ± SD	81, 17 ± 22, 61	82, 32 ± 37, 96	73, 81 ± 15, 33	79, 35 ± 27, 51	
Median (Min–Max)	71 (41–120)	72 (32–150)	81 (41–98)	74 (32–150)	
Fourteenth day					
n	10	11	15	36	[d]0.217
Mean ± SD	63, 8 ± 25, 94	68, 09 ± 32, 73	79, 87 ± 24, 54	71, 81 ± 27, 76	
Median (Min–Max)	56 (40–120)	56 (36–140)	73 (40–120)	68 (36–140)	
Ferritin					
First day					
n	30	30	30	90	[d]0.255
Mean ± SD	669, 63 ± 412, 96	599, 3 ± 464, 08	560, 43 ± 480, 99	609, 79 ± 450, 77	
Median (Min-Max)	500 (20-1503)	421,5 (32-1520)	376 (51-1572)	433,5 (20-1572)	
Seventh day					
n	23	25	21	69	[d]0.455
Mean ± SD	507, 83 ± 380, 16	462, 88 ± 430, 33	606, 9 ± 492, 58	521, 7 ± 432, 5	
Median (Min–Max)	402 (37–1,570)	328 (43–1,580)	412 (44–1,591)	397 (37–1,591)	
Fourteenth day					
n	10	11	15	36	[d]0.787
Mean ± SD	616, 2 ± 512, 04	441, 27 ± 409, 32	506, 93 ± 456, 95	517, 22 ± 451,07	
Median (Min–Max)	366, 5 (88–1,573)	307 (115–1, 507)	372 (80–1, 542)	350, 5 (80–1, 573)	

Table 4: Evaluation of mortality rates on days 7 and 14 according to treatment types

	Treatments			
	Anakinra (n = 30)	*Tocilizumab (n = 30)*	*Standard (n = 30)*	*p-value*
Seventh day				
Mortality (+)	7 (23, 3)	2 (6, 7)	5 (16, 7)	[c]0.234
Mortality (–)	23 (76,7)	28 (93,3)	25 (83,3)	
Fourteenth day				
Mortality (+)	10 (33,3)	7 (23,3)	9 (30,0)	[b]0.685
Mortality (–)	20 (66,7)	23 (76,7)	21 (70,0)	

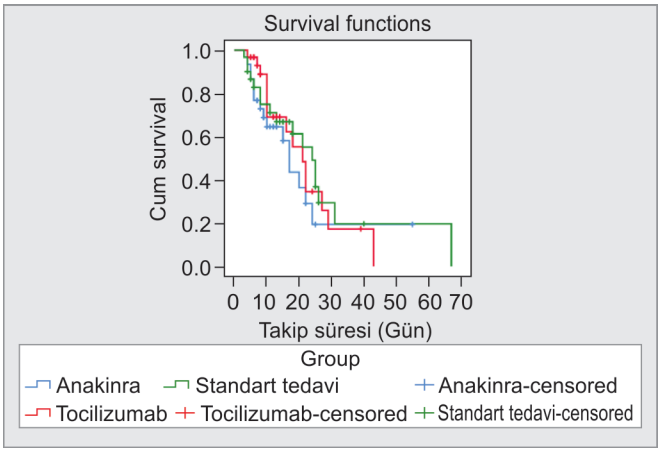


Fig. 1: Graph of survival analysis by treatment types

difference between the seventh and fourteenth days. In a study, it was shown that the early administration of anakinra as soon as the inflammatory pulmonary response occurs provides a rapid recovery in patients with COVID-19 pneumonia.[17] There are also observational cohort studies reporting that anakinra treatment has more positive effects at higher doses.[16] Kharazmi et al. reported in their study that anakinra significantly reduced mechanical ventilation requirement; no increase in the risk of infection due to anakinra use and a decrease in the length of hospital stay in patients given anakinra.[18] Similar positive effects were observed in another study in which anakinra treatment was given, and they emphasized that this may be related to route of administration.[19] Considering all these, the time, dose, and route of administration of the drug are of great importance for anakinra treatment.

In our study, ferritin values, which are known to contribute to cytokine release, decreased on the seventh day in the anakinra group, and we think that further research with larger sample groups needed. In the early period results of group II patients, an increase in lymphocyte levels and a decrease in ferritin values were found to be statistically significant. In this study, it is possible to say that it suppresses cytokine release more when compared with other groups. Comparing the early and late mortality rates, it shows that group II patients have the lowest mortality rate. However, when the long-term survival analyses are examined, no significant difference was found between the groups. In the comparison of early and late mortality rates, it was determined that group II had the lowest mortality rate. However, when the long-term survival analyses were examined, no significant difference was found between the groups. Similar to our findings, several studies using anti-IL-6 drugs have reported that although IL-6 blockade provides less mechanical ventilation requirement, it does not result in better survival.[20,21] Rosas et al., in their study on 452 patients, emphasized that the 28-day treatment results of tocilizumab did not differ on mortality.[22] Similarly, Salvarani et al. reported in their study that tocilizumab treatment did not make a significant difference on mortality and clinical improvement when compared to the placebo group.[23] In the literature, there are many studies concluding that the use of tocilizumab, either alone or with corticosteroids or antiviral drugs, makes significant contributions to clinical improvement and significantly reduces mortality.[24–26]

In the RECOVERY study, they reported that IL-6 blockade with the use of high-dose corticosteroids is more effective than the use of low-dose corticosteroid or corticosteroid-free treatment.[27] There are studies suggesting that medium to high-dose steroid regimens lead to a greater reduction in mortality, organ dysfunction, and mechanical ventilation requirement compared to low-dose regimens in ICU COVID-19 patients.[28] On the contrary, it is known that being late in starting corticosteroid treatment further deepens the hyperinflation picture and accelerates the progression to ARDS.[29] Since we do not know the exact time of starting corticosteroid treatment, we attribute the higher need for inotropes in group II patients compared to other groups in our findings. Considering all this information, we cannot give clear information about the role of tocilizumab in the treatment of COVID-19. Many variables such as dose, onset time, and medications to be given or patient clinic may have caused different results from tocilizumab treatment.

There are studies reporting that central nervous system (CNS) manifestations may be present in COVID-19 pneumonia, neuroradiological changes can be observed and this correlates with GCS values.[30–32] In our study, no difference was found in terms of GCS values. It is thought that one reason for this may be due to the fact that CNS manifestations has not yet been observed when the patients administered to the ICU. In addition, intubated patients had sedation and a real meaningful GCS assessment could not be made, which may have affected our results.

There are many studies on whether anticytokine therapy is beneficial or ineffective.[33,34] Although we could not show statistically that anticytokine therapy reduces mortality and the requirement for mechanical ventilator and increases survival between the groups, we showed that the percentage of early mechanical ventilator requirement is much higher in group III patients.

There are limitations in this study. Due to the fact that the study was retrospective, there were methodological limitations, especially the inability to provide randomization. Since the treatment could not be applied to the patients who did not meet the anticytokine treatment admission requirements, a small sample group in which the treatment was applied in this limited time was determined.

It is believed that more precise information will be obtained with prospective studies with larger sample sizes. Negative factors such as existing chronic diseases of the patients, gender and severity of pulmonary parenchymal damage could not be standardized. There was no definite information about the starting time of corticosteroid and anticytokine treatments; our study could not exactly analyze how it affects the treatment response. The long-term effects of the study, which was limited to 14 days, could not be compared, since the effect of bacterial and fungal diseases that may accompany long-term ICU patients on the results could not be compared. Studies with larger sample sizes are needed to determine the optimal dose and onset time, and we believe that our study will provide valuable information for future clinical trials.

Conclusion

As a result, it was observed that anticytokine therapy contributed to clinical improvement in the early period in ICU patients with COVID-19 pneumonia, and this was higher in the group given tocilizumab compared to those given anakinra. However, in our study comparing anakinra and tocilizumab, it was observed that anticytokine therapy was not superior to standard therapy in reducing the need for mechanical ventilation and in early mortality. Supporting this study with new cohort studies will increase the contribution.

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