ORIGINAL ARTICLE

Tocilizumab Use in COVID-19 Cytokine-release Syndrome: Retrospective Study of Two Centers

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Abstract

Introduction: Cytokine-release syndrome (CRS) in COVID-19 patients can cause multiorgan failure and higher mortality. We used a structured protocol based on clinical, biochemical, and interleukin 6 (IL-6) criteria for the identification of the subset of patients with CRS and analyzed the use of tocilizumab for their treatment.

Materials and methods: We did a retrospective case-control analysis of all COVID-19 patients between 15 March and 15 May 2020 with severe to critical disease in ICU. They were evaluated for CRS, and 22 patients who met the criterion were given tocilizumab. The primary objective was to evaluate the effect of tocilizumab on escalation of respiratory support and ICU mortality. The secondary objectives were ICU length of stay, trends of inflammatory markers, and any adverse effects.

Results: The need for escalation of respiratory support was significantly lower in the tocilizumab group as compared to standard treatment ($p = 0.001$). The mortality at day 7 and 28 was also significantly lower in the tocilizumab group ($p = 0.007$ and $p = 0.001$ respectively). There was a significant reduction in C-reactive protein (CRP) who received tocilizumab ($p = 0.033$).

Conclusion: In our limited number of patients, timely intervention with tocilizumab in COVID-19 patients with CRS significantly improved overall ICU outcome by reducing the need for invasive ventilation and mortality.

Keywords: Acute respiratory distress syndrome, Coronavirus, COVID pneumonia, COVID-19, Critically ill, Cytokine-release syndrome, Cytokine storm, SARS-CoV-2, Tocilizumab, Transfer, Transport.

Indian Journal of Critical Care Medicine (2020): 10.5005/jp-journals-10071-23566

Background

The COVID-19 pandemic has evolved into an unprecedented threat to human life and global economy. In the past few months intensive care units (ICU) globally are inundated by admissions of COVID-19 related respiratory failure. There is already enormous medical literature published on COVID-19, but clinicians across the world are searching for a pragmatic treatment approach for these patients. The pathogenesis of COVID-19 is still incompletely understood, but available evidence suggests disease severity is directly linked with increased inflammatory markers like cytokines (interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)-α) and chemokines.[1] Cytokine-release syndrome (CRS) is one of the key pathophysiological process involved in sudden deterioration with COVID-19 causing acute respiratory distress syndrome (ARDS) and other multiorgan failure (MOF).[1,2] Tocilizumab, a monoclonal antibody against IL-6 receptor, has been used "off-label" in some studies with variable success for these patients.[3–6] We used a structured protocol based on clinical, biochemical, and IL6 criteria for the identification of the subset of patients with CRS and used tocilizumab for their treatment.

Materials and Methods

From 15 March to 15 May, we received a total of 112 COVID-19 patients in our ICU. The respiratory severity of illness was decided by clinical, radiological, and oxygenation using arterial blood gas (Table 1). Eighty-five of the 112 (76.57%) patients developed severe and critical category of illness. We did a retrospective case-control analysis of all severe and critical COVID-19 patients who developed deterioration in ICU. There were 22 patients in the severe and critical category who received tocilizumab in addition to conventional care.

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How to cite this article: Nasa P, Singh A, Upadhyay S, Bagadia S, Polumuru S, Shrivastava PK, *et al.* Tocilizumab Use in COVID-19 Cytokine-release Syndrome: Retrospective Study of Two Centers. Indian J Crit Care Med 2020;24(9):771–776.

Source of support: Nil

Conflict of interest: None

Identification of CRS

All of the patients who developed severe and critical illness during their ICU stay (Table 1) were assessed independently by both an ICU physician and admitting physician using a protocol based on clinical grading, biochemical markers like C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, D-dimer, and IL6 (Table 2). The patients who met the criteria of CRS as per the three-step protocol and did not have any contraindications (Table 2) were

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given tocilizumab at 8 mg/kg (maximum 800 mg) in two divided doses 12 hours apart. The patients who did not meet complete CRS criteria continued to receive standard treatment.

Table 1: Respiratory severity assessment of COVID-19

Severity	*Clinical feature*
Asymptomatic	PCR positive but no symptoms
Mild	Upper respiratory tract symptoms or digestive tract
Moderate	Pneumonia and lower respiratory tract symptoms with no obvious hypoxemia, chest CT with lesions
Severe	Pneumonia with respiratory distress
	Hypoxemia (SpO_2 < 92%), PaO_2/FiO_2 less than 300
	RR >30 in adults and >40 in pediatrics
Critical	Acute respiratory distress syndrome (ARDS), may have shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction and acute kidney injury.

CT, computed tomography; RR, respiratory rate; PCR, polymerase chain reaction

Standard Treatment

The management of the patients in severe and critical category included antivirals—hydroxychloroquine, 400 mg 12 hourly on day 1 followed by 200 mg 12 hourly for 10 days, lopinavir 400 mg + ritonavir 100 mg combination twice a day for 10 days, or favipiravir 1600 mg 12 hourly on day 1 followed by 600 mg 12 hourly for 2–5 day as per national guidelines. The patients were daily monitored for the corrected QT (QTc) interval using electrocardiogram and received other supportive management such as low molecular weight heparin (enoxaparin) and low dose steroids (1 mg/kg/day of methylprednisolone) for 7–10 days.

The patients with acute hypoxemic respiratory failure (AHRF) were given a trial of high flow nasal canula (HFNC) and/or noninvasive ventilation (NIV) in ICU to achieve SpO_2 of 88–93%, if there was no contraindication. The decision of tracheal intubation in each patient was taken by at least two physicians, one of whom was an intensivist.

The indications for tracheal intubation were:

- Rapid progression of hypoxemia over hours.
- Signs of respiratory fatigue (excessive use of accessory muscles of breathing, hypercarbia (pCO_2 more than 45 mm Hg), and/or altered mental status)

Table 2: Criteria for diagnosis of CRS and tocilizumab administration

A. Clinical criteria		
	Definition	*Intervention*
Grade I mild	Pneumonia with no oxygen requirement	No treatment with TCZ
Grade II moderate	Fever, need for IV fluid (not hypotension), mild oxygen requirement (FiO_2 less than 40%)	No treatment with TCZ
		Send IL-6
Grade III severe	New organ dysfunction: liver test dysfunction, acute kidney injury, sepsis: IVF for resuscitation, low-dose vasopressor, supplemental oxygen (HFNC HFNBM, $FiO_2 \geq 40\%$, NIV)	Send IL-6
		Consider TCZ
Grade IV critical	Life-threatening, mechanical ventilation, high-dose vasopressors	Send IL-6
		Consider TCZ and steroids-low dose

B. Inflammatory markers	
Ferritin	300 µg/L with doubling within 24 hours
	>600 µg/L at presentation
LDH	>250 U/L
Elevated D-dimer	>1 mg/mL
CRP	>150

C. Interleukin-6 (IL-6): more than 10 times of upper limit of normal (<7 pg/mL)

D. Exclusion criteria for tocilizumab exclusion

- Active TB
- AST/ALT values higher than 5 times the normal levels.
- Neutrophil value lower than 500 cells/mm^3
- Platelets value lower than 50,000 cells/mm^3
- Complicated diverticulitis or intestinal perforation.
- Confirmed systemic bacterial and/or fungal infection (i.e., bacteremia with pathogenic bacteria, fungemia)
- Pregnant women
- Skin infection in progress (e.g., dermohypodermatitis not controlled by antibiotic therapy)
- Immunosuppressive antirejection therapy
- Absence of overt bacterial or fungal infection.

IL6, interleukin 6; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TB, tuberculosis; LDH, lactate dehydrogenase; CRP, C-reactive protein; TCZ, tocilizumab; HFNC, high-flow nasal canula; HFNBM, high-flow (more than 10 lit) nonrebreathing mask; NIV, noninvasive ventilation

- Unable to maintain oxygen saturation (SpO_2) >88% on HFNC with a flow of 50 L/minute and $FiO_2 \geq 60\%$
- Unable to maintain $SpO_2 > 88\%$ on NIV with $FiO_2 \geq 60\%$ and/or persistent use of NIV for more ≥48 hours.
- Hemodynamic instability.

Data Collection

We collected data of 22 patients who received two doses of tocilizumab for inflammatory markers, total leukocyte count (TLC) and lymphocyte percentage, oxygenation (PaO_2/FiO_2 ratio), and type of respiratory support for seven days. The patient demographics and comorbidities, ICU length of stay (ICU-LOS), and mortality at day 7 and day 28 of all 85 patients were collected. The informed consent was requested from all surviving patients as soon as they regained their mental competency or the next of kin where patient's consent was not possible. Data regarding any side effects or adverse events such as hepatotoxicity, allergic reactions during infusion of tocilizumab, and any secondary infection within one week of administration were also collected.

Statistical Calculation

The continuous variables were expressed as means [standard deviation (SD)], medians (interquartile ranges). The categorical variables were expressed in counts and percentages. Categorical variables compared using Fisher's exact or Chi square and paired *t* test and repeated measures ANOVA (trend in repeated measurements) for continuous variables. A *p* value less than 0.05 was taken as significant. IBM SPSS (version 26.0, Armonk, NY: IBM Corp.) was used for analysis. All investigations were conducted according to the principles expressed in the Declaration of Helsinki.

Objectives of the Study

Primary Objective

- Effect of tocilizumab on mortality at day 7 and 28 in patients with severe and critical illness as compared to standard treatment.
- Effect of tocilizumab on the need for escalation of respiratory support (invasive or noninvasive ventilation) as compared to standard treatment.

Secondary Objective

- Effect of tocilizumab on ICU-LOS vs standard treatment.
- To understand any significant trend in inflammatory markers in response to tocilizumab administration.

To identify any adverse events including hepatoxicity, allergic reaction, and secondary infections in tocilizumab group.

Results

The data from all 85 patients were collected.

Demographic Characteristics

Most of the patients were male in both tocilizumab and standard treatment groups. The average age was 51 years in the tocilizumab group vs 52 years in the standard treatment group ($p = 0.684$). Obesity (BMI > 30 kg/m^2) was a common risk among patients admitted to ICU, 63% in the tocilizumab group and 66.7% in standard treatment group ($p = 0.799$) (Table 3).

Comorbidities

Hypertension was the most common comorbidity in both the tocilizumab and standard treatment groups (72% vs 63%, $p = 0.604$) followed by diabetes mellitus (59% vs 55.6% $p = 0.808$).

Outcomes

Primary Outcome (Table 3)

Mortality: The mortality was significantly lower in the tocilizumab group vs standard treatment group at day 7 (9.1% vs 39.7%, $p = 0.007$) and 28 (9.1% vs 57.1%, $p = 0.001$) (Fig. 1).

Escalation of respiratory support: the need for escalation of respiratory support was also significantly lower in the tocilizumab vs standard treatment group (22.7% vs 65.1% $p = 0.001$) (Fig. 1). There

Table 3: Comparison between tocilizumab and standard treatment group

Variables	*Tocilizumab (percentage of total)*	*Standard treatment (percentage of total)*	*p value ($p \leq 0.05$, significant)*
Number of patients	22	63	
Gender (male/female)	22/0	60/3	
Average age (mean)	51	52	$p = 0.684$
BMI (>30 kg/m^2)	14(63%)	42 (66.7%)	$p = 0.799$
Comorbidities			
Hypertension	16(72%)	41 (63%)	$p = 0.604$
Diabetes mellitus	13 (59%)	35 (55.6%)	$p = 0.808$
Cardiovascular disease	5 (22.7%)	19 (30.1%)	$p = 0.590$
COPD or asthma	2 (8.6%)	10 (15.9%)	$p = 0.723$
Chronic kidney disease	3(13.6%)	9 (14.3%)	$p = 1.00$
Invasive ventilation	4(18.2%)	39 (61.9%)	**$p = 0.000$**
Outcome			
Escalation of treatment	5 (22.7%)	41 (65.1%)	**0.001**
Mortality at day 28	2 (9.1%)	36 (57.14%)	**0.001**
Mean ICU LOS (SD) (in days)	11.31 (5.21)	9.73 (8.32)	0.35

BMI, body mass index; COPD, chronic obstructive pulmonary disease; LOS, length of stay
p values ≤ 0.05

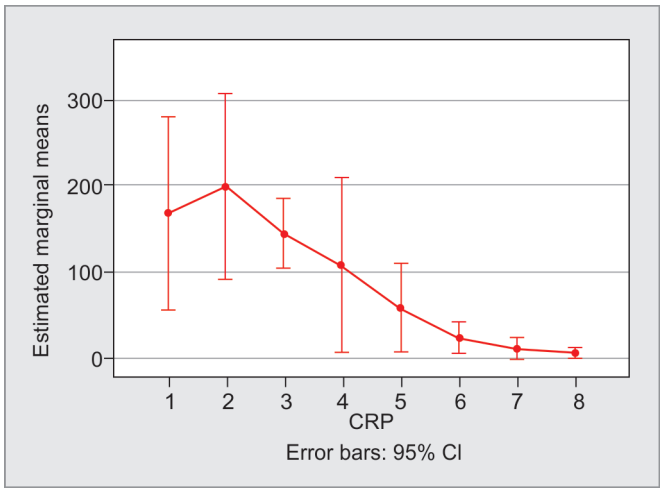

Fig. 1: Trend of CRP after tocilizumab administration

was also a requirement of less invasive ventilation in the tocilizumab group (18.2% vs 61.95%, $p = 0.000$).

Secondary Outcome

CRP reduction among the inflammatory markers showed a significant trend in the tocilizumab group by day 3 ($p = 0.033$) (Table 4 and Fig. 2).

ICU length of stay was more in the tocilizumab group vs standard treatment group (11.31 vs 9.73, $p = 0.35$) (Table 3).

There were two patients (9.1%) in the tocilizumab group with elevations of liver function tests (LFT)—five times the baseline and two patients (9.1%) developed secondary sepsis, both bacterial, within one week of administration requiring escalation or change of antibiotics.

The tocilizumab administration from day of hospital admission was a median of three (1–8) days.

Discussion

The understanding of pathophysiology in respiratory failure caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is still evolving. There is a definitive role of host immune response to SARS-CoV-2 related ARDS and MOF.[1,7] The hypercytokinemia is seen with COVID-19 in many epidemiological studies while the CRS which is characterized by exuberant systemic inflammation and higher mortality is seen with severe illness.[8] IL-6 is a major mediator in CRS, and its levels have been closely linked to SARS-CoV-2 viral load, ARDS severity, and outcome.[1,8–10]

The timely detection of CRS and its treatment can improve outcomes in such patients.[1,3,6] We used a pragmatic protocol to identify these patients. In our study we started tocilizumab when IL-6 was ten times the upper limit of normal in the absence of any obvious bacterial or fungal infection as a marker of CRS. The mean IL6 in our patients was 205.26 and median 145.9. There was male preponderance in our patients, and hypertension was the commonest associated comorbidity. The mortality at day 7 ($p = 0.007$) and day 28 ($p = 0.001$) and need for escalation of respiratory support ($p = 0.001$) were statistically significant lower in the patients who received tocilizumab vs standard treatment (Table 3, Fig. 1). Recent studies involving a large number of patients from Italy and New York have reported worse outcomes in COVID-19 patients requiring invasive ventilation.[11,12] Avoiding invasive mechanical

Table 4: Seven-day trend of inflammatory markers in the tocilizumab group

Variables		*Base*	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*	*p value*
LDH	Mean	563.13	666.23	671.53	555.55	760.02	845.90	755.88	654.08	0.082
	SD	223.97	273.25	199.44	288.25	254.93	271.89	296.50	196.41	
	n	6	6	6	6	6	6	6	6	
CRP	Mean	168.84	200.92	145.64	108.58	59.42	24.16	11.90	6.58	0.033
	SD	91.44	87.53	32.40	82.00	41.61	15.21	9.84	5.20	
	n	5	5	5	5	5	5	5	5	
Ferritin	Mean	1465.23	1623.82	1779.83	1766.50	1757.67	1568.17	1280.45	1309.50	0.245
	SD	838.01	582.81	469.66	571.96	590.17	697.04	657.22	627.01	
	n	6	6	6	6	6	6	6	6	
D-dimer	Mean	726.04	791.00	1395.00	934.00	1853.20	1931.20	1891.40	2277.60	0.438
	SD	479.85	505.73	2015.74	788.95	1993.19	1831.18	1251.84	1912.89	
	n	5	5	5	5	5	5	5	5	
Lympho	Mean	8.78	9.42	9.88	10.57	12.47	12.22	11.58	13.34	0.256
	SD	2.37	2.26	2.17	2.95	4.97	5.06	4.61	6.34	
	n	6	6	6	6	6	6	6	6	

LDH, lactate dehydrogenase (IU/L); CRP, C-reactive protein mg/dL; ferritin (ng/L); lymphocytes; D-dimer (ng/mL)

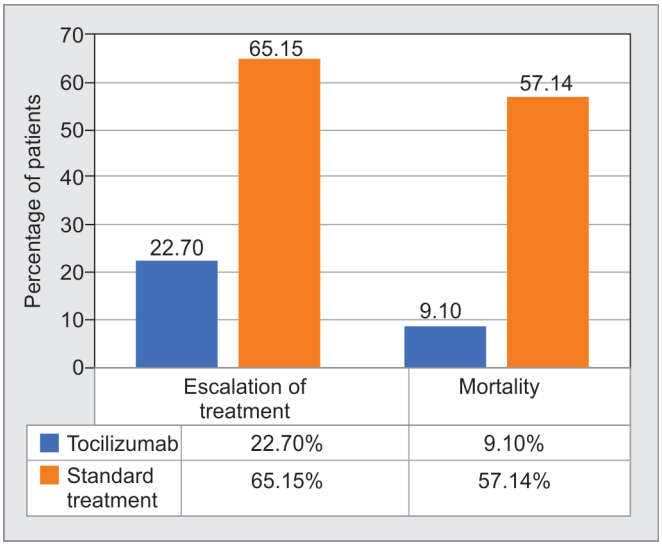

Fig. 2: Outcome between tocilizumab and standard treatment

ventilation may itself be a strategy to reduce the overall mortality. The timely identification of CRS and administration of tocilizumab to the patients reduce the need for escalation of respiratory support such as invasive ventilation in these patients and hence reduced mortality. The ICU-LOS was higher in the tocilizumab group but was not statistically significant, which can be partly explained by the higher need for escalation in standard treatment group and early mortality. On reviewing the trends of inflammatory markers, only CRP showed a significant decline with the use of tocilizumab by day 3 ($p = 0.033$) as reported by other studies (Table 4 and Fig. 2).[5]

Hypercytokinemia is a hallmark of COVID-19; however, serum levels of cytokines observed are generally below the usual levels observed in CRS or similar disorders such as macrophage activation syndrome/reactive hemophagocytic lympho-histiocytosis (MAS/reHLH).[1,2] Thus, CRS should be considered with SARS-CoV-2 infection only in cases of overly exuberant systemic inflammation leading to critical illness such as ARDS or MOF.[8,9] We used tocilizumab only in patients with IL6 above 70 (10 times the upper limit of normal laboratory value).

This is one of the few studies that reported use of tocilizumab only in severely and critically ill patients with ARDS, who are more likely to have the benefit of the immunomodulators on CRS. We also used higher values of IL-6 (10 times upper limit of normal) as our inclusion criteria. The steroids were used in all our severe and critically ill patients for 7–10 days. In a recently published RECOVERY trial on COVID-19 patients, dexamethasone, statistically reduces the mortality by one-third in patients on mechanical ventilation (hazard ratio = 0.65, $p = 0.003$).[13] The dramatic effect of dexamethasone in severe illness also proves the hypothesis that hyperinflammation significantly contributes to ARDS seen with COVID-19. The use of immunomodulator such as tocilizumab with specific action on IL6 and its possible synergistic action with steroids is likely responsible for good outcomes in our study.

The strength of this study was inclusion of only critically ill patients with IL6 value 10 times the upper limit of normal. This was important to separate the subset of CRS from hyperinflammation. The exclusion of secondary bacterial and fungal sepsis was another criterion. There are, however, a few limitations for our study retrospective cohort, small numbers of patients and effect of steroids on the outcomes. The effect size of outcome could have been exaggerated due to limited numbers of the patients in the study. Despite its limitations, this study proves use of simple pragmatic protocol for early identification of CRS and treatment with tocilizumab and steroids for 7–10 days can significantly improve the outcome in these patients.

Conclusion

Tocilizumab can improve outcome by reducing the need for invasive ventilation and mortality when used timely in patients with CRS. We propose a double-blind randomized study involving a larger sample size and using IL6 and other inflammatory markers to evaluate its potential therapeutic role of tocilizumab in CRS seen with COVID-19.

Highlights

- Cytokine release syndrome (CRS) can cause sudden deterioration in few patients of COVID-19 and can be identified using clinical deterioration with inflammatory markers and IL-6.
- Tocilizumab can improve outcome by reducing the need of invasive ventilation and mortality when used timely in patients with CRS.

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