Research Article

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# Tocilizumab Outcome in SARs-CoV-2 (COVID-19) Acute Respiratory Distress Syndrome Patients

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## Abstract

Objectives: Does Tocilizumab improved survival outcome in SARs-CoV-2 (COVID-19) Acute Respiratory Distress Syndrome patients?

Setting: Retrospective study was carried out in ICU and on floor patients at a secondary level hospital located in the Hudson Valley, New York, epicenter of Coronavirus pandemic.

Participants: 94 patients with COVID-19 Acute Respiratory Distress Syndrome (ARDS) were included in the study; 22 females and 72 males, at least 18 years old, with confirmed COVID-19 infection, admitted to the hospital between Mar 15, 2020 to Apr 20, 2020.

Interventions: Primary intervention included the administration of IV Tocilizumab 400 mg one-time dose amongst the study group.

Primary and Secondary Outcome Measures: We evaluated both the Tocilizumab and control group for survival as primary outcome. HS score, inflammatory markers, length of stay as secondary outcomes were also compared.

#### Background

The novel human coronavirus, severe acute respiratory syndrome coronavirus-2 (SARs-CoV-2), was declared a global pandemic by the World Health Organization on March 11, 2020 [1]. Hence, there is an urgency to find effective treatment. Of those patients afflicted in the United States, many have required treatment with ventilator secondary to ARDS. Data are needed regarding the benefit of treatment and prevention of the cytokine storms in COVID-19 patients with Tocilizumab.

**Methods:** We obtained data form patients admitted to Orange Regional Medical Center, (not for profit 383 bed hospital in the Hudson Valley, NY) with confirmed COVID-19 from Mar 15, 2020 to Apr 20, 2020 were identified through electronic health record chart review. We conducted a retrospective, single center study in confirmed COVID 19 positive patients with ARDS requiring mechanical ventilation and compared outcomes amongst those who received Tocilizumab as treatment modality opposed to those that did not.

**Results:** A total of 94 patients with COVID-19 ARDS were analyzed. 44 were in the study group and 50 in the control group. Average HS score was 114 in the Tocilizumab group and 92 in the control group, difference was statistically significant with P<0.0001. Also, the patients in the study group had elevated levels of IL-6, triglycerides, AST, ferritin which were statistically significant with p<0.0001 when compared to the control group. Length of stay was longer, average 17.9 days in the Tocilizumab. The overall survival rate was 61.3% in patients who received Tocilizumab compared to 48% in the control group; p = 0.1984. The number needed to treat (NNT) was 7.48, if we treat eight patients with Tocilizumab, one will survive.

**Conclusions:** Cytokine Release Syndrome (CRS) occurs in a large number of patients with severe COVID-19, which is also an important cause of death. IL- 6 is the key molecule of CRS, so IL-6R antagonist Tocilizumab may be of value in improving outcomes. In our study Tocilizumab group seemed to have increased survival outcome but result was not statistically significant. Results have to be interpreted with caution since this is a retrospective study and mortality is affected by multiple, confounding factors.

Keywords: COVID 19; Acute respiratory distress syndrome; Tocilizumab; IL-6; Cytokines; Survival outcome

Abbreviations: COVID-19: SARs-CoV-2; ARDS: Acute Respiratory Distress Syndrome; CRS: Cytokine Release Syndrome; SARS: Severe Acute Respiratory Syndrome; IL-6: Interleukin 6; ICU: Intensive Care Unit; RT-PCR: Reverse transcriptase polymerase chain reaction; IRB: Institutional Review Board

## Introduction

The novel human coronavirus, Severe acute respiratory syndrome coronavirus-2 (SARs-CoV-2), was declared a global pandemic by the World Health Organization on March 11, 2020 [1]. Over forty-six million confirmed cases and over a million deaths have been identified worldwide [2]. In the USA, there have been over 230,000 deaths as of October 2020 [2,3]. Hence, there is an urgency to find effective treatment. Of those patients afflicted in the United States, many have required treatment with ventilator secondary to acute respiratory distress syndrome.

The pathogenesis of severe acute respiratory syndrome (SARS) related to coronavirus involves a cytokine storm with high serum levels of proinflammatory cytokines and chemokines interleukin 6 (IL-6) [4]. The pro-inflammatory cytokine IL-6 seems to have a prominent role in this inflammatory cascade, which may result in increased alveolar-capillary blood-gas exchange dysfunction [4,5]. The most recent clinical experiences in Italy [6] and China [7] suggested that patients admitted to intensive care units, the cytokine storm syndrome was proportional to the severity of disease, often progressing to cardiovascular collapse, multiple organ dysfunction and death rapidly [8]. Therefore, early identification, treatment and prevention of the cytokine storms are of crucial importance for these patients.

Tocilizumab is a blocker of IL-6R, which can effectively block IL-6 signal transduction pathway. The safety of tocilizumab in phase III double-blind controlled trials was studied in patients with rheumatoid arthritis [9]. There were no complications associated with tocilizumab and no history of illness deterioration or death. Overall, the risk of secondary infection with Tocilizumab is not too high [9]. Data are needed regarding the benefit of treatment and prevention of the cytokine storms in COVID-19 patients with Tocilizumab. In our study we investigate use of Tocilizumab in COVID-19 ARDS patients and the effect on survival outcome.

A clinical trial in China has shown good efficacy in tocilizumab [10]. After a few days of treatment, patients experienced clinical improvement, became afebrile and with gradually decreased oxygen consumption, all other symptoms were significantly improved. CT chest showed regression of the pulmonary infiltrates and ground glass appearance [10]. Laboratory examination showed improvement in peripheral blood lymphocytes and C-reactive protein, suggesting that tocilizumab could be an efficient treatment for COVID-19 patients. Several multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of Coronavirus pneumonia (COVID-19) are underway [11,12]. A recent multicenter observational study of patients with COVID-19 requiring intensive care unit (ICU) support, receipt of tocilizumab was associated with a reduction in hospital-related mortality [13]. Similar results were also observed in retrospective studies [14,15].

## Methods

## **Study Population**

Orange Regional Medical Center serves diverse patient population in the Hudson Valley. In this study, patient data came from ICU and floor during the Coronavirus pandemic. We included patients who were at least 18 years old, had a laboratory confirmed COVID-19 infection with ARDS and were admitted to the hospital between Mar 15, 2020 to Apr 20, 2020. A confirmed case of COVID-19 was defined by a positive reverse transcriptase polymerase chain reaction (RT-PCR) assay of a specimen collected via nasopharyngeal swab. The Orange Regional Medical Center Institutional Review Board approved this research under a regulatory protocol allowing for analysis of limited patient data. Requirement for informed consent was waived by the IRB because this project represented a non-interventional study using data that had already been collected.

## **Study Design**

Retrospective, single center study with patients who received Tocilizumab as exposure group and those who did not receive as non-exposure group.

## **Data Collection**

We obtained demographics, laboratory test results, diagnosis codes (International Classification of Diseases-10) from ICU and floor progress notes during hospitalization. Demographics included age, sex, BMI in the electronic health records. All laboratory values (IL-6, triglyceride, ferritin, fibrinogen, AST) were obtained as part of indicated clinical care. Treatment modalities used were also compared (intravenous Tocilizumab – Dose 400 mg once). If patient required intubation; days on ventilator and proning was also taken into account for data analysis.

## **Definitions of Outcomes**

We assessed number of days on ventilator, total length of hospital stay, mortality, survival and number needed to treat.

#### **Statistical Analysis**

We used descriptive statistics to summarize the data; results are reported as Medians, ranges, mean, IQR and p-values as appropriate. Categorical variables were summarized as counts and percentages. Comparison of mean between Tocilizumab and non- Tocilizumab group within 1 Standard deviation and 95% Confidence Interval. Prism 8 software was used for statistical analysis using unpaired t test and statistical significance was defined as P<0.05.

A total of 94 patients with COVID-19 ARDS were analyzed. 44 were in the study group and 50 in the control group. The median age was 55.8 years [IQR 22] in the study group and 62.4 in the control [IQR 17]; p=0.0293. Mean BMI was 33.4 vs 32.5 comparatively p=0.5896. Average HS score was 115.7 in the Tocilizumab group and 85.3 in the control group; p = 0.0011. Also, the patients in the study group had elevated levels of IL-6, triglycerides, AST, ferritin which were statistically significant with p < 0.0001 when compared to the control group. Length of stay in hospital (including ICU days) was longer, average 17.9 days in the Tocilizumab vs 11.0 in the control group. Patients who received Tocilizumab also were on the ventilator for an average of 12.2 days as compared to 5.7 days; p = < 0.0001. Almost all patient in Tocilizumab group were proned (97.73%) compared to half (48%) of control group. Out of all patients who received Tocilizumab 84.1 % were male and 15.9% were females. The overall survival rate was 61.3% in patients who received Tocilizumab compared to 48% in the control group; p =0.1984. 59.4% of male patients survived compared to 71.4% females if they received Tocilizumab. Total 72 males and 22 females were enrolled in this study, indicating that male gender has predominance of being affected with COVID-19. The number needed to treat (NNT) was 7.48, if we treat eight patients with Tocilizumab, one will survive.

#### Discussion

The COVID-19 pandemic presents as a public health challenge and emergency. Limited data is available in the US to guide management with effective treatment. For COVID-19 infection, clinical studies have shown that serum levels of inflammatory mediators are significantly higher in patients with severe disease [16-18]. Excessive immune responses can trigger cytokine storms and cause damage to multiple target organs [18,19]. Recent guidelines also point that a progressive rise in IL-6 may be a clinical warning indicator for the deterioration of COVID-19 [19]. Tocilizumab, a monoclonal antibody against interleukin-6, emerged as an alternative treatment for COVID-19 patients with a risk of cytokine storms [20]. In our study, we aimed to discuss the treatment response of therapy in COVID-19 infected patients in terms of survival outcome.

This study provides a perspective on patients admitted with confirmed COVID-19 ARDS in both Intensive care and floor setting. Our hospital serves an ethnically and socioeconomically diverse population being close to New York City. A COVID-19 laboratory order set was used in the EMR to order labs at the time of hospital admission or ICU transfer which included IL-6, ferritin, CRP, triglyceride, Fibrinogen, D-dimer, CMP and CBC with differential. The majority of patients were admitted to the ICU because of acute hypoxemic respiratory failure that required respiratory support. Endotracheal intubation and invasive mechanical ventilation were needed in a significant proportion of the patients. Several key findings were observed in the Tocilizumab group laboratory values of IL-6, Ferritin, Triglyceride and Fibrinogen were significantly higher indicating that these patients demonstrated cytokine storms. Early laboratory evaluation may be crucial in identifying cytokine storm and may also aid clinicians in identifying patients at high risk of decompensation, ICU admission, and potentially even death. A study from China reported that increased expression of interleukin (IL)-2R and IL-6 in serum appears to predict the severity and prognosis of patients with COVID-19 [21]. Elevated levels of the inflammatory indicator IL-6 in the blood have been reported to be predictive of a fatal outcome in patients with COVID-19 [22].

Our study should be considered in light of several limitations with possibility of sampling bias and unknown confounders. Data was obtained on a retrospective basis to perform a rapid investigation during pandemic. It was focused on patients in the Hudson Valley, NY although US has diverse patient population. Patients who received Tocilizumab in our study had more severe disease with higher inflammatory markers. Also, with longer duration of ventilation and hospital stay, which probably skewed our mortality rates. In the study group 5 patients did not have fibrinogen level tested before they received Tocilizumab and in the control group 11 patients did not have the results for fibrinogen. A recent randomized, double-blind, placebo-controlled trial, also did not find any efficacy of Tocilizumab for the treatment of hospitalized patients with Covid- 19 [23].

## Conclusion

In the context of the urgent need for effective therapies in the current pandemic, particularly in severe cases. However, there is no systematically recommended treatment for COVID-19. Tocilizumab is a humanized monoclonal antibody against the in-terleukin-6 receptor (IL-6R) and is FDAapproved for cytokine release syndrome and recently, has been administered experimentally in the treatment of severe COVID-19 pneumonia in China and Italy with promising results [24]. Cytokine Release Syndrome (CRS) occurs in a large number of patients with severe COVID-19, which is also an important cause of death. IL- 6 is the key molecule of CRS, so Tocilizumab may be of value in improving outcomes. In our study Tocilizumab group seemed to have increased survival but was not statistically significant. Results have to be interpreted with caution since this a retrospective study and mortality is affected by multiple, confounding factors. COVACTA trial also did not demonstrate benefit for patients in either clinical status or reduced mortality [25]. In the largest clinical trials database (clinicaltrials. gov) there are several ongoing studies registered around the world regarding the use of Tocilizumab in COVID-19 patients.

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Ethics Approval and Consent to Participate: Orange Regional Medical Center Institutional Review Board (ethics committee) approved the study, committee's reference number HH2011, need for consent was waived.

Availability of Data and Material: The datasets analyzed during the current study is available from the corresponding author on request.

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# Table 1: Comparison of demographics, laboratory findings and out comes in the Tocilizumab and non - Tocilizumab group

	Tocilizumab group	No Tocilizumab
Age (years)		
Range	57.00	71.00
Mean	71.5	84.5
Median	55.86	62.48
P value	0.0293	0.0293
IQR	22.00	17.00
SD	13.02	15.59
SEM	1.96	2.20
Sex, n	n-44	n-50
Male	37 (84.09%)	35 (70%)
Female	7(15.91 %)	15 (30%)
BMI (kg/m <sup>2</sup> )		
Range	25.05	40.17
Mean	33.45	32.59
Median	33.27	31.22
P value	0.5896	0.5896
IQR	7.56	11.30
Standard deviation	6.08	8.86
SEM	0.91	1.25
IL-6 (pg/mL)		
Range	4068.00	2087.00
Mean	410.01	250.30
Median	143.37	118.60
P value	0.0004	0.0004
IQR	444.26	173.53
SD	718.7	402.6
SEM	113.6	62.12
Triglyceride (mg/dL)		
Range	954.00	960.00
Mean	381.69	268.60
Median	326.00	178.00
P value	0.0225	0.0225
IQR	194.00	272.8
Standard deviation	230.80	233.00
SEM	35.19	33.63
Ferritin (ng/mL)		
Range	7380.00	3117.00
Mean	1786.36	850.53
Median	1378	808
P value	0.0005	0.0005
IQR	1509.00	990.50
Standard deviation	1710.00	610.80
SEM	257.70	87.25
Fibrinogen (mg/dL)		
Range	763.00	639.00
Mean	690.64	622.61
Median	697	624
P value	0.0834	0.0834
IQR	262.00	304.00
Standard deviation	215.5	162.10
SEM	34.51	25.96

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Range	739.00	5357.00
Mean	115.77	195.14
Median	114	71
P value	<0.0001	< 0.0001
IQR	69.00	73.25
Standard deviation	139.80	751.30
SEM	21.08	106.30
Hscore		
Range	139.00	209.00
Mean	115.17	85.37
Median	114	92
P value	0.0011	0.0011
IQR	51.00	53.00
Standard deviation	35.04	43.79
SEM	5.61	6.67
Length of stay (days)		
Range	32.00	31.00
Mean	17.97	11.06
Median	18.00	9.00
P value	0.0001	0.0001
IQR	13.75	9.50
Standard deviation	8.39	8.11
SEM	1.26	1.14
Days on Ventilator (days)		
Range	25.00	22.00
Mean	12.26	5.76
Median	12.00	4.00
P value	<0.0001	<0.0001
IQR	12.00	9.25
Standard deviation	6.81	6.20
SEM	1.03	0.87
Proning		
N	43 (97.73%)	24 (48%)
Range	1.00	1.00
Mean	0.97	0.48
Median	1.00	0.00
P value	<0.0001	<0.0001
IQR	0.00	1.00
Standard deviation	0.15	0.50
SEM	0.02	0.07
Survival (n, %)		
N	27 (61.36 %)	24 (48.00%)
Range	1.00	1.00
Mean	0.61	0.48
Median	1.00	0.00
P value	0 1984	0.1984
IOR	1.00	1.00
Standard deviation	0.49	0.50
SEM	0.07	0.07
Mala	22(81.409/)	18(750/)
iviaiC	22(01.4070)	10(/370)

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