Clinics in Surgery

Research Article
Published: 30 Jul, 2021

Comparative Evaluation of Tocilizumab *vs*. High Dose Methylprednisolone Therapy in Mild Acute Respiratory Dyspnea Syndrome Related to COVID-19 Pneumonia: A Retrospective Cohort Study

Barış ÇİL* and Mehmet KABAK

Department of Chest Diseases, Mardin State Hospital, Turkey

Abstract

Coronavirus Disease 2019 (COVID-19) is a respiratory infection caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The underlying causes of severe COVID-19 are related to systemic inflammatory responses that can lead to lung damage. Tocilizumab and high-dose glucocorticoids are practically used in ARDS cases associated with COVID-19. Corticosteroids are inexpensive and easily available drugs compared to tocilizumab. There is no study comparing these two drugs, which are becoming widely used in treatment-unresponsive COVID-19 pneumonia. In this study, we wanted to compare the beneficial effects of tocilizumab and high-dose methylprednisolone therapy in mild Acute Respiratory Dyspnea Syndrome (ARDS) caused by COVID-19. The study included 152 patients who received two doses of tocilizumab 400 mg or pulsed methylprednisolone therapy (500 mg/day for three days) due to mild ARDS related to COVID-19 pneumonia. The two groups were compared in terms of age, gender, comorbid diseases, hospital stay, admission to intensive care unit, length of stay in the intensive care unit, intubation status, mortality, C-Reactive Protein (CRP) level, White Blood Cell (WBC) count, platelet, neutrophil, lymphocyte, ferritin and D-dimer levels. There was no statistically significant difference between the groups in gender, comorbid diseases, need for intubation, mortality and need for intensive care. There was no statistically significant difference between the groups in age, total length of hospital stay, length of stay in intensive care, CRP, WBC, platelet, neutrophil, lymphocyte counts, ferritin and D-dimer values. The average cost of tocilizumab therapy is $500 to $1000, while it is $30 in pulsed methylprednisolone treatment. The present study found that treatment with pulsed methylprednisolone which is cheap and easy to access can be a good alternative to tocilizumab therapy in mild ARDS related to COVID-19 pneumonia.

Keywords: COVID-19; Tocilizumab; Methylprednisolone

OPEN ACCESS

Correspondence:
Barış ÇİL, Department of Chest Diseases, Mardin State Hospital, Mardin, Turkey, Tel: 00905308750814; E-mail: drbariscil@hotmail.com

Received Date: *07 Jul 2021*
Accepted Date: *27 Jul 2021*
Published Date: *30 Jul 2021*

Citation:
Barış ÇİL, Mehmet KABAK. Comparative Evaluation of Tocilizumab vs. High Dose Methylprednisolone Therapy in Mild Acute Respiratory Dyspnea Syndrome Related to COVID-19 Pneumonia: A Retrospective Cohort Study. Clin Surg. 2021; 6: 3268.

Introduction

Coronavirus Disease 2019 (COVID-19) is a respiratory infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a newly emerging virus that was first detected in Wuhan/China [1]. Although the disease is mild to moderate, almost one third of patients are at risk of developing a more serious illness due to Acute Respiratory Distress Syndrome (ARDS). Mechanical Ventilation (MV) and the need to stay in the intensive care unit develop in almost one third of the patients. These patients with poor prognosis have an increased risk of developing Acute Respiratory Distress Syndrome (ARDS), which can lead to death. The mechanisms underlying severe COVID-19 are related to systemic inflammatory responses that can lead to lung injury and multisystem organ dysfunction [2,3]. Understanding the pathophysiology of cytokine storm in the treatment of COVID-19 pneumonia is important. Various immune cells such as T cells, B cells, Dendritic Cells (DCs) or macrophages are involved in this mechanism. Similarly, various inflammatory cytokines such as Tumor Necrosis Factor (TNF)-α, Type I and II Interferons (IFNs), Interleukin (IL)-1, IL-6, CCL2, or Monocyte Chemotactic Protein-1 (MCP-1) or immunosuppressive cytokines such as chemokines IL-10 or transforming growth factor-are included. Among these, attention has been paid to the activation of macrophages, particularly due to Macrophage Activation Syndrome (MAS) [4]. Based on this assumption, systemic anti-inflammatory drugs have been proposed as an alternative treatment tool to avoid the SARS-CoV-2-induced inflammatory

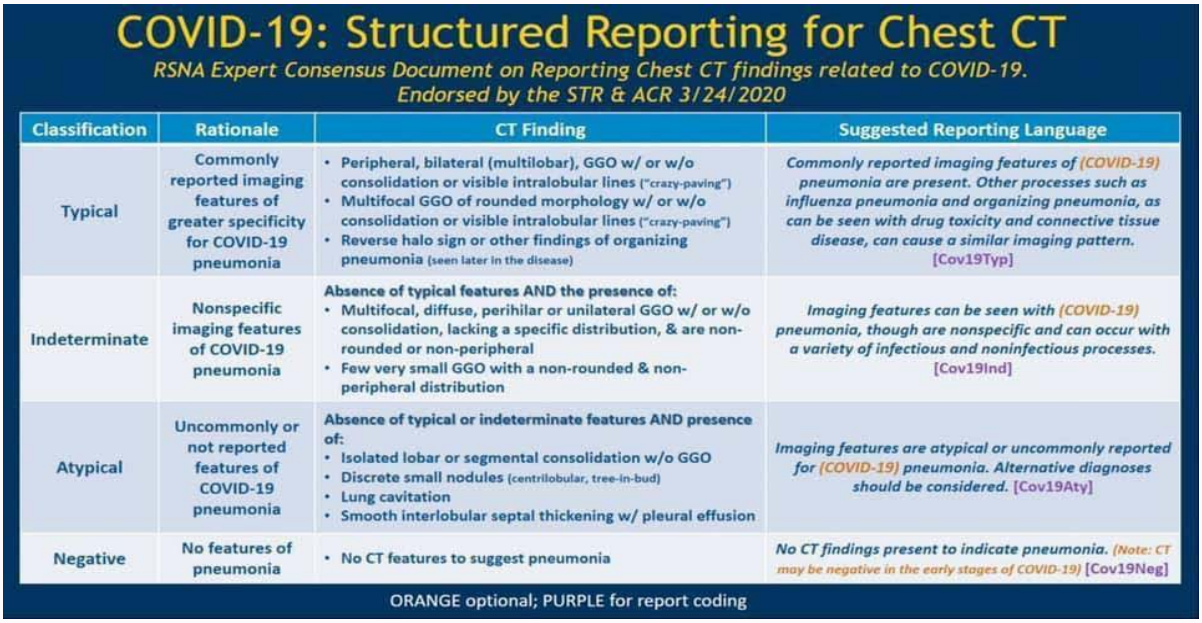

Figure 1: Consensus Statements on Chest Findings of COVID-19.

state and to reduce mortality in these patients [3,5-7]. Tocilizumab is a monoclonal antibody for IL-6 receptor and is now widely used in hospitals to treat COVID-19 [8,9]. The average price of a 400 mg vial of tocilizumab is $250 to $500, with an overall cost of $500 to $1000 for two doses. Thus, it is expensive and inaccessible. There are many studies supporting steroid treatment in COVID-19 and showing reduced mortality, ICU admission and the need for mechanical ventilation. Steroids are recommended for severe cases in China [10]. In addition, high dose glucocorticoids are used in practice in patients with ARDS associated with COVID-19 [11]. A 500 mg vial of methylprednisolone costs approximately $10. Corticosteroids are inexpensive and easily available drugs compared to tocilizumab. There is no study comparing these two drugs, which are becoming widely used in treatment-unresponsive COVID-19 pneumonia. The present study aimed to compare the benefits of tocilizumab and pulsed methylprednisolone which are among the treatment options in mild ARDS related to COVID-19 pneumonia. The mortality, length of hospital stay, need for intensive care, time spent in intensive care unit and need for intubation were compared in patients with mild ARDS who were treated with pulsed methylprednisolone (500 mg/day for 3 days) *vs.* tocilizumab.

Materials and Methods

During the pandemic, the first-line treatment in our hospital was administered as standard favipiravir, heparin, protein pump inhibitor and antibiotherapy. In our hospital, high-dose methylprednisolone or tocilizumab have been used in second-line treatment to patients who developed acute respiratory dyspnea syndrome due to COVID-19 and did not benefit from first-line treatment. The choice was entirely at the discretion of the doctor because there was no standard practice in this regard. The study started with the approval of a university's ethics committee. In this study, we have compared second-line treatments in COVID-19 pneumonia. The study included 152 patients who received two doses of tocilizumab 400 mg or pulsed methylprednisolone therapy (500 mg methylprednisolone/day for three days) due to mild ARDS related to COVID-19 pneumonia between 01-05-2020 and 01-12-2020. Patients with mild acute respiratory dyspnea syndrome due to COVID-19 pneumonia were selected retrospectively. The patients were divided into two groups; those who received tocilizumab 800 mg and those who received pulsed methylprednisolone (500 mg methylprednisolone/day for three days) therapy. The two groups were compared in terms of age, gender, comorbid diseases, hospital stay, admission to intensive care unit, length of stay in the intensive care unit, intubation status, mortality, C-Reactive Protein (CRP) level, White Blood Cell (WBC) count, platelet, neutrophil, lymphocyte, ferritin and D-dimer levels.

The inclusion criteria were as follows:

1. PCR positivity or thorax CT consistent with COVID-19 (Figure 1).

2. Patients who received first step (favipiravir, heparin, protein pump inhibitor and antibiotherapy) therapy for at least 5 days but were unresponsive to treatment and whose COVID-19 pneumonia progressed.

3. Patients with mild ARDS manifestations related to COVID-19 (200 mmHg<PaO2/FiO2<300 mmHg + PEEP or CPAP ≥ 5 cmH2O) (Figure 2).

The exclusion criteria were follows:

1. Receiving a single dose of tocilizumab, different dose methylprednisolone treatment other than 500 mg/day for 3 days, immune plasma therapy.

2. Those who receive treatment other than favipiravir, heparin, and protein pump inhibitor and antibiotherapy in initial treatment.

3. Age under 18 years.

Statistical analysis

Statistical analysis was performed using the SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The assumption of normal distribution of data was tested by kolmogorov-smirnov test. Descriptive statistics of continuous variables were shown with mean and Standard Deviation (SD) values. The Chi-square test was

Berlin Criteria for the Diagnosis of ARDS	
Timing	➢ New or worsening respiratory distress occurring within 1 week
Chest X-ray	➢ Bilateral opacities that cannot be explained with effusion, collapse or nodule
Source of edema	➢ Showing that respiratory distress is not due to heart failure or hypervolemia using objective criteria such as ECHO
Oxygenation	
• Mild	➢ 200 mmHg<PaO2/FiO2<300 mmHg +PEEP or CPAP ≥ 5 cmH2O
• Moderate	➢ 100 mmHg<PaO2/FiO2<200 mmHg + PEEP ≥ 5 cmH2O
• Severe	➢ PaO2/FiO2 ≤ 100 mmHg + PEEP ≥ 5 cmH2O

Figure 2: Berlin Criteria for the Diagnosis of ARDS.
Abbreviations: PaO2: Arterial Partial Oxygen Pressure; FiO2: Fractioned O2 in Inspired Air; CPAP: Continuous Positive Airway Pressure; PEEP: Positive End-Expiratory Pressure

used to compare nominal variables while Student's t test was used to compare the means values of scalar data between the two groups. The hypotheses are two-sided and $p \leq 0.05$ was considered statistically significant at 95% confidence interval.

Results

Of the 152 patients retrospectively reviewed between 01-05-2020 and 01-12-2020, 70 were treated with pulsed methylprednisolone and 82 were treated with tocilizumab. Comparisons of the parameters of the groups treated with pulsed methylprednisolone or tocilizumab are provided in Table 1, 2. There was no statistically significant difference between the groups in gender, comorbid diseases, need for intubation, mortality and need for intensive care (p>0.05). There was no statistically significant difference between the groups in age, total length of hospital stay, length of stay in intensive care, CRP, WBC, platelet, neutrophil, lymphocyte counts, ferritin and D-dimer values (p>0.05).

Discussion

In this study, no statistically significant difference has been found between the tocilizumab and pulsed methylprednisolone in patients developing mild ARDS related to COVID-19 pneumonia. A comparison between the two patient groups showed that there were no statistically significant difference in the length of hospital stay, the rate of need for intensive care, the length of stay in intensive care, and the rates of intubation and mortality (p<0.05). Similarly, no statistically significant difference was found between the two groups in age, comorbid diseases, ferritin levels, neutrophil values, lymphocyte values, platelet values, CRP and WBC levels which are other variables that may affect mortality, length of stay in the hospital and in the intensive care unit and status of intubation (p>0.05). There are many controversial therapies in COVID-19 as it is a new disease. Tocilizumab therapy has shown promising outcomes in COVID-19 pneumonia in subjects that were not responsive to treatment. Malgie et al. [12] published that tocilizumab treatment have reduced mortality by 12% in COVID-19 patients. Xiaoling et al. [9] also stated that tocilizumab was an effective treatment in COVID-19 pneumonia and reduced mortality. Similarly, in another study, 29 patients receiving tocilizumab treatment were compared with 58 patients receiving only routine care, and patients treated with tocilizumab have required less ventilation and extubation was performed at an earlier stage in more patients. Both the length of stay in the intensive care unit and the length of stay in the hospital were significantly shorter in patients treated with tocilizumab [13]. The relative benefits of tocilizumab compared to other immune modulator drugs have not yet been reported. In the literature, there are reports on high-dose glucocorticoids in COVID-19 pneumonia. In an intensive care study by Ramin Hamidi Farahani et al. including 29 patients, significantly higher systolic (P=0.018) and diastolic (P=0.001) blood pressures were detected in patients with high-dose methylprednisolone. Patients who were given high-dose methylprednisolone therapy had significantly (P<0.001) higher Glasgow Coma Scale (GCS) in the methylprednisolone group and with improvement in SpO2 in the methylprednisolone group, none of the patients required mechanical ventilation [11]. Guillermo Ruiz-Irastorza et al. stated that patients with respiratory distress that deepened with respiratory failure and who showed inflammatory activity might benefit from high-dose glucocorticoids. They pointed out that this group should be identified in the early period with good observation [14]. Wu et al. also showed that treatment with methylprednisolone in COVID-19 patients who developed ARDS was associated with a reduced risk of mortality (risk ratio: 0.38; 95% CI: 0.20-0.72) [15]. In another study with high-dose methylprednisolone and dexamethasone (1000 mg methylprednisolone for 3 days plus 8 mg dexamethasone for another 3 to 5 days), the treatment showed a rapid anti-inflammatory effect,

Table 1: Comparison of the parameters between the two groups.

	Pulsed Methylprednisolone n=70	Tocilizumab n=82	p
GENDER			
Female	14 (20%)	30 (36.6%)	0.1
Male	56 (80%)	52 (63.4%)	
Hypertension	24 (34.3%)	40 (48.8%)	0.2
Diabetes mellitus	10 (14.3%)	16 (19.5%)	0.5
Chronic Renal Failure	2 (2.9%)	4 (4.9%)	0.6
Heart failure	12 (17.1%)	4 (4.9%)	0.08
Chronic obstructive pulmonary disease	8 (11%)	6 (7%)	0.5
Other chronic diseases	4 (5%)	6 (7%)	0.7
Comorbid diseases			
Yes	38 (54.3%)	50 (60.9%)	0.5
No	32 (45.7%)	32 (39.1%)	
Need for intubation	12 (17.1%)	12 (14.6%)	0.7
Mortality	8 (11.4%)	8 (9.8%)	0.8
Need for intensive care	14 (20%)	18 (22%)	0.8

p ≤ 0.05 was considered statistically significant
There was no statistically significant difference between the groups in gender, comorbid diseases, need for intubation, mortality and need for intensive care (p>0.05)

Table 2: Comparison of the parameters between the two groups.

	Pulsed Methylprednisolone n=70 median (range min-max)	Tocilizumab n=82 median (range min-max)	P value
Age	67 (32 to 90)	65 (28 to 88)	0.3
Total length of hospital stay	13 (5 to 47)	13 (6 to 41)	0.7
Length of stay in intensive care	0 (0 to 10)	0 (0 to 24)	0.7
C Reactive Protein (CRP)	70 (11.30 to 254)	72.5 (4 to 306)	0.3
White Blood Cell (WBC)	8.1 (4,74 to 24,60)	9.56 (1.50 to 91)	0.5
Platelets	199 (112 to 486)	208 (88 to 373)	0.5
Neutrophils	6.80 (2.30 to 21.49)	7.94 (0.27 to 21.00)	0.4
Lymphocytes	0.88(0.21 to 2.73)	0.90 (0.23 to 5.90)	0.5
Ferritin	700 (82 to 1777)	807 (71.10 to 3669)	0.2
D-dimer	860 (315 to 7570)	785 (188 to 4420)	0.4

$p \leq 0.05$ was considered statistically significant

There was no statistically significant difference between the groups in age, total length of hospital stay, length of stay in intensive care, CRP, WBC, platelet, neutrophil, lymphocyte counts, ferritin and D-dimer values ($p>0.05$)

but it was also observed that it increased the risk of thromboembolism. Neutrophil/Lymphocyte ratio and D-dimer level [16]. On the other hand, there are also some studies that do not recommend treatment with high-dose glucocorticoids and tocilizumab [17-19]. The limitation of our study can be elaborated as the beneficial effects of these two treatment modalities seemed similar, we did not have enough data about their short-term and long-term adverse effects and we did not have a placebo group and the absence of a control group that did not receive both treatments. The average cost of tocilizumab therapy is $500 to $1000, while it is $30 in pulsed methylprednisolone treatment. The present study found that treatment with pulsed methylprednisolone was cheap and easy to access could be evaluated as an alternative to tocilizumab therapy in mild ARDS related to COVID-19 pneumonia. Future studies with control group are required to obtain more data on this topic.

ICMJE Statement

Barış Çil was responsible for the organization and coordination of the study. Barış Çil was the chief investigator and responsible for the data analysis. Barış Çil and Mehmet Kabak developed the study design. All authors contributed to the writing of the final manuscript. All members of the team contributed to the management or administration of the study.

Ethical Approval

Ethical approval was obtained from the ethics committee of Mardin Artuklu University Ethics committee number: 79906804-050.06.04.

References

1. World Health Organization. Novel coronavirus - China. Accessed 09 July 2020.
2. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43.
3. Vardhana SA, Wolchok JD. The many faces of the anti-COVID immune response. J Exp Med. 2020;217(6):e20200678.
4. Crayne CB, Albeituni S, Nichols KE, Cron RQ. The immunology of macrophage activation syndrome. Front Immunol. 2019;10:119.
5. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH across Speciality Collaboration, UK. COVID-19: Consider cytokine storm syndromes and immune suppression. Lancet. 2020;395(10229):1033-4.
6. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe Coronavirus Disease 2019 (COVID-19): The perspectives of clinical immunologists from China. Clin Immunol. 2020;214:108393.
7. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2- mediated inflammatory responses: From mechanisms to potential therapeutic tools. Virol Sin. 2020;35(3):266-71.
8. Potere N, Nisio MD, Cibelli D, Scurti R, Frattari A, Porreca E, et al. Interleukin-6 receptor blockade with subcutaneous tocilizumab in severe COVID-19 pneumonia and hyper-inflammation: A case-control study. Ann Rheum Dis. 2021;80(2):1-2.
9. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA. 2020;117(20):10970-5.
10. Zhao JP, Hu Y, Du RH, Chen ZS, Jin Y, Zhou M, et al. Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia. Zhonghua Jie He He Hu Xi Za Zhi. 2020;43(3):183-4.
11. Farahani RH, Mosaed R, Nezami-Asl A, Chamanara M, Soleiman-Meigooni S, Kalantar S, et al. Evaluation of the effectiveness of methylprednisolone pulse treatment in the treatment of Covid-19 adult patients with severe respiratory failure: A randomized. Clinical Trial. 2020.
12. Malgie J, Schoones JW, Pijls BG. Decreased mortality in COVID-19 patients treated with Tocilizumab: A rapid systematic review and meta-analysis of observational studies. Clin Infect Dis. 2021;72(11):e742-9.
13. Eimer J, Vesterbacka J, Svensson AK, Stojanovic B, Wagrell C, Sönnerborg A, et al. Tocilizumab shortens time on mechanical ventilation and length of hospital stay in patients with severe COVID-19: A retrospective cohort study. J Intern Med. 2021;289(3):434-6.
14. Ruiz-Irastorza G, Pijoan J, Bereciartua E, Dunder S, Dominguez J, Garcia-Escudero P, et al. Second week methyl-prednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: An observational comparative study using routine care data. PLoS One. 2020;15(9):e0239401.
15. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan. JAMA Intern Med. 2020;180(7):934-3.
16. Mareev VY, Orlova YA, Pavlikova EP, Matskeplishvili ST, Krasnova TN, Malahov PS, et al. Steroid pulse -therapy in patients with coronavirus Pneumonia (COVID-19), systemic inflammation and risk of venous the Rombosis and thromboembolism (WAYFARER Study). Kardiologiia. 2020;60(6):15-29.
17. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. N Engl J Med. 2020;383(24):2333-44.
18. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P, et al. Effect of tocilizumab *vs.* usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: A randomized clinical trial. JAMA Intern Med. 2021;181(1):32-40.
19. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: A systematic review and meta-analysis. J Infect. 2020;81(1):e13-20.