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Efficacy of anticytokine treatments added to corticosteroids in patients with COVID-19-associated pneumonia and hyperinflammation: a single center experience

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Abstract. – OBJECTIVE: Pneumonia and hyperinflammatory state related to COVID-19 infection are fatal clinical conditions without definite treatment modalities. Interleukin-6 and Interleukin-1 targeted therapies have been proposed as treatment options. This study was conducted to investigate the efficacy of anakinra and tocilizumab added to corticosteroids in patients with COVID-19-associated pneumonia and hyper-inflammatory syndrome in our tertiary clinical center.

PATIENTS AND METHODS: Patients with COVID-19-associated pneumonia and hyperinflammatory state who did not respond to initial treatments, including corticosteroids, were included in the study. The patients' electronic records were reviewed retrospectively and recorded according to a standardized data table. Univariate and multivariate regression analyses were used to identify risk factors associated with intubation.

RESULTS: 388 patients were included in the study. 197 patients were intubated and most of them died (n=194/197, 98%). 67 patients received tocilizumab, and 97 patients received anakinra. Anakinra [OR: 0.440, 95% CI=0.244-0.794, *p*=0.006] and tocilizumab [OR: 0.491, 95% CI=0.256-0.943, *p*=0.033] were both associated with a decreased risk for intubation. However, having a neutrophil/lymphocyte ratio ≥ 10 [OR: 2.035, 95% CI=1.143-3.623, *p*=0.016], serum lactate dehydrogenase (LDH) level ≥ 400 [OR: 3.160, 95% CI=1.937-5.156, *p*<0.001] and age ≥ 50 [OR: 4.048, 95% CI=2.037-8.043, *p* < 0.001] was associated with an increased risk for intubation.

CONCLUSIONS: Both anakinra and tocilizumab, added to initial standard COVID-19 treatments (including glucocorticoids) reduced the need for intubation in patients with COVID-19-associated severe pneumonia and hyperinflammatory syndrome. Given the high mortality rate of intubated patients with COVID-19, both treatments may have added benefits on mortality.

Key Words:
COVID-19, Pneumonia, Hyperinflammation, Anakinra, Tocilizumab.

Abbreviations

PCR: Polymerase chain reaction; MAS: Macrophage Activation Syndrome; cHIS: Coronavirus Associated Hyperinflammatory Syndrome; LDH: Lactate dehydrogenase; AST: Aspartate aminotransferase; Il-1: Interleukin 1; Il-6: Interleukin 6; CRP: C Reactive Protein; CS: Corticosteroid; RCT: Randomized controlled trial.

Introduction

During the COVID-19 pandemic, treatment strategies have changed widely due to lack of experience and insufficient and conflicting data for the underlying pathophysiology of COVID-19-associated lung damage and hyper-inflammatory state. There is still no consensus on entitling this clinical condition due to its several similarities and discrepancies with the previous infection-related hyperinflammatory syndromes[1].

Clinicians struggled to manage severe COVID-19 cases due to the double edge sword character of the condition (infectious complications and hyper-inflammatory response occur together), and the lack of incisive treatment options.

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As a result, several classification and scoring systems have been proposed to identify patients with hyperinflammatory states and predict patients with high mortality risk[2-6].

Patients with COVID-19 and macrophage activation syndrome (MAS) share several clinical and laboratory features. They also have similar cytokine profiles with an increase in Il-1β, Il-6, Il-10, and TNF levels compared to healthy individuals[7-9]. Thus, drugs used to treat patients with MAS, such as corticosteroids, IL-1, and IL-6 inhibitors and intravenous immunoglobulin have been used for a while, although the lack of robust evidence.

In this study, we planned to share our experiences with these treatments in patients who developed COVID-19-associated pneumonia and hyperinflammatory state in our tertiary center.

Patients and Methods

The electronic records of the patients hospitalized in Istanbul Başaksehir Çam and Sakura City Hospital due to COVID-19 infection between November 2020 and April 2021 and who were consulted with the rheumatology clinic for the necessity of anti-cytokine treatment were investigated retrospectively. Demographic and clinical data of patients were recorded using the standard data table. Inclusion criteria for the study were: COVID-19 infection (having a PCR test positivity of combined nose/throat swab or presence of relevant clinical, laboratory, and lung imaging findings even if the PCR test is negative) with oxygen need requiring hospitalization and/or persistent acute phase reactant elevation. Coronavirus Associated Hyperinflammatory Syndrome (cHIS) score was calculated for all patients. CHIS scores have been developed and proposed to identify patients with hyperinflammatory states and predict patients with a high mortality risk by Webb et al[2].

The available anti-cytokine therapies during the study period in our center were anakinra and tocilizumab and administered to the patients according to a standardized protocol. Tocilizumab was administered with a dose of 400-800 mg once (in one and two divided doses). Anakinra started with a dose of 600 mg/day and continued with a dose de-escalation protocol for ten days. The choice between anakinra and tocilizumab did not depend on a predefined standardized algorithm but on the clinician's judgment. Intubation was determined as the primary endpoint in the study. Patients with solid or hematological malignancies were not included in the multivariate regression model. The study was approved by the local ethics committee. The research adhered to the tenets of the Declaration of Helsinki, as amended in 2008.

Statistical Analysis

Statistical analyses were done using the SPSS software v. 22 (IBM Corp., Armonk, NY, USA). Visual histograms, probability plots, and analytical methods (Kolmogorov-Smirnov test) were used to analyze the variables' distribution and select the test method. Descriptive statistics were used for the non-normal distributed variables. For comparative analyses, the Student's *t*-test or one-way ANOVA was used for continuous variables, Chi-square or Fischer's Exact test for categorical variables. Multivariate logistic regression (forward: LR) was used to determine the factors associated with intubation. A p-value < 0.05 was considered statistically significant. No imputation method was used for missing values, and analyses were done for each variable's reported number of patients.

Results

388 patients [M/F:1.4] were included in the study after excluding 6 patients due to the lack of data. The median age was 63 [IQR: 52-71] and 80% (309/388) of the patients were over 50 years old. 35% [116/338] had at least two comorbidities. Hypertension was the most common comorbid condition [47.9%]. 94% of the patients [363/388] had a cHIS score equal to or more than 2 points, and 89.7% [348/388] of the patients met severe pneumonia criteria. The demographic and clinical characteristics of the patients and laboratory features are shown in Table I and Table II.

All patients received at least 1 mg/kg prednisolone (or equivalent) of CS (Corticosteroid), and 86.6% received pulse CS. The number of patients who received tocilizumab and anakinra was 67/388 (17.3%) and 97/388 (25%), respectively. The median time to receive anti-cytokine treatment after COVID-19 symptom onset was 14 days [for tocilizumab IQR: 10-16, for anakinra IQR: 11-19], and 14% were intubated when they received treatment.

Table I. Demographic and clinical features of patients.

	All patients, N = 388	Patients who were intubated	Patients who were not intubated
Age, median, (IQR)	63 (52-71)	66 (58-73)	58 (48-67)
Number of patients according to the age, n/N (%)			
< 50 years old	79 (20.4)	19 (9.6)	60 (31.4)
≥ 50 years old	309 (79.6)	178 (90.4)	131 (68.6)
Gender, n/N (%)			
Male	250 (64.4)	127 (64.5)	123 (64.4)
Female	138 (35.6)	70 (35.5)	68 (35.6)
Lung parenchyma involvement, n/N (%)			
< 50%	42 (10.8)	11 (5.6)	31 (26.2)
≥ 50%	346 (89.2)	186 (94.4)	160 (83.8)
Number of patients using immunosuppressives before COVID-19, n/N (%)	29 (7.5)	18 (9.1)	179 (90.9)
Number of patients with comorbidities, n/N (%)			
Rheumatic disease	11 (2.8)	3 (1.5)	8 (4.2)
Active solid cancer	20 (5.2)	17 (8.6)	3 (1.6)
Active hematological cancer	9 (2.3)	9 (4.6)	0
Heart failure	25 (6.4)	17 (8.6)	8 (4.2)
Ischemic heart disease	64 (16.5)	40 (20.3)	24 (12.6)
Obstructive lung disease	51 (13.1)	30 (15.2)	21 (11)
Hypertension	186 (47.9)	104 (52.8)	82 (42.9)
Diabetes mellitus	142 (36.6)	75 (38.1)	67 (35.1)
Renal failure (chronic or acute)	73 (18.8)	44 (22.3)	29 (15.2)
Having at least 2 comorbidities	136 (35.1)	78 (39.6)	58 (30.4)
Number of patients with severe pneumonia, n/N (%)	348 (89.7)	196 (99.5)	152 (79.6)
Pulse CS, n/N (%)	336 (86.6)	169 (85.8)	167 (87.4)
Number of patients received tocilizumab, n/N (%)	67 (17.3)	24 (12.2)	43 (22.5)
Time of between COVID-19 symptoms and tocilizumab, days, median (IQR)	14 (10-16)	12 (10-15)	14 (10-16)
Number of patients according to the time of between COVID-19 symptoms and tocilizumab			
≤ 14, n/N (%)	31 (8)	11 (50)	20 (47.6)
> 14, n/N (%)	33 (8.5)	11 (50)	22 (5.4)
Number of patients received anakinra, n/N (%)	97 (25)	43 (21.8)	54 (28.3)
Duration between COVID-19 symptoms and anakinra, days, median (IQR)	14 (11-19)	16 (11-20)	14 (10.5-16.5)
Number of patients according to the time between COVID-19 symptoms and anakinra			
≤ 14, n/N (%)	49/385 (12.7)	18 (43.9)	31 (58.5)
> 14, n/N (%)	45/385 (11.7)	23 (56.1)	22 (41.5)
Number of patients who were intubated when they received anticytokin, n/N (%)	23 (5.9)	20 (29.9)	3 (3.1)
Number of patients received plasmapheresis, n/N (%)	48 (12.4)	39 (19.8)	9 (4.7)
Number of patients who received IVIG, n/N (%)	57 (14.7)	44 (22.3)	13 (6.8)
Hospitalization time, days, median (IQR)	17 (12-25)	16 (12-24)	18 (12-27)
Follow-up time in ICU, days, median (IQR)	9 (2-16)	13 (8-19)	10 (7-15)

IVIG: intravenous immunoglobulin, ICU: intensive care unit, CS: corticosteroid.

In multivariate analyses, patients who received tocilizumab [OR: 0.491, 95% CI=0.256-0.943, p = 0.033] and anakinra [OR: 0.440, 95% CI=0.244-0.794, p = 0.006] had a reduced risk of intubation compared to patients who did not receive. Having a neutrophil/lymphocyte ratio ≥10 [OR: 2.035, 95% CI=1.143-3.623, p=0.016], serum LDH level ≥ 400 U/L [OR: 3.160, 95% CI=1.937-5.156, p<0.001] and age ≥ 50 [OR: 4.048, %95 CI=2.037-8.043, p<0.001] were associated with an increased risk of intubation. Independent predictors of intubation according to the results of multivariate regression analysis are shown in Table III.

Table II. Laboratory features of the patients.

	All patients, N = 388	Patients who were intubated	Patients who were not intubated
Neutrophil counts, $\times 10^6$/per L, median [IQR]	9,710 (6,142-13,937)	11,670 (6,925-16,385)	12,360 (5,850-11,480)
Number of patients according to Neutrophil counts			
< 10,000, n/N (%)	183 (47.2)	83 (42.1)	122 (63.9)
≥ 10,000, n/N (%)	205 (52.8)	114 (57.9)	69 (36.1)
Lymphocyte counts, $x10^6$/per L, median [IQR]	540 (390-870)	490 (310-735)	700 (440-930)
Number of patients according to neutrophil /lymphocyte ratio		23 (12-41)	12.3 (7.6-20.6)
< 10, n/N (%)	110 (28.4)	39 (10.8)	71 (37.2)
≥ 10, n/N (%)	278 (71.6)	158 (80.2)	120 (62.8)
Platelet count, $\times 10^9$/per L, median [IQR]	249 (833-1,800)	240 (165-326)	255 (182-361)
Number of patients according to platelet counts			
< 110, n/N (%)	29 (7.5)	16 (8.1)	13 (6.8)
≥ 110, n/N (%)	359 (92.5)	181 (91.9)	178 (93.2)
AST, U/L, median [IQR]	33 (22-48)	33 (23-50)	33 (21-47)
Number of patients according to AST value			
< 100, n/N (%)	363 (93.6)	183 (92.9)	180 (94.2)
≥ 100, n/N (%)	25 (6.4)	14 (7.1)	11 (5.8)
ALT, U/L, median [IQR]	32 (19-58)	32 (18-53)	32 (19-60)
Number of patients according to ALT value			
< 60, n/N (%)	297 (76.5)	153 (77.7)	144 (75.4)
≥ 60, n/N (%)	91 (23.5)	44 (22.3)	47 (24.6)
LDH, U/L, median [IQR]	469 (349-630)	551 (401-709)	421 (299-534)
Number of patients according to LDH value			
< 400, n/N (%)	194/387 (50)	72 (36.2)	123 (64.4)
≥ 400, n/N (%)	193/387 (49.7)	125 (63.8)	68 (35.6)
CRP, mg/L, median [IQR]	100.75 (47-163)	123 (60-190)	87 (37-142)
Number of patients according to CRP value			
< 100, n/N (%)	193 (49.7)	83 (42.1)	110 (57.6)
≥ 100, n/N (%)	195 (50.3)	11 (57.9)	81 (42.4)
Procalcitonin, ng/mL, median [IQR]	0.26 (0.1-0.68)	0.31 (0.18-0.88)	0.17 (0.07-0.47)
Number of patients according to procalcitonin value			
< 0.5, n/N (%)	118/386 (30.4)	73 (37.2)	45 (23.7)
≥ 0.5, n/N (%)	268/386 (69.1)	123 (62.8)	145 (76.3)
Ferritin, ng/mL, median [IQR]	937 (465-1,803)	993 (544-1,843)	827 (395-1,724)
Number of patients according to ferritin value			
< 1000, n/N (%)	180/387 (46.4)	99 (50.3)	108 (56.8)
≥ 1000, n/N (%)	207/387 (53.4)	98 (49.7)	82 (43.2)
D-dimer, µgFEU/mL, median [IQR]	1.47 (0.8-3.96)	1.85 (1-5.67)	1.15 (0.62-2.44)
Number of patients according to D-dimer value			
< 2.5, n/N (%)	183/373 (47.2)	109 (58)	74 (40)
≥ 2.5, n/N (%)	190/373(49)	79 (42)	111 (60)
IL-6, pg/mL, median [IQR]	47.6 (18-131)	75.6 (33-278)	21.1 (9.9-56.6)
Number of patients according to IL-6 value			
< 15, n/N (%)	19/95 (4.9)	4 (6.8)	15 (41.7)
≥ 15, n/N (%)	76 /95 (19.6)	55 (93.2)	21 (58.3)

AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CRP: C- reactive protein, IL-6: interleukin-6.

Discussion

According to our results, 89% of the patients included in this study had COVID-19-associated severe pneumonia and 94% had a high cHIS score. In addition, the mortality rate was 56% and the intubation rate was 51% in the study. The mortality rate was 98% among intubated patients. It was noteworthy that the patients included in the study were high-risk patients. This study showed that the intubation and mortality rate of COVID-19-associated pneumonia is quite high, and both anakinra and tocilizumab reduce the intubation rate in the group of patients with COVID-19-associated severe pneumonia and hyperinflammation.

Due to the uncontrolled hyperinflammatory response during the COVID-19 infection, anti-inflammatory treatments, including CS and anti-cy-

Table III. Logistic-multivariate regression analyses for intubation, generally.

	OR (95% CI)	*p*-value
Neutrophil/lymphocyte ratio > 10	2.035 (1.143-3.623)	0.016
LDH ≥ 400	3.160 (1.937-5.156)	< 0.001
Tocilizumab	0.491 (0.256-0.943)	0.033
Anakinra	0.440 (0.244-0.794)	0.006
Age ≥ 50	4.048 (2.037-8.043)	< 0.001

LDH: lactate dehydrogenase, CI: confidence interval, OR: odds ratio.

tokines, have been at the center of the management strategy of this devastating pandemic. CS has been used as a standard initial treatment worldwide in many centers, as in our center, for patients with severe lung involvement and hyperinflammatory response[10-13]. However, there are conflicting results on the dose of CS and whether the pulse steroid has an additional benefit[14-16]. In our study, all patients received CS, and most patients (86.6%) received pulse CS treatment (250 mg or 1.000 mg methylprednisolon). Thus, we do not have a chance to assess the effect of CS in our patients. On the other side, tocilizumab and anakinra were used as second-line treatments to control hyperinflammatory response or severe pneumonia in our center, and they reduced the risk of intubation. We think intubation is an essential outcome in patients with COVID -19 because of the increased risk of mortality, as among patients intubated in our study (194/197, 98%). Several studies[17-21] support using anakinra in severe COVID-19 infections with reduced mortality and intubation rates, but there are also conflicting results. According to prospective, open-label study published by Balkhair et al[17], anakinra (200 mg/day for 3 days, followed by 100 mg/day for 7 days) reduced the need for mechanical ventilation in patients with severe COVID-19 associated pneumonia. In a randomized controlled study (RCT), published by Kharazmi et al[18], in patients admitted to the intensive care unit (ICU), anakinra (100 mg/day, maximum 14 days) reduced the need for mechanical ventilation due to severe COVID-19 infection. In the CORIMUNO-ANA-1 study[19], anakinra (400 mg/day for 3-6 days) did not reduce the need for non-invasive mechanical ventilation, high-flow oxygen, or mechanical ventilation in patients with COVID-19-associated mild and moderate pneumonia. A study by Declercq et al[20] showed that anakinra (100 mg/day for 28 days) did not shorten the recovery time in patients with COVID-19. Davidson et al[21] reviewed randomized controlled studies about the use of anakinra and another IL-1 inhibitor (canakinumab) in the treatment of COVID-19 infection and reported that there was insufficient evidence that these agents were beneficial in the treatment of COVID-19 infection. In our study, one-quarter of the patients [97/388] received anakinra, which effectively prevented intubation. It is unknown if the conflicting results are related to differences in treatment protocols and patient groups regarding disease severity and baseline demographics. But we should emphasize that the dose of anakinra used in our patients was distinctly higher than in the aforementioned studies above. However, patients included in our study had severe lung involvement and high cHIS, similar to previously reported studies.

The acceptability of tocilizumab in the treatment of COVID-19 associated pneumonia and hyperinflammatory syndrome appears to be higher than anakinra. It has been included in the standard treatments for eligible patients in multiple national treatment guidelines. In a RCT conducted by Salama et al[22], tocilizumab has been shown to reduce the need for mechanical ventilation in hospitalized patients. Gordon et al[23] reported that tocilizumab improved survival compared to standard care in patients who were followed ICU. However, two RCTs did not favor tocilizumab over standard care for COVID-19[24,25]. Also, meta-analyses have shown conflicting results on the effect of tocilizumab[26,27]. In contrast to studies[24-27] that previously reported unfavorable results with tocilizumab, in our study, 95% (64/67) of patients receiving tocilizumab had signs of COVID-19-associated severe pneumonia and a high cHIS score. In our study, tocilizumab was administered at a maximum dose of 800 mg. The dose of tocilizumab was similar to other studies in the literature. Our study determined that tocilizumab added to corticosteroids as an anti-inflammatory treatment reduced the need for intubation in patients with COVID-19-associated severe pneumonia and hyperinflammatory syndrome. Although it was difficult to compare with previous studies due to differences in patient selection criteria and the retrospective nature of our study, this result was consistent with most studies in the literature.

Limitations

Besides the study's retrospective design, the main limitation was including only patients who had consulted with us, which might have caused

selection bias because patients with milder clinical courses might not have been included. In addition, the severity of comorbidities mostly depended on patients' history but not on essential clinical investigations, and the severity of these conditions is lacking. Also, we do not have detailed data about the secondary bacterial or fungal infection or the history of acute thrombotic complications, which may have affected multivariate analyses.

Conclusions

Tocilizumab or anakinra added to corticosteroids (with standard care) reduced the intubation rate in patients with severe pneumonia and hyperinflammatory syndrome associated with COVID-19. This positive effect of anticytokine drugs in the treatment of COVID-19-associated hyperinflammation suggests that these drugs may be used in the treatment of hyperinflammation associated with other infections in the future.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

No funding.

Data Availability

The data of the study will be shared with those who want to access the data.

Ethical Statement

Ethical approval was obtained from the Başakşehir Çam ve Sakura City Hospital Ethics Committee, in Istanbul. The research adhered to the tenets of the Declaration of Helsinki, as amended in 2008.

Informed Consent

According to the local Ethical Guidelines, the need for patient consent was waived for data analysis due to the retrospective nature of the study, and the patients' anonymity was secured. However, informed consent was obtained from the patients for all drugs and interventions.

Authors' Contribution

Conception and design: Fatih YILDIRIM and Mustafa ERDOGAN. Material preparation and data collection: Fatih YILDIRIM, Mediha İrem ONAR, Melek YALCIN MUTLU and Ozan Cemal ICACAN. Statistical analyzes: Mustafa ERDOGAN. Manuscript preparation and writing: Fatih YILDIRIM. As a mentor, Cemal BES contributed at every stage throughout the entire study.

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