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ORIGINAL ARTICLE

Outcome Comparison Between Tocilizumab and Pulse Solumedrol in Severe Covid Disease Among Resource Depleted Areas

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ABSTRACT

Introduction: Pandemic coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 coronavirus has recently emerged.

Objectives: The main objective of the study is to find the outcome comparison between tocilizumab and pulse solumedrol in severe COVID disease among resource depleted areas.

Material and methods: This cross sectional study was conducted in Central Park Medical College and Teaching Hospital, Lahore and the duration of this study was from August 2021 to March 2022. The data was collected through non-probability consecutive sampling technique. The data was collected into two groups. Men and non-pregnant women over 18 years old COVID diagnosis confirmed by real time polymerase chain reaction (RT-PCR) Pao2 / FIO2 <200 Laboratory: high sensitivity C reactive protein> 5 mg / L; lactic dehydrogenase (LDH) > 245 U / l; Ferritin> 300; D-dimer> 1500; Interleukin-6> 7.0 pg / ml were included.

Results: The data was collected from 300 patients, 150 in each group. There were 72.9% male aged 41–60 years 45.8% were female with a mean age of 55.4 ± 10.6 years. Diabetes and hypertension was the most common comorbidity in selected patients. Tocilizumab group had more number of males (P = 0.017), with higher incidence of coronary artery disease (CAD, P = 0.008).

Conclusion: It is concluded that Tocilizumab decreased the propensity of severe COVID-19 patients to require invasive mechanical ventilation when compared to high-dose solumedrol pulse, especially in those with severe ARDS, but this did not translate to improved 30-day survival in them.

INTRODUCTION

Pandemic coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 coronavirus has recently emerged. Although most of the infected patients will remain asymptomatic or develop mild symptoms, up to 20% may develop severe disease with pneumonia and respiratory failure. Oxygen administration is the cornerstone of supportive treatment and is required in approximately 15% of cases, while invasive mechanical ventilation is necessary in up to 5–7% of severe cases [1]. Since mortality in patients with invasive ventilation can be very high, halting the progression from moderate to severe respiratory failure should reduce the mortality in COVID-19 [2]. Indeed, some real life experiences in COVID-19 patients showed that the use of anti-inflammatory treatments might be beneficial [3]. In fact, short-term steroid therapy was associated with lower mortality in 201 patients with acute respiratory distress syndrome (ARDS) [4]. Additionally, following the data on presence of inflammatory cytokine storm in severe COVID-19, tocilizumab use has been advocated. This monoclonal antibody, which binds to interleukin 6 (IL-6) receptor and blocks the IL-6 mediated inflammatory response, is approved for treatment of rheumatologic disorders and cytokine-release syndrome associated with Chimeric Antigen Receptor T-cell (CAR-T) administration. It was reported to reduce COVID-19-associated inflammation, and was approved in China for this indication [5].

Based on the first evidences, we formulated the hypothesis of potential benefit of anti-inflammatory treatment, and progressively modified our therapeutic approach to COVID-19. We started using tocilizumab in patients with respiratory failure, and subsequently, we introduced into our protocol early administration of methylprednisolone treatment, followed in more severe cases by the administration of tocilizumab [6].

Methylprednisolone is a well-known and low-cost drug with broad access to the population, with which we have a good practice of its use for treating already known diseases. Supported by studies in the Middle East, which provides the pulse's effectiveness using 250 mg of Methylprednisolone and our choice relies on pulsing with a large and classic dose—1000 mg on the first day to 500 g on the second and third days. These higher doses attempt to block neutrophils from bone marrow riding into the tissues infected with Sars-CoV-2, mainly to the lungs [7].

Objectives: The main objective of the study is to find the outcome comparison between tocilizumab and pulse solumedrol in severe COVID disease among resource depleted areas.

MATERIAL AND METHODS

This cross sectional study was conducted in Central Park Medical College and Teaching Hospital, Lahore and the duration of this study was from August 2021 to March 2022. The data was collected through non-probability consecutive sampling technique. The data was collected into two groups:

Group I: treated with solumedrol
Group II: Treated with tocilizumab

Inclusion Criteria: Men and non-pregnant women over 18 years old COVID diagnosis confirmed by real time polymerase chain reaction (RT-PCR) Pao2 / FIO2 <200 Laboratory: high sensitivity C reactive protein> 5 mg / L; lactic dehydrogenase (LDH) > 245 U / l; Ferritin> 300; D-dimer> 1500; Interleukin-6> 7.0 pg / ml.

Exclusion Criteria:

- Known sensitivity/Allergy to tocilizumab
- Active tuberculosis
- Pregnancy
- Individuals, in the opinion of the investigators where progression to death is imminent and inevitable in the next 24 hours

Data collection: The data was collected from 300 patients with the permission of ethical committee of hospital. Those patients who are fulfilling the inclusion and exclusion criteria, was selected for the study. Chest X-ray was done at the time of admission and all other baseline values, CBC, CRP and all labs was noted. Patients with oxygen saturation <93% on room air with normal chest x-ray and CRP between 30 and 50, were labelled as having moderate covid-19 disease. Patients with CRP> 50 and having infiltrates on chest x-ray at the time of admission were considered having severe covid-19 disease. The dose of solumedrol 1mg/kg/day twice a day and Tocilizumab, 8 mg / kg diluted in 100 ml of saline and administered IV for 60 minutes was given for consecutive 5

days. The dose was repeated only once 12 hours after the first dose. After that we again noted the saturation level of oxygen and all other necessary labs. Chest X-ray was also repeated after 5 days. Patients were converted to nasal oxygen and ICU if they are not improving and sometime mechanical ventilation is also needed. The primary outcomes was a seven-category ordinal scale consisting of: 1) Death; 2) on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3)con non-invasive ventilation or high flow oxygen devices; 4)requiring supplemental oxygen; 5)not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6)not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities. The secondary outcome was improving oxygenation and length of stay in hospital.

Data analysis: The data was collected and analyzed using SPSS version 19. All the values were expressed as mean and standard deviation.

RESULTS

The data was collected from 300 patients, 150 in each group. There were 72.9% male aged 41–60 years 45.8% were female with a mean age of 55.4 ± 10.6 years. Diabetes and hypertension was the most common comorbidity in selected patients. Tocilizumab group had more number of males (P = 0.017), with higher incidence of coronary artery disease (CAD, P = 0.008). The lag-period from onset of symptoms to admission and admission to the administration of test drug was comparable. The presenting mean arterial pressure, temperature, serum ferritin, serum leucocyte dehydrogenase, d-Dimer, and procalcitonin were comparable in both groups. However, the patients in tocilizumab group had more tachypnea (P = 0.001), more leukocytosis (P = 0.043), higher baseline mean C-reactive protein (CRP) levels (P = 0.005), higher number of patients with CRP >100 (P = 0.003), and more number of patients with P: Fr <100 (55%, P = .007) at presentation, than patients in the MPS group.

Table 1: Comparison of High Dose Solumedrol and Tocilizumab in Both Groups

Parameters	Mean±SD		Z	P
	Group I	Group II		
Age (years)	56.48±10.28	54.10±9.69	0.310	0.757
Days between first symptoms and admission	5.11±2.69	5.04±1.55	0.890	0.331
Baseline parameters				
Respiratory rate (per minute)	23.16±4.46	26.32±5.62	3.97	0.001
Heart rate (per minute)	95.69±10.25	99.91±10.11	2.89	0.004
Mean arterial pressure (mm of Hg)	94.89±11.14	90.28±10.88	1.872	0.062
Temperature (Fahrenheit)	98.34±1.06	98.04±1.43	1.707	0.089
PaO_2/FiO_2 ratio	176.11±110.44	155.63±145.42	1.311	0.191
CRP (in mg/L)	121.24±98.37	156.75±100.65	-2.804	0.005
D-Dimer (ng/ml)	745.75±891.91	712.98±789.67	0.154	0.878
Total leucocyte count (in cells/cm)	11.34±5.36	13.42±12.66	-2.055	0.041
Neutrophil/lymphocyte ratio	12.40±12.56	14.37±11.98	-1.197	0.232
Leucocyte dehydrogenase (U/L)	445.76±288.03	413.00±180.30	0.923	0.357
Ferritin (ng/ml)	885.47±1248.61	753.55±637.22	0.888	0.375
Procalcitonin (ng/ml)	0.47±0.89	0.42±0.50	0.459	0.647
Hospital course				
Lag-time from admission to administration of drug (days)	2.41±1.12	2.46±0.95	-0.344	0.731
Hospital stay (days)	13.23±6.00	14.99±6.12	-2.342	0.020

Table 2: Variables of Selected Patients and Length of Stay in Hospital

Treatment	Variables	Mean ± SD		P-value
		Group I	Group II	
Initial	Temperature (F°)	101.77 ± 1.51	101.66 ± 1.20	0.69
	Oxygen (ppm)	11.9 ± 4.29	12.8 ± 4.9	0.47
	CRP (mg/dl)	141.67 ± 69.6	126.89 ± 61.39	0.52
	D-Dimer (ng/ml)	786.90 ± 109.98	889.9 ± 230.98	0.001
	Ferritin level (ng/mL)	1006.16±10.54	987.98±20.98	0.32
Day 5	Temperature	98.9 ± 1.09	98.7 ± 1.03	0.43
	Oxygen	9.34 ± 7.48	7.84 ± 6.44	0.10
	CRP	73.9 ± 56.0	59.07 ± 50.88	0.181
	Length of stay in hospital (days)	5 ± 5.67	6 ± 3.56	0.40
	Ferritin level	401 ±10.98	345 ± 9.00	0.001

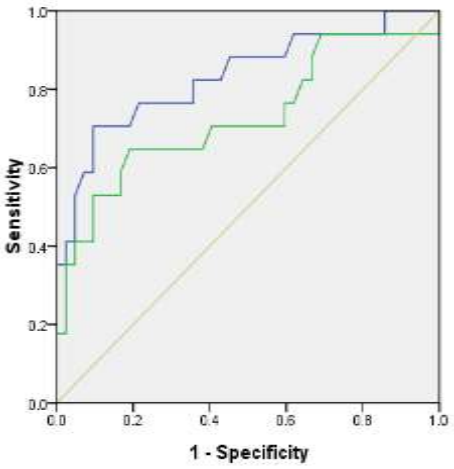

Figure 1: ROC Curve Of Both Therapies In Selected COVID-19 Patients

Table 02 shows the outcomes of both groups according to medication and severity of disease. This shows the time to get rid of oxygen, length of stay in hospital and decreases in inflammatory markers in patients.

DISCUSSION

To face the pandemic, drugs used in the previous SARS-COV and MERS epidemics, including chloroquine and hydroxychloroquine, lopinavir/ritonavir, azithromycin, and ivermectin, among others, showed some usefulness in vitro against SARS-CoV2 [8-9]. In a retrospective multicenter study in Michigan, United States, the administration of hydroxychloroquine alone or in combination with azithromycin was associated with a reduction in mortality. However, in randomized clinical trials, no favorable effect was evidenced [10-12]. Tocilizumab group also had higher co-morbid CAD. Studies reveal that the presence of CAD adds to poor prognosis in COVID with higher mortality, thromboembolic events, and septic shock rates, but another study contradicts this by showing that CAD itself was not associated with increased

mortality and poorer outcome, when other covariates were adjusted [13-14].

Pulse glucocorticoid therapy is used in many immuno-inflammatory conditions to obtain a quick and strong suppression of inflammation in emergency situations. However, despite its diffuse use in clinical practice, very few studies, often uncontrolled and underpowered, have evaluated the efficacy and safety of this therapy [15]. Indeed, a systematic literature review on safety and efficacy of pulse glucocorticoid therapy for SARS-CoV, Middle East Respiratory Syndrome (MERS)-CoV or SARS-CoV-2 showed that the quality of the evidence is poor and randomised controlled trials are highly needed [16].

CONCLUSION

It is concluded that Tocilizumab decreased the propensity of severe COVID-19 patients to require invasive mechanical ventilation when compared to high-dose solumedrol pulse, especially in those with severe ARDS, but this did not translate to improved 30-day survival in them.

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