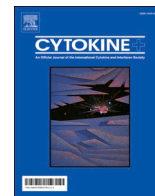**ELSEVIER**

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Short communication

Experience of using tocilizumab for treatment in Indonesian patients with severe COVID-19

Allen Widysanto [a], Andree Kurniawan [b,*], Nata Pratama Hardjo Lugito [b], Mira Yuniarti [c], Catherine Gunawan [d], Angela [d], Jessica Wiryanto [d], Levinna [d], Tasya Meidy Pradhana [d]

[a] Department of Pulmonology, Faculty of Medicine, Pelita Harapan University, Tangerang, Banten, Indonesia
[b] Department of Internal Medicine, Faculty of Medicine, Pelita Harapan University, Tangerang, Banten, Indonesia
[c] Department of Radiology, Faculty of Medicine, Pelita Harapan University, Tangerang, Banten, Indonesia
[d] Faculty of Medicine, Pelita Harapan University, Tangerang, Banten, Indonesia

ABSTRACT

COVID-19 is a public health emergency of international concern with millions confirmed cases globally including in Indonesia with more than two hundred thousand confirmed cases to date COVID-19. (1) COVID-19 has wide clinical manifestation ranging from asymptomatic, acute respiratory illness, respiratory failure that necessitates mechanical ventilation and support in an ICU, to MODS. (2) Several comorbidities have been demonstrated to be associated with the development of severe outcomes from COVID-19 infection, such as hypertension, diabetes, cardiovascular disease, dyslipidemia, thyroid disease, and pulmonary disease. (3)–(5) Severe COVID-19 is associated with increased plasma concentrations of IL-6, resulting in cytokine storm. (6) Tocilizumab, an interleukin-6 inhibitor, might alleviates the cytokine storm, prevents significant lungs and organs damage, thus improving clinical outcomes. (7) Therefore, tocilizumab, might be one of the promising therapies for severe COVID-19. (8) However there were limited studies regarding the efficacy in COVID-19 patients, especially with control group. We would like to report our experience in using tocilizumab as treatment in severe COVID-19 patients in Indonesia, which is the first in Indonesia to the best of our knowledge.

1. Introduction

COVID-19 is a public health emergency of international concern with millions of confirmed cases globally, including in Indonesia, with more than five hundred thousand confirmed cases to date [1]. COVID-19 has wide clinical manifestations, ranging from asymptomatic acute respiratory illness and respiratory failure that necessitates mechanical ventilation and support in an ICU to MODS [2]. Several comorbidities have been demonstrated to be associated with the development of severe outcomes from COVID-19 infection, such as hypertension, diabetes, cardiovascular disease, dyslipidemia, thyroid disease, and pulmonary disease [3–5]. Severe COVID-19 is associated with increased plasma concentrations of interleukin 6 (IL-6), resulting in cytokine storms [6]. Tocilizumab, an IL-6 inhibitor, might alleviate cytokine storms and prevent significant lung and organ damage, thus improving clinical

outcomes [7]. Therefore, tocilizumab might be a promising therapy for severe COVID-19 [8]. However, there were limited studies regarding the efficacy in COVID-19 patients, especially with control groups. Most of the studies regarding tocilizumab's effects were conducted in Europe and the US, with China as the only country in Asia. This study was conducted in Indonesia, which is the fourth most populous country in the world and the third in Asia, with a population of 255.46 million people. Therefore, this population helps describe the characteristics of patients with COVID-19 in Southeast Asia and Asia. We would like to report our experience of using tocilizumab as a treatment in severe COVID-19 patients in Indonesia; to the best of our knowledge, this is the first such report in Indonesia.

Table 1
Baseline Characteristics of overall, tocilizumab treated group, and control group.

	Overall (n = 30)	Tocilizumab (n = 14)	No Tocilizumab (n = 16)	P-value
Baseline Characteristics				
Age	58.0 ± 10.945	58.71 ± 10.09	57.38 ± 11.93	0.744
Gender				0.657
Male	24 (80%)	12 (75%)	12 (86%)	
Female	6 (20%)	4 (25%)	2 (14%)	
Weight (kg)	71.7 ± 11.27	70.92 ± 9.36	72.31 ± 12.99	0.744
Height (cm)	170(160–180)	170 (160–178)	170 (160–180)	0.481
Body mass index (BMI) (Mean ± SD)	25.13 ± 0.62	24.69 ± 2.72	25.51 ± 3.93	0.522
Swab				
Positive	30 (100%)	14 (100%)	16 (100%)	
Negative	0 (0%)	0 (0%)	0 (0%)	
Comorbid Conditions				
Hypertension	12 (40%)	6 (42.9%)	6 (37.5%)	0.765
Dyslipidemia	1 (3.3%)	1 (7.1%)	0 (0.0%)	0.467
Diabetes Mellitus	9 (30%)	4 (28.6%)	5 (31.3%)	1.000
Coronary Artery Disease	3 (10%	2 (14.3%)	1 (6.3%)	0.586
Valve Disease	1 (3.3%)	1 (7.1%)	0 (0.0%)	0.467
Arrhythmia	1 (3.3%)	0 (0.00%)	1 (6.3%)	1.000
Hyperthyroid	1 (3.3%)	0 (0.00%)	1 (6.3%)	1.000
Stroke	1 (3.3%)	0 (0.00%)	1 (6.3%)	1.000
Autoimmune Disease	1 (3.3%)	1 (7.1%)	0 (0.0%)	0.467
Number of Comoribidities				
No Comorbidity	12(40%)	6 (42.9%)	6 (37.5%)	0.747
Single Comorbidity	9 (30%)	3 (21.4%)	6 (37.5%)	
Two Comorbidities	6 (20%)	3 (21.4%)	3 (18.8%)	
Three Comorbidities	2 (10%)	2 (14.3%)	1 (6.3%)	
Presenting symptoms				
Fever	22 (73.3%)	10 (71.4%)	12 (75%)	1.000
Shortness of Breath	19 (63.3%)	7 (50%)	12 (75%)	0.299
Cough	19 (63.3%)	9 (64.2%)	10 (62.5%)	1.000
Rhinorrhea	1 (3.3%)	1 (7.1%)	0 (0.0%)	0.467
Sore Throat	4 (13.3%)	0 (0%)	4 (25%)	0.103
Anosmia	2 (6.7%)	2 (14.3%)	0 (0.0%)	0.209
Dysgeusia	2 (6.7%)	2 (14.3%)	0 (0.0%)	0.209
Gastrointestinal	6 (20%)	4 (28.6%)	2 (12.5%)	0.378
Other	9 (30%)	6 (42.9%)	3 (18.8%)	0.236
Vital Signs				
Temperature D1	337.3 ± 0.63	37.31 ± 0.61	37.29 ± 0.67	0.931
Respiratory Rate D1	24 (18–42)	24 (20–36)	25.5 (18–42)	0.202
Baseline Laboratory Values on D1				
WBC (10^3/ul)	7.41 (2.52–20.5)	7.41 (4.29–20.5)	7.44 (2.52–19.36)	0.934
Band Neutrophil (%)	4 (0–75)	4 (2–6)	4 (0–75)	0.812
Segment Neutrophil (%)	77 (8–88)	76.50 (50–88)	77.5 (8.4–88)	0.917
Lymphocyte (%)	10.15 (0.3–38.0)	11.5 (4.9–38)	8.5 (0.3–36)	0.308
Neutrophil Lymphocyte Ratio (NLR)	6.67 (0.42–304.00)	6.67 (1.39–17.94)	6.05 (0.42–304)	0.983
Absolute Lymphocyte Count (10^9/L)	981.49 ± 526.39	1122.63 ± 563.73	857.99 ± 474.79	0.174
Platelet Count (10^3/ul)	201.5 (85.0–443.0)	213 (153–441)	190 (85–443)	0.418
RDW (%)				0.103

Table 1 (*continued*)

	Overall (n = 30)	Tocilizumab (n = 14)	No Tocilizumab (n = 16)	P-value
	12.85 (11.1–23.9)	12.65 (11.6–13.2)	13.0 (11.1–23.9)	
Random Blood Glucose (mg/dl)	145 (82.0–395.0)	145 (104–256)	165 (82–395)	0.635
Erythrocyte Sedimentation Rate (seconds)	30.5 (3.0–107.0)	23.5 (14–107)	41 (3–92)	0.626
C-Reactive Protein (CRP) (mg/L)	121.8 ± 86.32	114.54 ± 75.15	128.03 ± 97.26	0.700
D-dimer (ug/mL)	2.11 (0.27–35.2)	0.90 (0.27–35.2)	2.16 (1.52–35.2)	0.209
SGOT (U/L)	48.00 (18.00–236.00)	53.5 (21–236)	44.5 (18–71)	0.204
SGPT (U/L)	45.00 (15.00–236.00)	47.5 (18–236)	33 (15–110)	0.231
Lactate Dehydrogenase (U/L)	706.87 ± 312.98	667.83 ± 398.06	732.89 ± 265.48	0.709
BUN	13.12 ± 2.96 (n = 21)	13.49 ± 3.21 (n = 8)	12.89 ± 2.91 (n = 13)	0.661
Creatinine (mg/dL)	0.85 ± 0.16 (n = 24)	0.87 ± 0.19 (n = 10)	0.83 ± 0.13 (n = 14)	0.639
O2 Saturation (%)	95.7 (65.7–98.5)	94.25 (65.7–96.2)	96.4 (84.5–98.5)	0.088
PO2 (mmHg)	71.60 ± 18.86	65.41 ± 16.91	75.31 ± 19.53	0.220
Chest Radiological Abnormality				
Consolidation and Ground Glass Opacities (GGO)	30 (100%)	14 (100%)	16 (100%)	
Bilateral Involvement	30 (100%)	14 (100%)	16 (100%)	

2. Methods

This retrospective cohort study was approved by the Siloam Hospital ethical committee with ethical clearance number 391/SHLV-HA/VI/2020. We included 30 patients in Siloam Hospital Kelapa Dua with severe to critical manifestations according to WHO severity classifications. Day one (D1) in the study was used to describe the first day of tocilizumab administration in the case group and the first day of hospital admission in the control group. The aim of this study was to comprehend the characteristic differences between tocilizumab-treated and control groups before and after treatment.

3. Results

We reported the clinical characteristics and outcomes of 30 severe COVID-19 patients, including 14 who received tocilizumab therapy and 16 patients who did not. The characteristics of the subjects are described in Tables 1 and 2. Our study showed that in comparison to the control group, after 5 days of tocilizumab treatment, patients had lower body temperatures and respiratory rates. More patients experienced negative swab conversion and had lower WBC and segment neutrophil counts with higher lymphocyte counts, resulting in a lower NLR. Random blood glucose and CRP levels were lower, and D-dimer levels were slightly higher [9,10]. However, our study showed that patients treated with tocilizumab had lower SpO2 than in previous studies [9,10]. In addition, male sex was also associated with higher mortality [11]. BMI and an increased number of comorbidities were associated with higher mortality in both treatment groups [3]. The respiratory rate on D5 appeared to be higher in nonsurvivors than in survivors in both treatment groups [12]. Swab conversion to a negative outcome and on day 5 appeared to be higher in survivors than in nonsurvivors in both treatment groups. Higher WBC count, segment neutrophils, NLR, random blood glucose, CRP, D-dimer, and BUN on day 5 were associated with higher mortality

Table 2

Characteristics of the survivor and non-survivor in tocilizumab treated group and control group on the fifth day of observation (D5).

	Tocilizumab (n-14)		No Tocilizumab (n-16)	
	Survive (n = 10)	Death (n = 4)	Survive (n = 10)	Death (n = 6)
Age (Mean ± SD)	58.90 ± 9.972	58.25 ± 11.96	59.30 ± 11.53	54.17 ± 12.95
Gender				
Male	9 (75%)	3 (25%)	6 (50%)	6 (50%)
Female	1 (50%)	1 (50%)	4 (100%)	0 (0%)
BMI (Mean ± SD)	24.36 ± 3.01	25.54 ± 1.93	25.03 ± 3.55	26.30 ± 4.75
Number of Comoribidities				
No Comorbidity	4 (40%)	2 (50%)	3 (30%)	3 (50%)
Single Comorbidity	2 (20%)	1 (25%)	5 (50%)	1 (16.7%)
Two Comorbidities	3 (30%)	0 (0%)	1 (10%)	1 (33%)
Three Comorbidities	1 (10%)	1 (25%)	1 (10%)	0 (0%)
Temperature Day 5	36.50 (36.00–38.00)	36.85 ± 0.45	36.67 ± S0.38	36.90 (36.5–38.9)
Respiratory Rate Day 5 Tocilizumab Treatment	20 (16–25)	25.25 ± 6.60	20.80 ± 2.30	32.17 ± 8.50
Swab D5				
Positive	4 (10%)	2 (50%)	9 (90%)	6 (100%)
Negative	6 (60%)	2 (50%)	1 (10%)	0 (0%)
Swab Outcome				
Positive	0 (0%)	3 (75%)	1 (10%)	3 (50%)
Negative	10 (100%)	1 (25%)	9 (90%)	3 (50%)
Laboratory Results Day 5				
White Blood Cell (10^3/ul)	4.94 (3.64–22.65)	11.85 ± 3.37	8.47 ± 4.47	20.21 (10.03–64.54)
Band Neutrophil (%)	3.00 (2.00–6.00)	4.25 ± 1.26	4.10 ± 1.37	4.00 (4.00–6.00)
Segment Neutrophil (%)	54.00 ± 17.99	81.00 ± 6.16	68.00 ± 13.49	87.50 (15.00–91.00)
Lymphocyte (%)	26.78 ± 14.53	10.00 ± 2.83	15.80 ± 10.28	4.50 (2.00–81.00)
Neutrophil Lymphocyte Ratio (NLR)	1.68 (0.38–16.60)	8.89 ± 3.75	6.69 ± 7.26	21.94 ± 16.17
Absolute Lymphocyte Count (10^9/L)	1440.46 ± 334.64	981.20 (870.60–1794.00)	1071.89 ± 574.48	662.40 (489.60–52277.40)
Platelet Count (10^3/ul)	338.11 ± 58.30	249.00 ± 96.75	342.90 ± 96.60	204.00 ± 48.66
Red Cell Distribution Width (RDW) (%)	13.49 ± 0.97	13.95 ± 1.24	14.20 ± 3.44	13.25 (12.10–17.00)
Random Blood Glucose (mg/dl)	101.50 (0.86–117.00)	155.33 ± 86.12	117.00 ± 25.46	162.00 ± 32.91
Erythrocyte Sedimentation Rate (seconds)	13.89 ± 10.42	32.25 ± 29.97	44.50 ± 29.76	31.00 ± 30.09
C-Reactive Protein (CRP) (mg/L)	2.10 (0–17)	47.65 ± 48.95	13.05 ± 11.68	271.00 (120–422)
D-dimer (ug/mL)	4.54 ± 2.71	34.84 (16.01–35.20)	3.53 (1.80–35.00)	32.35 (6.83–36.50)
SGOT (U/L)	50.20 ± 26.71	76.75 ± 28.39	53.75 ± 37.62	41.00 ± 12.08
SGPT (U/L)	69.00 ± 36.83	61.50 ± 28.86	37.25 ± 28.11	34.50 ± 24.71
Blood Urea Nitrogen (BUN)	33.44 (21.70–45.17)	44.11 ± 13.83	15.73 ± 7.64	22.70 (14.40–156.20)
Creatinine (mg/dL)	0.82 ± 0.12	1.15 ± 0.91	0.82 ± 0.27	0.80 (0.60–11.44)
O2 Saturation (%)	96.93 ± 1.72	95.67 ± 1.53	98.96 ± 0.22	96.00 (80.2–99.30)

in both treatment groups [12–17]. Lower lymphocyte count, absolute lymphocyte count, platelet count, and SpO2 on day 5 were associated with higher mortality in both treatment groups [18,16,19,20].

4. Discussion

A previously published meta-analysis showed that COVID-19 patients treated with tocilizumab had reduced mortality, less need for mechanical ventilation, improved respiratory function, rapid defervescence, and successful discharge compared with the control group, especially when the subgroup analysis was restricted to studies that only included patients with severe COVID-19 based on the clinical picture and laboratory parameters [21–23]. Our study is consistent with these studies, and the samples were restricted to severe COVID-19 patients. This is important, as healthcare providers need to identify severe COVID-19 patients to obtain the maximum benefit from tocilizumab. However, an ongoing randomized controlled COVACTA trial failed to show improved clinical status and mortality, although tocilizumab-treated patients spent roughly a week less in the hospital than the control group. This might be caused by different patients having different durations and severities of illness and previous treatments when they were treated with tocilizumab and assessed on the same day [24]. This might cause the study to miss clinically relevant differences between patient groups; therefore, it is important to stratify patients by clinical signs of hyperinflammation, divide them into subpopulations with different illness characteristics, and set the optimal timing to start tocilizumab treatment. To date, there is no clear optimal time to start this drug; however, previous studies recommended starting tocilizumab treatment during the severe phase of the disease, i.e., the beginning of inflammation, at the first signs of decreasing O2 saturation [25], when

the patient has a high risk of mechanical ventilation and death [26] and an increased requirement for oxygen support, with progression of thoracic CT and elevation of inflammation markers, including IL-6, CRP, ferritin, and D-dimer, and decreased % lymphocytes [27]. The limitations of this study include its retrospective nature and the lack of determination of serum IL-6 levels before and after tocilizumab therapy.

5. Conclusions

Our study showed that the tocilizumab-treated group had better clinical outcomes, laboratory results, and swab conversion to negative than the control group. Further study with measurement of IL-6 is recommended.

Declarations

Ethics approval and consent to participate: This study was approved by the Siloam Hospital ethical committee with ethical clearance number 391/SHLV-HA/VI/2020.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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