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Comparison of interleukin-6 receptor antagonist and pulse steroid therapy in critically ill patients with COVID-19: retrospective analysis

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ABSTRACT

Aims: Severe COVID-19 is characterized by acute respiratory distress syndrome (ARDS) accompanied by hypercytokinemia. In our study, we aimed to demonstrate the efficacy of the treatments interleukin-6 (IL-6) receptor antagonists and corticosteroids used in critically ill patients with COVID-19.

Methods: COVID-patients with cytokine storm (CS) treated in the intensive care unit between March 2020 and July 2021 were included in the study. Patients with increased neutrophil/lymphocyte ratio, lactate dehydrogenase, C-reactive protein (CRP), and ferritin and patients with oxygen saturations of 90% or lower, lymphopenia and fever were also considered in CS. Patients were divided into three groups: tocilizumab group, steroid group, standard treatment group.

Results: There was no statistically significant difference between the groups in terms of age and body-mass index (BMI) averages, gender ratios and concomitant diseases. There was no difference in mortality and the need for mechanical ventilation between the groups. On the other hand, the incidence of ventilator-associated pneumonia was higher in the pulse steroid group.

Conclusion: The close and early diagnosis of hypercytokinemia increase the success of the treatment, and accelerate to discharge from intensive care units. We think that it is important to select appropriate patients and pulse steroid is more suitable for use in CS because it is cheaper and more accessible.

Keywords: COVID-19, corticosteroids, ARDS, interleukin-6, tocilizumab

INTRODUCTION

Severe COVID-19 pneumonia is characterized by acute respiratory distress syndrome (ARDS) accompanied by a hypercytokinemia, as in inflammatory cytokine release syndrome (CRS) or hemophagocytic lymphohistiocytosis (HLH)/macrophage activation (MAS) syndrome.[1-7] Published studies have shown that this disruption of interferon signaling, called cytokine storm (CS), is related to inflammatory pathology and the severity of the disease.[8,9] Increased neutrophil/lymphocyte ratio, elevated C-reactive protein (CRP) levels, increased interleukin-6 (IL-6) levels were also associated with disease severity.[10-14]

IL-6 plays a central role in the inflammatory pathology of COVID-19, and there is a consistent association between increased cytokine levels and severe disease outcomes. Cytokine modulator therapies have been introduced to break this hyperinflammatory cycle. Reports from China and Italy, which were the most affected regions in early 2020, showed miraculous improvements with anti-IL-6 (tocilizumab) treatments. However, results from subsequent large-scale studies have shown that IL-6 modulation does not benefit every patient in the treatment of COVID-19.[15] Corticosteroids, like IL-6 antagonists, have been widely used in various doses

all over the world due to their immune modulatory properties, and the studies have been announced to the scientific world. The largest of these studies is the multicenter RECOVERY study conducted in England. This study that 6 mg dexomethasone given to hospitalized COVID-19 patients for an average of 7-10 days reduced 28-day mortality. This effect was more pronounced in patients receiving mechanical ventilation or oxygen support, but this positive effect did not occur in patients who did not require oxygen support.[16] After the meta-analysis of World Health Organization's (WHO) corticosteroid studies, WHO and our Ministry of Health added a low-dose steroid recommendation to the guide.[17-19]

In the next period high-dose corticosteroid treatments (pulse steroids) were started to be used in critical cases that did not respond to low-dose corticosteroid treatment, or needed intensive care due to worsening of pneumonia and rapid decrease in saturation. The first pulse steroid studies on this subject that mortality was reduced in severe COVID-19 patients.[20,21]

With the experience gained in the treatment of critically ill patients in intensive care units, IL-6 antagonists have started to be used in combination with steroids. There are some studies supporting the use of these two medications together, as well as studies showing that the treatment has no effect. It is also recommended to be used together with the results of active ongoing study groups.[22-26]

Laboratory tests are performed to assess the severity of the disease and to observe the patient's response to treatment. Parameters such as lymphocytes, neutrophils, LDH, CRP, and ferritin, which indicate the severity of inflammation, are frequently examined. The course of these values and their ratios to each other give the physician an idea about the development of hypercytokinemia and enable him to decide on a treatment plan.

In this study, we aimed to determine the effective treatment for severe pneumonia cases accompanied by hypercytokinemia, which we treated in our intensive care unit by examining the responses of IL-6 antagonist (tocilizumab) and pulse steroid therapy.

METHODS

Ethics committee approval was obtained from the Clinical Researches Ethics Committee of the Keçiören Training and Research Hospital (Date 28.09.2021, Decision No: 2372). The study was conducted according to the Helsinki Declaration.

The patients with CS were divided into three groups those who received an IL-6 receptor antagonist (n=14, tocilizumab 800 mg/day), pulsed corticosteroids (n=30, methylprednisolon 250 mg/day), control group (n=37) who were followed up with standard treatment without these treatments.

Blood samples were taken from the patients on the day of admission to the intensive care unit, during the hypercytokinemia period and afterwards. The results of the hemogram and biochemical tests at these times were analyzed.

Patients with increased neutrophil/lymphocyte ratio, high LDH, CRP, and ferritin (>700 ng/ml) levels, and those whose values continued to increase in consecutive measurements and patients with oxygen saturations of 90% or lower, lymphopenia and persistent fever (>38 C°) were also considered to be in CS. Patients' age, gender, weight, nutritional scores (nutric score), comorbidities, treatments, length of stay intensive care unit, acute physiology and chronic health evaluation (APACHE) II scores, lymphocytes, neutrophils, LDH, CRP, D-Dimer, ferritin levels, arterial blood gase analysis results, secondary infections, and mortality rates were recorded and analyzed.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation, categorical data as numbers and percentages. In the intergroup analysis of continuous variables, normality analyzes were performed with the Kolmogorov-Smirnov Goodness of Fit test. The Oneway ANOVA test (Post hoc: Bonferroni) was used for the analysis of data within normal distribution, and the Kruskal-Wallis test (Mann-Whitney U test with Bonferroni correction) was used for the analysis of data out of normal distribution. Comparisons of categorical data were made with the Chi-square test. Analyzes were performed with IBM SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). Statistical significance level was considered as $p<0.05$.

RESULTS

There was no statistically significant difference between the groups in terms of age and body-mass index (BMI) averages and gender ratios ($p>0.05$). The rates of patients with a nutric score of three or more were 57.1% in the tocilizumab group, 93.3% in the pulse steroid group, and 47.2% in the control group ($p=0.002$). There was no significant difference between the groups in terms of comorbidities like chronic obstructive pulmonary disease, asthma, hypertension, diabetes mellitus, coronary artery diseases, cerebrovascular disease, chronic kidney failure, and immunosuppressive use rates ($p>0.05$) (Table 1).

It was determined that length of stay in hospital, the intensive care unit and the ward (pre ICU), the partial oxygen pressure/oxygen fraction (P/F) ratios at ICU admission, and initial lactate values were statistically significantly higher in the tocilizumab group compared to the steroid group and the control group ($p<0.05$). The duration of mechanical ventilation was found to be statistically significantly higher in the tocilizumab group than in the steroid group (p: 0.019) (Table 2).

While there was no difference in the rate of nasocomial infection between the groups, the rate of ventilator-associated pneumonia was found to be highest in group receiving steroid treatment in terms of focus of infection (p:0.016). The most frequently detected bacteria in all groups was Acinetobacter baumannii (71.4-91.7%), followed by *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (Table 2).

In the tocilizumab group, the lymphocyte values after CS were found to be statistically significantly lower than the control group ($p=0.001$), and the ferritin values after CS were found to be significantly higher ($p=0.001$). Lymphocyte level during and after CS in the steroid group was found to be lower than the other two groups. Ferritin and LDH values after CS were found to be statistically significantly lower in the group receiving standard treatment compared to the control group ($p=0.001$, $p<0.001$, respectively) (Table 3).

Table 1. Comparison of the groups in terms of some socio-demographic and clinical characteristics

	Tocilizumab group (n=14)	Steroid group (n=30)	Standard treatment group (n=37)	p value
Age (mean+SD)	59.14±13.43	65.37±15.59	67.46±14.99	0.215*
BMI (kg/m²) (mean±SD)	30.48±5.20	30.90±5.89	30.21±6.75	0.904*
Gender (n,%)				
Female	4 (28.6%)	10 (33.3%)	17 (45.9%)	0.409**
Male	10 (71.4%)	20 (66.7%)	20 (54.1%)	
Nutric score (n, %)				
0				
1	6 (42.9%)	1 (3.3%)	12 (33.3%)	**0.002****
2	0 (0.0%)	1 (3.3%)	7 (19.4%)	
3	5 (35.7%)	16 (53.3%)	12 (33.3%)	
4	3 (21.4%)	12 (40.0%)	5 (13.9%)	
COPD (n, %)	3 (21.4%)	5 (16.7%)	3 (8.1%)	0.382**
Asthma (n, %)	2 (14.3%)	0 (0.0%)	4 (10.8%)	0.136**
HT (n, %)	4(28.6%)	17 (56.7%)	17 (45.9%)	0.404**
DM (n, %)	5 (35.7%)	16 (53.3%)	12 (32.4%)	0.144**
CAD (n, %)	1 (7.1%)	6 (20.0%)	7 (18.9%)	0.540**
CVD (n, %)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0.089**
CKD (n, %)	0 (0.0%)	3 (10.0%)	1 (2.7%)	0.252**
Favipiravir (n, %)	12 (85.7%)	29 (96.7%)	31 (83.8%)	0.228**

* Oneway ANOVA test, ** Chi-square test, SD: Standard deviation, BMI: Body-mass index, COPD: Chronic obstructive pulmonary disease, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary arterial disease, CVD: Cerebrovascular disease, CKD: Chronic kidney disease

Table 2. Comparison of the groups in terms of clinical parameters related to hospitalization and intensive care unit stay

	Tocilizumab group (n=14)	Steroid group (n=30)	Standard treatment group (n=37)	p value
LOS in hospital (day) (mean±SD)	30.48±5.20[a]	17.57±7.82[a]	25.38±17.07	0.003*
LOS in the ICU (day) (mean±SD)	23.64±16.27	13.17±7.78	19.16±17.49	0.063*
APACHE II score (mean±SD)	14.78±5.69	17.10±5.22	19.75±10.47	0.125*
LOS in the ward (day) [median (min-max)	4.5 (0-12)[b]	1 (0-7)[b]	1 (0-9)	0.016**
P/F ratio [median (min-max)]	143.5(63-295)[b]	74.5 (48-117)[b]	77 (42-250)[b]	0.002**
Initial lactate level [median (min-max)]	0.92(0.29-0.18)[b]	1.53(0.80-6.97)[b]	1.19 (0.08-11.7)	0.004**
MV (n, %)	8 (57.1%)	16 (53.3%)	22 (59.5%)	0,881***
MV support (day) [median (min-max)]	22 (17-59)	11 (1-33)	15.5 (1-84)	0.019**
Secondary infection (n, %)	4 (28.5%)	9 (30.0%)	12 (32.4)	0.957***
Infection type (n, %)				
VAP	0 (0.0%)	8 (100.0%)	6 (50.0%)	**0.016*****
UTI	1 (25.0%)	0 (0.0%)	0 (0.0%)	
Central catheter	1 (25.0%)	0 (0.0%)	3 (25.0%)	
Blood circulation	1 (25.0%)	0 (0.0%)	3 (25.0%)	
Surgical field	1 (%25.0)	0 (0.0%)	0 (0.0%)	
Microorganism (n, %)				
Klebsiella	0 (0.0%)	1 (14.3%)	1 (8.3%)	0.527***
Pseudomonas	1 (25.0%)	1 (14.3%)	0 (0.0%)	
Acinetobacter	3 (75.0%)	5 (71.4%)	11 (91.7%)	
Mortality (n, %)	4 (28.6%)	16 (53.3%)	15 (40.5%)	0.275***

* Oneway ANOVA test (aPostoc: Bonferroni corrected), ** Kruskal Wallis test (a,b Mann Whitney U test with Bonferroni correction), *** Chi-square test, LOS in hospital: Length of stay in hospital, LOS in ICU: Length of stay in the intensive care unit, LOS in ward: Length of stay in the ward (pre ICU), APACHE II score: Acute physiology and chronic health evaluation II score, P/F ratio: PaO_2/FiO_2 at admission to ICU, MV: Mechanical ventilation, VAP: Ventricle-associated pneumonia, UTI: Urinary tract infections, SD: Standard deviation, Min-max: Minimum-maximum

Table 3. Comparison of the groups in terms of some inflammatory markers

	Tocilizumab group (n=14)	Steroid group (n=30)	Standard treatment group (n=37)	p value
CRP*				
CS period	310 (42-469)	255 (95-384)	272 (68-491)	0.407**
Post CS	13.5 (1.5-218)	15 (2.2-124)	16 (0.12-223)	0.741**
Lymphocyte *				
CS period	375 (100-740)	330 (30-700)[b]	470(180-1770)[b]	**0.008****
Post CS	1370 (290-2330)[a]	1070 (310-11800)[b]	2410(660-5200)[a,b]	**<0.001****
Ferritin*				
CS period	1301.5(592-11391)	1242 (84-12286)	931 (178-4687)	0.546**
Post CS	429 (77-1470)[a]	445.5 (35-1296)[b]	225.5 (26-734)[a,b]	**0.001****
D-dimer*				
CS period	4265 (820-15440)	3670 (1220-35200)	4340(780-44980)	0.719**
Post CS	735 (220-2300)	625 (260-2120)	540 (170-2150)	0.090**
LDH*				
CS period	557.5(348-3315)	676 (309-2363)	621 (233-2851)	0.198**
Post CS	288 (172-669)	309 (161-806)[b]	228 (133-543)[b]	**<0.001****

* Values are given as median (minimum-maximum) initial value measured during hypercytokinemia,**Kruskal Wallis test (a,b Mann Whitney U test with Bonferroni correction), CS: Cytokine storm

DISCUSSION

In this study we examined COVID-19 patients who developed CS and were treated with pulse steroids or tocilizumab. The length of stay in hospital before intensive care unit, the length of stay in the intensive care unit, the P/F ratios and LDH levels of the patients who received tocilizumab were found to be high and the duration of mechanical ventilation was longer in the tocilizumab group.

In the meta-analysis of Tleyjeh et al.[15] investigating the efficacy and safety of tocilizumab in COVID-19 patients, a decrease was found in the length of hospital stay and mechanical ventilation, but no decrease in mortality in the short term. In addition, there was no increase in side effects and nosocomial infections, and these effects were thought to be important for reducing mortality. In our study, the length of hospital stay, intensive care unit stay and total hospital stay was longer in the tocilizumab group. However, it was the group with the lowest secondary infection rate. This might be related to the efficacy of infection control, despite long hospital stays in our hospital's intensive care unit and services.

Prior to the introduction of low-dose steroids into treatment guidelines, the RECOVERY preliminary report noted that various high doses were widely used and promising in the treatment of COVID-19 hypercytokinemia.[16] After RECOVERY, several studies have reported that pulse steroid reduces mortality in patients with hypercytokinemia who do not respond to low-dose steroids.[20,21] Although there was no difference in the rate of nosocomial infections in this patient group, the prevalence of ventilator associated pneumonia (VAP) in infections suggests that it prevents a decrease in mortality.[27] We think that these infections are due to the predisposition of steroids to serious infections.

A meta-analysis of 73 studies by Cano et al.[28] including 21350 cases stated that low-dose steroid administered in these patient groups reduced mortality, and that there was no difference in mortality and side effects between high-dose and low-dose. In our study, although there was no difference in the rate of nosocomial infections between our groups, there was a significant difference in the focus of nosocomial infections. VAP was more common in patients receiving pulse steroids. Since the target organ of the disease is the lung, VAP is primarily the expected nosocomial infection. It is thought that high VAP rates prevent a decrease in mortality rates. No difference was found between the groups in the agents in our study. The same agents were reported in similar patient groups.[29]

Limitations

Analyzing a small patient group from a single center can be considered as a limitation of our study. However, it is important for each center to conduct and share treatment analysis results, especially for specific diseases, in terms of creating a resource for meta-analyses. For this purpose, we believe that the results of our study will contribute to the literature.

CONCLUSION

With the use of low-dose corticosteroids in the treatment, hypercytocinemia was easily controlled in many patients, and the use of IL-6 antagonists and the need for intensive care were significantly reduced. Early treatment is also effective in the success of the treatment in the patient group who need intensive care due to their serious clinics and accelerates the process of discharge from these units. Although both treatment models have their shortcomings, we think that appropriate patient selection is important and because it is cheaper and more accessible, pulse steroids can be preferred in suitable patients in CS.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics committee approval was obtained from the Clinical Researches Ethics Committee of the Keçiören Training and Research Hospital (Date 28.09.2021, Decision No: 2372).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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