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Tocilizumab Initiation based on Indicator in Patients Infected by Coronavirus-19 to Prevent Intubation

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Abstract

BACKGROUND: The coronavirus disease 2019 (COVID-19) pandemic has created severe medical and economic consequences worldwide since 2019. Tocilizumab is one of the therapies considered capable of improving the condition of patients with COVID-19. However, there is not much information about the best time to give tocilizumab.

METHODS: This was an analytical study with a retrospective cohort design, using the data of 125 patients infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with signs of acute respiratory distress syndrome in Dr. Moewardi Hospital, Surakarta, from March to August 2020. We analyzed various available clinical data to see which factors into clinical improvement with tocilizumab therapy.

RESULTS: Most patients showed clinical improvement after administration of tocilizumab. During the follow-up period, 21 patients died despite tocilizumab therapy. Significant risk factors associated with the need for intubation were heart rate, neutrophil, lymphocyte, pH, $PaCO_2$, and PO_2. The most influential variable on the need for intubation without being associated with other risk factors was PaO_2 ($p = 0.003$, Confidence Intervals 95%).

CONCLUSIONS: Tocilizumab has a role in treating patients infected by SARS-CoV-2, preventing the need for intubation when given to patients in good saturation condition with oxygen supplementation without positive pressure (PaO2 >65mmHg; SpO_2 >93%).

Introduction

Coronavirus disease 2019 (COVID-19), a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a pandemic with serious medical and economic consequences worldwide. Globally, more than 20 million people have been infected with SARS-CoV-2 [1]. The infection in critically ill patient causes alveolar epithelial cell destruction, activation of the innate immune system, and dysregulation of adaptive immune responses, including the release of proinflammatory cytokines and chemotherapy caused by hyperactivation of the humoral immune pathway that includes interleukin (IL)-6 as a critical mediator for respiratory failure, shock, and multiorgan failures [2], [3]. Knowing that IL-6 playing a role on the development of cytokine release syndrome (CRS) as pathologic underpinning for disease progression of severe COVID-19. Therefore, it is essential to find the available treatment to reduce the severity of illness and death caused by COVID-19.

Tocilizumab is a recombinant monoclonal antibody targeting the IL 6 receptor subunit alpha (IL-6Rα) [4]. In COVID-19 pandemic era, tocilizumab has been used off-label to reduce the CRS associated with chimeric antigen receptor cell therapy and has been proposed as a potential therapy for the cytokine storm syndrome associated with severe COVID-19 pneumonia based from some studies [5], [6], [7]. However, those studies never mentioned any standardized indicators to initiate administration of tocilizumab. Due to the lack of information regarding the initiation time of tocilizumab, this study explored the relationship of risk factors including HsCRP, HCO3, PaO2, D-Dimer, and PaCO2, to the need for intubation in COVID-19 patients before administration of tocilizumab. The focus of this study is to observe the indicators which can be used as a reference for initiating tocilizumab to prevent cytokine storms.

Methods

Setting

This study is an analytical retrospective cohort study conducted in Dr. Moewardi Hospital, Surakarta.

Data were obtained from the medical records of patients infected by SARS-CoV-2 hospitalized in Dr. Moewardi Hospital Surakarta, Central Java, Indonesia, from March to August 2020. This study was approved by the Ethics Committee of Dr. Moewardi Hospital Surakarta, Central Java, Indonesia No. 125/II/HREC/2021.

Study participants

We used purposive sampling technique due to the small population size, which did not allow random selection. This sampling technique used specific criteria previously determined by the researchers until the minimum number of samples was reached.

The study samples were all patients confirmed positive for SARS-CoV-2 by RT-PCR test and then received tocilizumab therapy. We included adult patients aged ≥18 years old with criteria for severe pneumonia, clinical signs of pneumonia (fever, cough, shortness of breath, and rapid breathing), and at least one of the following: respiratory rate >30 ×/min, severe respiratory distress, or SpO_2 <93% on room air. Samples are grouped by their comorbid into three groups, which is samples with just 1 comorbid, 2 or more than 3. The comorbid that includes in these groups are hypertension, diabetes, dyslipidemia, and obesity.

Patients with coinfections other than COVID-19, a history of autoimmune disease, malignancy, a PaO_2/FiO_2 ratio >300 mmHg, a history of chronic glucocorticoid use (≥2 months), a history of severe allergic reactions to monoclonal antibodies, active diverticulitis, inflammatory bowel disease, or other gastrointestinal conditions which can potentially lead to intestinal perforation, and impaired liver, kidney, or severe liver function were excluded from the study.

Outcome and definitions

In-hospital treatment was defined as either under mechanical ventilation assistance or not. The clinical information was drawn from a thorough review of unstructured records and structured data. If multiple positive or uncertain results for SARS CoV-2 were found in the patient records, the first initial positive test was used as the date of diagnosis. Administration of tocilizumab was defined as administration of the drug as found in the patient's medical record. If there was no evidence of tocilizumab administration, the patient was stated for not receiving tocilizumab.

Statistical analysis

Univariate analysis was used to describe the characteristics of each variable. Descriptive data on the characteristics of the subjects were presented in the form of narratives, tables, and figures. Categorical data were displayed in the form of proportions. Numerical data with normal distribution were presented with mean and standard deviation. Data distribution that was not normal was presented with median and interquartile range.

We used a correlation test to determine the association between variables. Before correlative analysis, a normality test was conducted using the Kolmogorov–Smirnov test to determine the type of data distribution. If the data were normally distributed, a parametric test would be performed using Pearson for the numerical dependent variable. If the data were not normally distributed, then the dependent variables with ordinal, interval, and ratio scales would be tested with a non-parametric test, Spearman's rho test. A significance limit of 0.05 was used, and $p < 0.05$ was considered statistically significant. The magnitude effect of the independent variables on the dependent variable was calculated with the Cohen's d formula. If the magnitude effect is $0.2 \leq d < 0.5$, then the effect size is interpreted as small, if it is in the range of $0.5 \leq d < 0.8$, then the effect size is interpreted as moderate, and if it is in the range of $0.8 \leq d \leq 2$, then the effect size is interpreted as large.

The multivariate analysis used multiple linear regression on the dependent variable with a numerical scale and logistic regression on the dependent variable with a categorical scale to determine whether each independent variable was positively or negatively correlated and to predict the value of the dependent variable.

Results

A total of 125 patients with COVID-19 comprising 95 males and 30 females were included

Table 1: Patients demographic and clinical characteristic

Characteristic	n	(%)
Male	95	76
Female	30	24
Ethnicity		
Hispanic	0	0
Black	0	0
White	0	0
Asian	125	100
WHO Ordinal Scale		
8 (deceased)	0	0
7 (invasive mechanical ventilation + organ support)	0	0
6 (invasive mechanical ventilation)	11	8.8
5 (non-invasive ventilation or high-flow oxygen)	12	9.6
4 (oxygen by mask or nasal prongs)	90	72
3 (hospitalized without oxygen therapy)	12	9.6
1–2 (not hospitalized)	0	0
Heart Rate >100	41	32.8
Respiratory Rate >30	62	49.6
Oxygen supplementation		
Room air	12	9.6
Nasal cannula	38	30.4
Non-rebreather mask	52	41.6
High-flow nasal cannula	12	9.6
Non-invasive ventilation	3	2.4
Invasive mechanical ventilation	8	6.4
Comorbid		
No	24	19.2
1	59	47.2
2	32	25.6
≥3	10	8

in this study. Most of the patients presented with one comorbid disease (59%) and two comorbid diseases (32%) (Table 1).

Regarding the disease severity, most patients scored 4 (72%), while the remaining 8.8% scored 6. Most patients received oxygen supplementation with a non-rebreathing mask (52%) or nasal cannula (38%). Twenty-one patients (16.8%) died despite tocilizumab therapy during the study period. The blood laboratory parameters that we observed were neutrophils, lymphocytes, hematocrit, lactate, arterial blood gas analysis (BGA), D-dimer, IL-6, and hsCRP. These parameters were checked before tocilizumab administration until the treatment ended.

The bivariate analysis showed that the significant risk factors associated with the patient's need for intubation were heart rate, neutrophil, lymphocyte, pH, $PaCO_2$, and PO_2 before initiating tocilizumab therapy. We found that administering tocilizumab when the heart rate <100 bpm significantly (p = 0.014) reduced the risk of the need for intubation. Similar results were also obtained when the patient's neutrophils were >75% (p = 0.005), lymphocytes >20% (p = 0.041), PCO_2 <45 mmHg (p = 0.173), PaO_2 >65 mmHg (p = 0.001), and when the patient's SaO_2 was still >80% (p = 0.084). Other risk factors did not significantly affect the need for intubation incidence after administration of tocilizumab (Table 2). Furthermore, multivariate analysis revealed that the most influential variable on the need for intubation without being associated with other risk factors was PaO_2 (Table 3). Administration of tocilizumab in patients with PaO_2 >65 mmHg with oxygen supplementation without positive pressure resulted in a significantly lower risk of the need for intubation (p = 0.003, 95% Confidence Intervals).

Table 2: Pearson Chi-square of all clinical and laboratories finding

Clinical and laboratories finding	Value	df	Asymptotic significance (2-sided)
Heart rate (<99 bpm)	6.036	1	0.014
Mean arterial pressure (<99 mmHg)	0.683	1	0.409
Core temperature (<37.0°C)	0.079	1	0.778
Respiratory Rate (<24 per minute)	0.206	1	0.650
Neutrophil (<75%)	7.760	1	0.005
Lymphocyte (>20%)	4.157	1	0.041
Hematocrit (<47.5 g/dl)	1.364	1	0.243
Blood pH (<7.40)	1.598	1	0.206
PaCO2 (<45 mmHg)	1.853	1	0.173
PaO2 (>65 mmHg)	12.034	1	0.001
Base Excess (<5 mmol/L)	0.100	1	0.752
HCO3 (>32 mmol/L)	1.425	1	0.233
SaO2 (>80%)	2.982	1	0.084
Blood lactate (<3.50 mmol/L)	0.791	1	0.374
D dimer <2000 (ng/ml)	0.078	1	0.781
HsCRP <20	0.321	1	0.571

Discussion

With the increasing number of COVID-19 cases in a short time, immediate research required to find the appropriate and effective therapies to prevent

Table 3: Multivariate analysis

Characteristic	B	SE	Wald	df	Sig.	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
Step 1[a]								
Pre_Neutrofil (1)	−1.086	0.777	1.955	1	0.162	0.338	0.074	1.547
before_HR (1)	−0.527	0.730	0.520	1	0.471	0.591	0.141	2.470
pre_pH (1)	0.331	0.730	0.205	1	0.650	1.392	0.333	5.816
Pre_pCO_2 (1)	0.858	0.712	1.452	1	0.228	2.359	0.584	9.529
pre_pO_2(1)	−1.772	0.731	5.881	1	0.015	0.170	0.041	0.712
Step 2[a]								
Pre_Neutrofil (1)	−0.998	0.750	1.773	1	0.183	0.369	0.085	1.602
before_HR (1)	−0.336	0.594	0.321	1	0.571	0.714	0.223	2.287
Pre_pCO_2 (1)	0.719	0.639	1.266	1	0.261	2.053	0.586	7.189
pre_pO_2 (1)	−1.669	0.695	5.767	1	0.016	0.189	0.048	0.736
Step 3[a]								
Pre_Neutrofil (1)	−1.107	0.725	2.330	1	0.127	0.331	0.080	1.369
Pre_pCO_2 (1)	0.583	0.588	0.982	1	0.322	1.791	0.566	5.668
pre_pO_2 (1)	−1.693	0.691	6.002	1	0.014	0.184	0.047	0.713
Step 4[a]								
Pre_Neutrofil (1)	−0.745	0.614	1.471	1	0.225	0.475	0.143	1.582
pre_pO_2 (1)	−1.343	0.582	5.327	1	0.021	0.261	0.083	0.817
Step 5[a]								
pre_pO_2 (1)	−1.609	0.548	8.634	1	0.003	0.200	0.068	0.585

[a]Variable (s) entered on step 1: Pre_Neutrofil (neutrophil before administration of tocilizumab), before_HR (heart rate before administration of tocilizumab), pre_pH (Blood oH/acidity before administration of tocilizumab), Pre_pCO_2 (arterial CO_2 before administration of tocilizumab), pre_pO_2 (arterial O_2 before administration of tocilizumab).

morbidity and the need for intubation due to COVID-19. At present, all over the world has been focusing on the study of this topic. Many studies have reported the relationship between tocilizumab and the need for intubation in patients infected with COVID-19, but the results were inconsistent. For instance, study by Stone *et al*. [8] found that tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19. Systematic review from low-quality evidence by Lan *et al*. [9] also showed that there's non-significant differences between tocilizumab and control groups in patients with severe COVID-19. However, several other studies showed that tocilizumab was significantly associated with reduced risk of death and lower need for intubation, [5], [6], [7], [10], [11] despite the fact that the level of evidence of those studies were varied. Biran *et al*. [12] reported that patients with COVID-19 who received tocilizumab during hospitalized had a lower need for intubation.

In this study, we evaluated the effect of administering tocilizumab in patients with COVID-19 admitted to the hospital. This study supports the effectiveness of tocilizumab therapy in preventing worsening symptoms in patients with COVID-19, particularly in preventing the occurrence of cytokine storms during treatment.

Elevated IL-6 is associated with COVID-19 cytokine storm, increasing ICU care need, acute respiratory distress syndrome (ARDS) severity, and need for intubation [3]. Close to previous studies, patients with severe COVID-19 showed an increase in neutrophils and lymphocytes followed by an increase in the neutrophil-lymphocyte ratio (NLR). In the study by Vu *et al*. [13], there was a rapid increase in IL-6 as an effect of tocilizumab therapy. This effect occurs because tocilizumab is a competitor to the IL-6 receptor. Tocilizumab administration will cause a transient increase in free IL-6 in the plasma [4], [13], [14], followed by a gradual decrease of IL-6, which is the advantage

of the inflammatory inhibiting activity of tocilizumab, providing clinical improvement in patients [15]. This study demonstrated that tocilizumab played a significant role in reducing the risk of intubation need in COVID-19 patients when administered to patients with moderate-to-mild sign and symptoms of ARDS. However, neutrophils, lymphocytes, and NLR cannot be used as a basis for the right time of administration as these two risk factors are interrelated with other risk factors (Table 3).

There are inconsistent results on oxygenation requirements after tocilizumab administration in COVID-19 patients. Some studies have reported increased oxygenation, while others have not [12], [13], [16]. Vu *et al*. [13] observed an overall increase in PaO_2/FiO_2 ratio after tocilizumab administration, but it was not clear whether this was a drug effect or the natural course of ARDS. Biran *et al*. [12] did not find an association between tocilizumab and FiO_2 reduction in their study. A study by Putra *et al*. [16] showed that in the severe group, the hypoxemic condition was significantly different compared to the mild-moderate group, as indicated by the mean PaO_2. A retrospective study by Tang *et al*. [17] reported that the mean PaO_2 of 58.0 mmHg on BGA examination of patients with COVID-19 showed a hypoxemic condition with a decrease of the PaO_2/FiO_2 ratio. Another study by Wang *et al*. [18] also reported a similar finding, in which the mean PaO_2 in patients treated in the ICU was 68 mmHg. A study by Dhont *et al.* [19] stated that the mean PaO_2 value was 72.11 mmHg in severe patients. The low PaO_2 occurred due to intrapulmonary shunting, causing early arterial hypoxemia mainly due to ventilation/perfusion imbalance, persistent pulmonary blood flow to unventilated alveoli, and the relative failure of pulmonary vasoconstriction [19].

In a study by Grasselli *et al*. [20], there was a hypoperfusion area consistent with thromboembolic diseases in 94% of patients with an increase in D-dimer. The study further stated that COVID-19 patients who progressed to ARDS had decreased respiratory system compliance along with increased D-dimers and higher intubation rates [20]. This condition is thought to have a role in intravascular pathology in increasing dead space and causing hypoxemia in ARDS of COVID-19 [19], [20].

The mechanisms underlying hypoxemia and ARDS in COVID-19 are complicated. COVID-19 patients who develop ARDS have an increased risk of the need for intubation. At the end of our study, 104 patients showed improvement and were discharged from the COVID-19 ward alive, while the remainder (16.8%) died. Of the 84.2% of patients who survived, the need for intubation was significantly lower when tocilizumab was given to patients with PaO_2 >65 mmHg. The reference PaO_2 value in this study is in line with the studies by Tang *et al.* and Wang *et al*. regarding the mean PaO_2 value of patients with COVID-19 who experienced hypoxemia [17], [18]. The PaO_2 value of 65 mmHg belongs to the category of hypoxemia, reflected as 93% on oximetry. In this study, we found that giving tocilizumab to patients with PaO_2 value >65 mmHg, in which SpO_2 was >93% reduced the need for intubation in patients with severe COVID-19 infection.

This study has several limitations. First, incomplete medical records could lead to misclassification in manual data collection, both from structured and unstructured medical record data, resulting in missing data for multivariate linear regression statistical analysis. In this study, all samples are from the same ethnicity (Asian), in which the application of our study result may not be eligible for other geographical areas with different ethnicities. Furthermore, we recognize the possibility of bias in this study, as there was no reason in choosing, in which patients were given tocilizumab and which were not. We also realize that sampling could be biased due to the data collection, which was done in a short time during this pandemic.

Conclusions

This study showed clinical improvement after the administration of tocilizumab in patients with moderate-to-mild ARDS in good saturation on oxygen supplementation without positive pressure. Giving the tocilizumab earlier in patients who have not experienced desaturation and severe respiratory distress will give a better outcome.

Although we reported good responses in patients with tocilizumab, the use of limited laboratory parameters to determine disease activity is still a challenge. Therefore, research and observation of COVID-19 patients is still needed to determine the appropriate timing of tocilizumab administration in preventing the need for intubation in terms of the patients' clinical characteristics and laboratory profiles.

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