Original Article

Clinical experience of tocilizumab treatment among a cohort of patients with COVID-19 infection from Western India

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Abstract

Background: Initiation of tocilizumab (TCZ) treatment in patients with coronavirus disease 2019 (COVID-19) during the early phases of cytokine storm is crucial. This study evaluated the clinical experience of TCZ use in the treatment of patients with COVID-19. **Methods:** This retrospective observational study included patients (>18 years) with confirmed COVID19 treated with TCZ alone/in combination with other drugs. Data related to demographics, clinical characteristics, radiological parameters, oxygen/ventilator/vasopressor support, treatment parameters, laboratory investigations pre- and post-TCZ treatment, and clinical outcomes were retrieved from medical records. **Results:** Out of 95 patients (mean age, 55 years), 68.4% and 31.6% of patients had moderate and severe COVID-19 disease, respectively. The mean time to TCZ administration from symptom onset was 8.7 days. At the time of admission, the mean oxygen saturation (SpO_2) was 90.4% and mean concentration of fraction of inspired oxygen (FiO_2) was 80.6%. The most commonly received dose of TCZ was 400 mg (84.2%) intravenously. The mean concentration of FiO_2 and SpO_2 improved significantly during the treatment ($P < 0.001$) compared to before TCZ initiation. The change in median levels of C-reactive protein (CRP) from baseline to post-treatment (63.0 vs. 4.5 mg/dL; $P < 0.001$) was significant. Post TCZ treatment, 73.6% of patients improved; whereas 26.4% of patients died. Acute respiratory distress syndrome (23.2%) and elevated transaminases (12.6%) were the most commonly reported adverse events. **Conclusion:** Tocilizumab administration during earlier phase of cytokine storm syndrome leads to reversal of abnormal SpO_2 and FiO_2 concentrations to normal levels and rapid decline of elevated CRP levels in patients with COVID-19.

Keywords: Cytokine storm syndrome, inflammatory markers, moderate and severe, oxygen saturation, TCZ treatment

Introduction

Effective and early treatment is a key to successful recovery from coronavirus disease 2019 (COVID-19) infection. Since the start of COVID-19 pandemic and as the time progresses, the knowledge of different pathogenic mechanisms that may be involved in COVID-19 disease is getting revealed. Evidence indicates cytokine storm syndrome leading to hyperinflammation, is one of the important predictors of morbidity and mortality in patients with COVID-19. Furthermore, rapid rise in proinflammatory cytokine interleukin-6 (IL-6) levels is associated with severity of COVID-19 infection.[1-3] Therefore, tocilizumab (TCZ), an IL-6 inhibitor, is being explored in various studies for its efficacy and safety in alleviating the inflammatory responses and thereby improving survival outcomes.

Onset of cytokine storm seems to occur within the 8--10 days of symptom occurrence and then aggravates to severe respiratory

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failure leading to death. Therefore, the key element that may decide efficacy and safety of TCZ therapy is the time of initiation during the course of COVID-19 disease.[1,4,5] Indian studies evaluating clinical effectiveness and tolerability of TCZ in patients with COVID-19 are scarce[5,6] and there is a need to establish a better efficacy and safety profile of TCZ in COVID-19. Therefore, the present retrospective study aimed to assess the clinical experience of TCZ use in the treatment of patients with COVID-19 from Western India. Further this study will add evidence to the presently available literature and help primary care physicians to understand effectiveness of TCZ in Indian clinical practice.

Methods

Study design and settings

This was a retrospective observational study conducted in patients with confirmed COVID19 infection admitted at two tertiary care centers from Maharashtra, India (MPCT hospital, Navi Mumbai and Surana Sethia Hospital and Research center, Chembur, Mumbai) during 26 May, 2020 to 17 July, 2020.

The study protocol was approved by the ethics committee. The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines.

Inclusion criteria

Adult patients (>18 years) of either sex, with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection through reverse transcription polymerase chain reaction (RT-PCR) and treated with TCZ alone or in combination with other drugs were included.

Patients were treated with TCZ mainly on the basis of treating clinicians' judgement of clinical condition of each patient. The indications for TCZ administration were as follows: a) deterioration of clinical condition (patient during the second week of presentation with high oxygen requirement or those who presented with moderate disease with progressively increasing oxygen requirements or in mechanically ventilated patients not improving despite use of steroids or those with persistent fever at 101 degree F); and/or b) evidence of cytokine storm or elevated inflammatory markers (patients with any two criteria out of three criteria: i) serum ferritin level >3-fold rise; ii) c-reactive protein (CRP) level >20 mg/L and rising; or iii) IL 6 level >3-fold rise).[7]

Exclusion criteria

Patients with pregnancy, malignancy, active tuberculosis, bacterial/fungal infection, abnormal liver function test (transaminitis >5 times of normal), platelets <50000/mm^3 or who were in immunocompromised state were excluded from the TCZ treatment and subsequently from this study as well.

Data collection

Data related to patient demographics and clinical characteristics (age, sex, clinical symptoms at presentation, severity of COVID-19 illness [mild/moderate/severe], and comorbidities), radiological parameters (chest X-ray findings and computed tomography severity score), duration from symptom onset to hospital admission, duration from symptom onset to TCZ administration, duration of intensive care unit (ICU) stay, oxygen/ventilator/vasopressor support, COVID-19 treatment parameters (TCZ with or without other antiviral/antibacterial/anti-inflammatory drugs, dosage pattern, frequency, and duration of treatment), concomitant medications, laboratory investigations pre- and post-TCZ treatment (ferritin, CRP, IL-6, D-dimer, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) profile, total bilirubin, procalcitonin, and complete blood count parameters) and clinical outcomes (improved/death) were retrieved from medical records of each patient. In addition, average oxygen saturation (SpO_2) levels, body temperature, and concentration of fraction of inspired oxygen (FiO_2) before treatment initiation and during seven-day period of treatment were recorded. Changes in oxygen support requirement during the hospitalization period and oxygen status were also extracted.

Definitions

- Mild COVID-19 infection was defined as symptomatic patients with uncomplicated upper respiratory tract infection, mild symptoms, such as fever, cough, sore throat, nasal congestion, malaise, and headache without evidence of viral pneumonia or hypoxia.
- Moderate COVID-19 infection was defined as patients with pneumonia with no signs of severe disease (with presence of clinical features of dyspnea and or hypoxia, fever, cough, including oxygen saturation (SpO_2) <94% (range 90-94%) on room air, respiratory rate ≥24 breaths/min.
- Severe COVID-19 infection was defined as patients with clinical signs of pneumonia plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, oxygen saturation (SpO_2) <90% on room air.
- Patients whose oxygen requirement decreased after administration of TCZ and got discharged in stable haemodynamic status were considered as clinically improved.
- High-flow oxygen support: High-flow systems are specific devices that deliver the patient's entire ventilatory demand through nonrebreathing mask, meeting, or exceeding the patients peak inspiratory flow rate, thereby providing an accurate FiO_2.
- Low-flow oxygen support: Low-flow systems are specific devices that do not provide the patient's entire ventilatory requirements; room air is entrained with the oxygen, diluting the FiO_2.
- Mechanical ventilation: Mechanical ventilation can be defined as the technique through which gas is moved toward and from the lungs through an external device connected directly to the patient.
- Ambient air means at room air concentration.
- Noninvasive ventilation (NIV) is the use of breathing support administered through a face mask, nasal mask, or a helmet.

Air, usually with added oxygen, is given through the mask under positive pressure; generally, the amount of pressure is alternated depending on whether someone is breathing in or out.[8,9]

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 23.0. The one-way analysis of variance test was used to analyze change in continuous parameters across different time-points. The paired nonparametric Wilcoxon signed-rank test was used to compare variables pre- and posttreatment. The Kaplan-Meier plots were used to analyze time-to-event outcomes (clinical improvement and mortality).

Results

Patients

A total of 95 patients with confirmed COVID-19 infection administered with TCZ were included in this study. Of these, 77 were men (81.1%) and 18 were women (18.9%). The mean age of the patients was 55.5 years. The most common presenting symptoms were difficulty in breathing (90.5%; $n = 86$), cough (80.0%; $n = 76$), followed by fever (67.4%; $n = 64$) and sore throat (64.2%; $n = 61$). Majority of study patients were diagnosed with moderate (68.4%) COVID-19 disease, whereas 31.6% with severe COVID-19 disease. Hypertension (51.6%) and diabetes mellitus (34.7%) were the most common comorbidities observed [Table 1].

Table 1 summarizes results of baseline laboratory tests before TCZ administration. Patients showed elevated median levels of IL-6 (56.4 pg/mL), CRP (63.5 mg/dL), ferritin (0.4 μg/mL), procalcitonin (0.1 nmol/L), AST (40.5 IU/L), ALT (44.0 IU/L), and a positive D-dimer test (0.6 μg/mL) at the time of admission. The median lymphocyte count was in the normal range (16.0×10^9 cells/L) indicating absence of lymphopenia in the overall study patients. While median neutrophil-lymphocyte ratio was abnormal/elevated.

Chest X-ray at initial presentation showed inhomogeneous opacities in both mid and lower zones in 27.4% of patients. Bilateral consolidation, infiltrates, haziness were observed in 24.2%, 20.0%, and 20.0% patients, respectively. Four patients had increased broncho-vascular prominence. The average CT severity score was 16.6. The mean time to TCZ administration from the day of symptom onset was 8.7 days. At the time of admission (baseline), majority (47.4%) of patients were on high-flow oxygen therapy, followed by other types of oxygen therapies including mechanical ventilation (16.8%), ambient air (15.8%), low-flow oxygen (13.7%), and NIV (6.3%) [Table 2]. Among patients who were on ambient air at baseline (12 with moderate and three with severe COVID-19 illness), the mean time of TCZ administration from symptom onset was 9.6 days. Among patients who were on high-flow oxygen support at baseline (36 with moderate and nine with severe COVID-19 illness), the mean time of TCZ administration from symptom onset was 8.9 days. Among patients who were on low-flow oxygen support at baseline (12 with moderate and one with severe COVID-19 illness), the mean time of TCZ administration from symptom onset was 10 days. Among patients who were on mechanical ventilation at baseline (three with moderate and 13 with severe COVID-19 illness), the mean time of TCZ administration from symptom onset was 6.6 days. Among patients who were on NIV at baseline (two with moderate and four with severe COVID-19 illness), the mean time of TCZ administration from symptom onset was 6.7 days. The mean oxygen saturation (SpO_2) and concentration of FiO_2 at the time of admission were 90.4% and 80.6%, respectively [Table 1].

Clinical course of treatment

The most commonly received dose of TCZ (intravenous) during the entire course of treatment was 400 mg (84.2%) by total of 58 patients. Of these, 20 (34.4%) patients received single dose, 37 (63.7%) received two doses, and one patient received three doses of TCZ 400 mg. Total of 93 patients received TCZ in combination with other antiviral drugs and remdesivir (42.1%) was the most commonly used antiviral. All patients received a combination of TCZ with antibiotic regimen of either piperacillin (57.9%), tazobactam (57.9%), cephalosporin (25.2%), meropenem (23.2%), teicoplanin (14.7%), doxycycline (12.6%), sulbactam (5.2%), amoxicillin and clavulanic acid, metronidazole, and polymyxin (1.0% each). The choice of corticosteroids was either methylprednisolone (76.8%), or dexamethasone (16.8%). The most commonly used anticoagulant was enoxaparin (93.7%) followed by heparin (6.3%) and antiplatelets such as aspirin was used in 2.1% of patients. The median duration of treatment period was 10.0 days (3.0-17.0 days) [Table 3].

Effect of tocilizumab on concentration of FiO_2, oxygen saturation, and body temperature

The mean concentration of FiO_2 showed decreasing trend from day 0 to day 7 during the course of the treatment ($P < 0.001$) as compared to before treatment initiation [Figure 1a]. While after initiation of treatment, mean oxygen saturation improved significantly with stable levels within the range of 95.6% to 96.3% between day 0 and day 7 ($P < 0.001$) [Figure 1b]. Temperature monitoring showed significant difference at days 2, 3, 4, and 7 when compared to temperature before administration ($P < 0.001$) [Figure 1c].

Effect of tocilizumab on laboratory parameters

The CRP levels improved remarkably after the initiation of treatment (from day 0 to day 7). The pretreatment median CRP level was 63.5 mg/mL which declined post-TCZ treatment to 4.1 mg/mL on day 7 and to 0.8 mg/dL on day 16 [Table 4]. The change in median levels of CRP from baseline to posttreatment (pre- vs. posttreatment: 63.0 [1.7-324.9] vs. 4.5 [0.1-234.0]; $P < 0.001$) was significant. In patients who

Table 1: Demographic characteristics

Parameters	Number of patients (*n*=95)*
Sex	
Men	77 (81.1)
Women	18 (18.9)
Age [years], mean (SD)	55.5 (14.4)
Symptoms	
Difficulty in breathing	86 (90.5)
Cough	76 (80.0)
Fever	64 (67.4)
Sore throat	61 (64.2)
Loss of taste	23 (24.2)
Loss of smell	21 (22.1)
Diarrhea	8 (8.4)
Vomiting	2 (2.1)
Other [*n*=52]	22 (42.3)
Generalized weakness	17 (32.7)
Body ache	8 (15.3)
Headache and weakness	1 (1.9)
Mouth ulcer	1 (1.9)
Palpitation	1 (1.9)
Joint pain	
Severity of illness [*n*=95]	
Moderate	65 (68.4)
Severe	30 (31.6)
Comorbidities	
Hypertension	49 (51.6)
Diabetes	33 (34.7)
CVD	9 (9.4)
Asthma	4 (4.2)
Hypothyroidism	4 (4.2)
COPD	2 (2.1)
CKD	1 (1.1)
Other	3 (3.2)
Laboratory values on admission, median (range)	
Interleukin-6 level (pg/mL) [*n*=26]	56.4 (1.0-301.0)
C-reactive protein (mg/dL) [*n*=68]	63.5 (1.5-324.9)
D-dimer (µg/mL) [*n*=87]	0.6 (0.1-18.0)
Ferritin (µg/mL) [*n*=64]	0.4 (0.03-3.3)
Procalcitonin (nmol/L) [*n*=89]	0.1 (0.1-10.5)
Aspartate aminotransferase (IU/L) [*n*=94]	40.5 (17.0-258.0)
Alanine aminotransferase (IU/L) [*n*=94]	44.0 (14.2-154.0)
Lymphocyte count (10^9 cells/L)	16.0 (3.0-46.0)
Neutrophil-lymphocyte ratio	5.0 (1.0-32.3)
White cell count (10^9/L)	9.6 (4.2-73.0)
Platelet count (10^9/L)	213.0 (107.0-520.0)
Total bilirubin (mg/dL) [*n*=92]	0.6 (0.4-6.4)
Concentration of fraction of inspired oxygen (FiO_2) on admission [%], mean (SD)	80.6 (14.6)
Oxygen saturation (SpO_2) on admission [%], mean (SD)	90.4 (7.5)
Temperature on admission [^{0}F], mean (SD)	98.7 (1.1)

Data shown as *n* % unless otherwise specified. *n=95 unless otherwise specified. Other comorbid conditions, cerebrovascular accident (*n*=2); ischemic heart disease (*n*=1); dyslipidemia (*n*=1). CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease

improved vs. those who died, the median levels of CRP before administration of TCZ and after administration of TCZ (on day 5, 6, or 7) were comparable (pre-treatment CRP, $P = 0.130$; post-treatment CRP, $P = 0.251$) [Table 5].

Change in laboratory parameters after tocilizumab administration

The mean levels of ferritin and D-dimer showed comparative reduction from baseline to the post-treatment with a mean difference of 0.6 (95% CI: -0.3, 1.5; $P = 0.214$) and 0.2 (95% CI: -1.7, 2.0; $P = 0.864$) [Figure 2a and 2c].

Outcomes

Total of 73.6% ($n = 70$) of patients improved post-TCZ treatment; while 26.4% ($n = 25$) of patients died. The mean length of hospital stay was 13.6 days. More than three-quarters of patients (76.3%) required ICU admission with a mean duration of ICU stay of 10.3 days. Nearly, 50.5% of patients received

Table 2: Diagnostic work-up, and treatment

Parameters	Number of patients (*n*=95)*
Chest radiography findings on admission	
Inhomogeneous opacities in both mid and lower zones	26 (27.4)
Bilateral consolidation	23 (24.2)
Bilateral infiltrates	19 (20.0)
Bilateral haziness	19 (20.0)
Increased broncho-vascular prominence	4 (4.2)
Mid and lower zone haziness	2 (2.1)
Linear atelectatic bands in lower zone with in homogenous opacities	2 (2.1)
CT severity score, mean (SD) [*n*=22]	16.6 (2.3)
Days from symptom onset to hospital admission, mean (SD)	6.2 (2.9)
Days from symptom onset to tocilizumab administration, mean (SD)	8.7 (3.5)
Days from hospital admission to tocilizumab administration, Median (range)	3 (0-11)
Oxygen therapy received at the time of admission	
High-flow oxygen	45 (47.4)
Mechanical ventilation	16 (16.8)
Ambient air	15 (15.8)
Low-flow oxygen	13 (13.7)
Noninvasive ventilation	6 (6.3)

Data shown as *n* % unless otherwise specified. *n=95 unless otherwise specified. SD, standard deviation

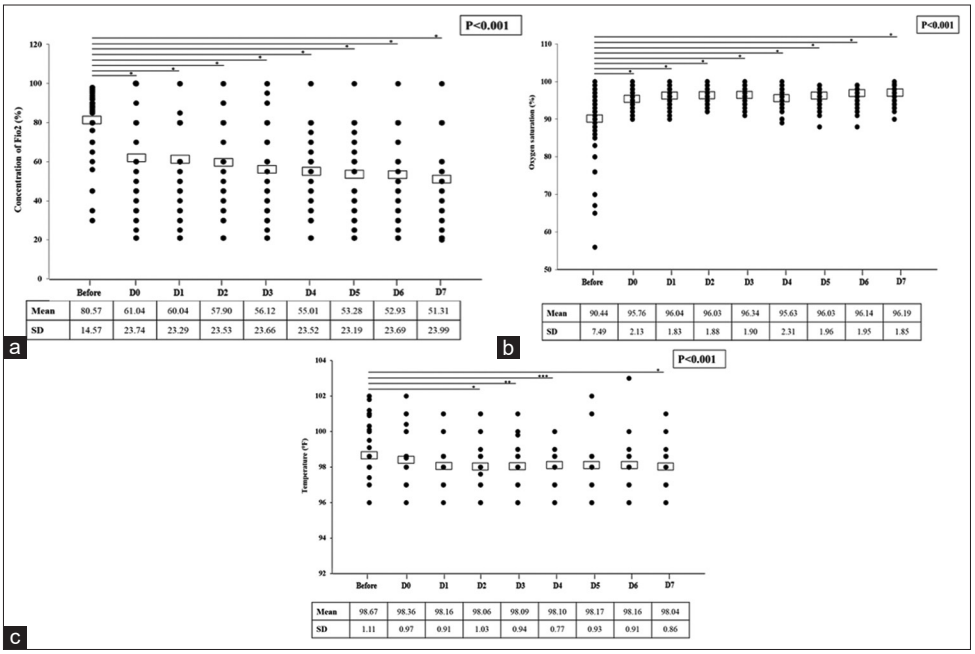

Figure 1: The values of concentration of FiO_2, oxygen saturation, and body temperature before and after the treatment with tocilizumab. a) The values of concentration of FiO_2 before and after the treatment with tocilizumab b) The values of oxygen saturation before and after the treatment with tocilizumab c) The values of body temperature before and after the treatment with tocilizumab. *P*-values presented in boxes represents overall significance within groups calculated using One-way ANOVA analysis while *p*-values presented with */**/*** represent comparison between parameters at different time points calculated using paired sample t-test. *$P < 0.001$, **$P = 0.001$, ***$P = 0.002$; D, day after tocilizumab; FiO_2, fraction of inspired oxygen

ventilator support and mean duration of ventilator support was 8.5 days [Table 6].

Clinical improvement and mortality

The median (95% CI) time to clinical improvement was 15.0 (13.8-16.1) days [Figure 3a] and median (95% CI) time to death was 21.0 (15.1-26.9) days [Figure 3b].

Safety

Acute respiratory distress syndrome was seen in 22 (23.2%) patients following TCZ treatment. Twelve patients had elevated transaminase levels. Cardiac arrest occurred in eight (8.4%) patients and four patients (4.3%) developed pneumonia. Total three patients (3.1%) experienced multiorgan dysfunction [Table 7].

Time to death approach

Table 8 presents the summary of the total number of cases and deaths that occurred due to COVID-19 during the different time-periods of the study (patients admitted during T1, 26th May to 9th June; T2, 10th June to 24th June; T3, 25th June to 9th July; T4, 10th July to 24th July; T5, 25th July to 7th August). Majority of the COVID-19 infected cases were admitted during the T3 period (25th June to 9th July 2020) and the majority of the deaths occurred during the T2 period (10th June to 24th June).

Table 3: Clinical Management

Therapy	Number of patients (*n*=95)*
TCZ alone	2 (2.1)
TCZ with other antiviral drugs	
Remdesivir	40 (42.1)
Favipiravir	15 (15.8)
Oseltamivir	6 (6.3)
Lopinavir	4 (4.2)
Ritonavir	4 (4.2)
Dose of TCZ (mg)	
400	80 (84.2)
320	8 (8.4)
800	5 (5.2)
600	2 (2.1)
Frequency of treatment	
One dose	41 (43.1)
Two doses	51 (53.7)
Three doses	3 (3.2)
Use of antibiotics	
Piperacillin	55 (57.9)
Tazobactam	55 (57.9)
Cephalosporin	24 (25.2)
Meropenem	22 (23.2)
Teicoplanin	14 (14.7)
Doxycycline	12 (12.6)
Sulbactam	5 (5.2)
Amoxicillin and clavulanic acid	1 (1.0)
Metronidazole	1 (1.0)
Polymyxin	1 (1.0)
Use of steroids	
Methylprednisolone	73 (76.8)
Dexamethasone	16 (16.8)
Use of anticoagulants	
Enoxaparin	89 (93.7)
Heparin	6 (6.3)
Use of antiplatelets	
Aspirin	2 (2.1)
Use of other drugs	
Hydroxychloroquine	27 (28.4)
Montelukast	6 (6.3)
Ivermectin	1 (1.0)
Rosuvastatin	1 (1.0)
Clopidogrel	1 (1.0)
Duration of treatment [days], median (range)	10.0 (3.0-17.0)

Data shown as *n* % unless otherwise specified. *n=95 unless otherwise specified. BD, twice daily; TCZ, tocilizumab; OD, once daily; TID, thrice daily

Discussion

A scarcity of data from India evaluating efficacy and safety of TCZ in the patients with COVID-19 reveals the need of such studies to validate the inconsistency in the previous observations. The present study retrospectively analyzed the clinical experience of TCZ treatment among a cohort of patients with COVID-19 infection from Western India. To the best of our knowledge, till date there are only two published studies from India on TCZ usage in COVID-19 and this study is the third study from India that has looked into detailed clinical experience of TCZ treatment and its impact on survival of patients.

The salient observations of this study are: a) around 74% of survival rate post TCZ treatment; b) a remarkable improvement in required concentration of FiO_2 and the oxygen saturation (SpO_2); c) a significant reduction in CRP levels post TCZ treatment.

Hypertension (51.4%) and diabetes (34.7%) were the most prevalent comorbidities observed among the present study population. A retrospective study from India (*n* = 20) reported that half of the patients with COVID-19 had diabetes and hypertension.[5] Similarly, other studies also reported corroborating findings indicating diabetes and hypertension as the most common comorbidities to be observed in patients with COVID-19 treated with TCZ.[5,10,11]

Patel *et al.*[5] included patients with moderate-to-severe disease and reported the median CT severity score of 11.06 (95% CI: 7-13). However, the mean CT severity score in the present study was slightly higher (16.6) than the previously reported studies. This can be attributable to the patients with moderate to severe stage of COVID-19 illness with around one-third of patients having moderate disease.

In patients with COVID-19 infection, after 8-10 days of symptoms onset, precipitation of the cytokine storm leads to an exuberant hyperinflammatory response substantially contributing to morbidity and mortality among these patients. Therefore, early identification of cytokine storm and timely use of TCZ treatment could benefit patients in achieving marked

Table 4: CRP levels before and after tocilizumab (day zero to day 16)

Parameter	Before treatment	Day zero	Day one	Day two	Day three	Day four	Day five	Day six	Day seven	Day sixteen
CRP (mg/dL)										
Number of patients	[*n*=68]	[*n*=18]	[*n*=25]	[*n*=20]	[*n*=27]	[*n*=29]	[*n*=27]	[*n*=24]	[*n*=28]	[*n*=30]
Median (range)	63.5 (1.5-324.9)	62.3 (1.2-102.7)	40.5 (0.2-208.0)	25.4 (3.2-101.4)	24.8 (0.6-140.60)	14.5 (1.4-69.0)	7.7 (1.2-154.8)	7.0 (0.05-234.0)	4.1 (0.5-43.2)	0.8 (0.2-86.8)

CRP, C-reactive protein; IL-6, Interleukin-6

Table 5: Comparative analyses of CRP level pre treatment and post treatment with TCZ

Parameter	Comparative analysis		*P*
	Pretreatment	Posttreatment (day 5/6/7)	
CRP (mg/dL)	[*n*=47] 63.0 (1.7-324.9)	[n=47] 4.5 (0.1-234.0)	<0.001
	Improved	**Death**	
CRP	[*n*=35]	[*n*=12]	
Pre-treatment CRP (mg/dL)	59.1 (1.8-324.9)	73.1 (18.9-168.3)	0.130
Post-treatment CRP (mg/dL)	4.5 (0.05-154.8)	16.5 (0.5-234.0)	0.251

Data shown as median (range). CRP, C-reactive protein; IL-6, Interleukin-6

Table 6: Clinical status and outcomes of patients

Parameters	Number of patients (*n*=95)*
Clinical status	
Improved	70 (73.6)
Death	25 (26.4)
Outcomes	
Length of hospital stay [days], mean (SD)	13.6 (5.7)
Intensive care unit admission [*n*=93]	71 (76.3)
Intensive care unit length of stay [days], mean (SD)	10.3 (5.6)
Duration of oxygen support [days], mean (SD)	10.3 (6.0)
Patients on vasopressor support	17 (17.9)
Duration of vasopressor support [days], mean (SD) [*n*=10]	4.1 (2.0)
Patients on ventilator support	48 (50.5)
Duration of ventilator support [days], mean (SD) [*n*=47]	8.5 (6.4)

Data shown as *n* % unless otherwise specified. *n=95 unless otherwise specified

Table 7: Adverse events and safety of tocilizumab

Events	Number of patients (*n*=95)*
Acute respiratory distress syndrome	22 (23.2)
Elevated transaminases	12 (12.6)
Cardiac arrest	8 (8.4)
Pneumonia	4 (4.3)
Multiorgan dysfunction	3 (3.1)
Acute renal shut down	2 (2.1)
Septic shock	2 (2.1)
Dialysis	1 (1.0)
Other	6 (6.3)

Data shown as *n* %. Other, acute myocarditis (*n*=1); left thalamic bleed (*n*=1); ventricular tachycardia (*n*=1), stroke (*n*=1); pericardial effusion (*n*=1), non-ST segment elevation myocardial infarction (*n*=1)

Table 8: Death according to the time of the study

Time period	Number of admissions	Number of deaths (%)
T1	18	4 (22.2)
T2	26	9 (34.6)
T3	29	6 (20.7)
T4	13	4 (30.7)
T5	9	2 (22.2)

T1, patients admitted during 26th May 2020 to 9th June 2020; T2, patients admitted 10th June 2020 to 24th June 2020; T3, 25th June 2020 to 9th July 2020; T4, 10th July 2020 to 24th July 2020; T5, 25th July 2020 to 7th August 2020

reduction in inflammatory markers and thereby better survival outcomes.[2,4] Further, the mean time to TCZ administration from the day of symptom onset was 8.7 days. This observation concords with the previous study indicating average time of TCZ initiation was between 8 and 10 days after the appearance of first symptom.[5]

The length of hospital stay (13.6 days) and ICU stay (10.3 days) reported in the present study was in accordance with the previous studies. In a study by Patel *et al.*,[5] about 55% of patients required ICU admission and the median duration of ICU stay was 11 days (95% CI: 3–13 days). Kewan *et al.* reported a relatively lower median length of hospital stay (11 [interquartile range, IQR: 6-22.25] days) and ICU stay (8.5 [IQR: 6.75-17] days) as compared to the present study.[10] This could be attributed to the small sample size in the Kewan *et al.* study.[10]

The present study demonstrated efficacy of TCZ in significantly reducing CRP levels to normal levels post treatment. Further, comparable CRP levels between patients who improved and those who died may suggest no association between mortality and CRP levels. However, these findings need validation. Previous studies have shown significant reduction in CRP levels post TCZ treatment.[5,11,12] In the present study, other proinflammatory markers, such as ferritin and D-dimer concentrations showed comparative reduction which were insignificant. On the parallel lines, study by Patel *et al.*[5] also reported no significant change in ferritin and D-dimer levels from day 0 to day 7.

A short report of a retrospective cohort study from India indicated the association of TCZ use with survival benefit (hazard ratio, HR 0.616; 95% CI: 0.382-0.992) in patients with persistent hypoxia in severe COVID-19 pneumonia. The mortality rates were significantly lower in patients treated with TCZ (47.1%) compared to control group (67%) ($P = 0.011$).[6] The present study reported a mortality rate of 26.6%. Among these, majority of deaths were observed in severe group ($n = 18$, 72.0%) compared to moderate group ($n = 7$, 28.0%). These observations are in concordance with Patel *et al.*[5] study which reported a mortality rate of 25% [95% CI: 11%–63%] among moderate and severe COVID-19 disease. Initiation of TCZ treatment at appropriate time (mean days from symptom onset to TCZ administration, 9.0 days) during the disease course may reduce the risk of mortality. Among observed deaths, the proportion of male patients (68%) was more than female patients (32%) and more than half of patients had ≥2 comorbidities ($n = 14$).

It is interesting to note that a study by Xu *et al.*,[11] that included 21 patients with severe and critical COVID-19, showed 100% survival along with immediate improvement in the symptoms, hypoxemia, and CT opacity changes post TCZ treatment. Patel *et al.*[5] showed that the cumulative incidence of the clinical improvement was 74% (95% CI: 37%-89%). In concordance with the Patel *et al.*[5] study, the present study also reported incidence of improved status in 73.4% of patients. In a systematic review and meta-analysis of 13 retrospective case-control studies ($n = 2285$) and six retrospective single-armed studies (n = 208), patients treated with TCZ demonstrated better clinical improvement compared with the patients treated with standard treatment (odds

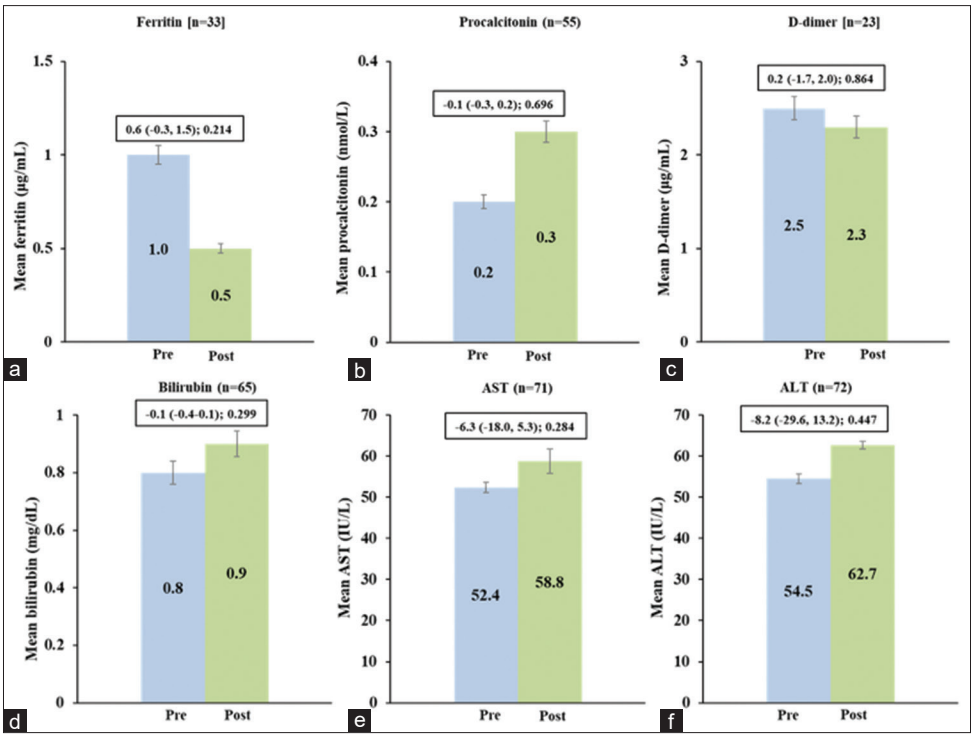

Figure 2: Change in laboratory parameters pre- and post-TCZ treatment. Change in a) ferritin b) procalcitonin c) D-dimer, d) bilirubin e) AST and f) ALT levels. Data shown as mean difference (95% CI); *P* value. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TCZ, tocilizumab

ratio, OR, 1.24; 95% CI, 0.96-1.62).[12] Furthermore, a recently conducted meta-analysis of 25 peer-reviewed publications (n = 10,201 individuals) demonstrated a reduced risk of mortality and mechanical ventilation requirement among COVID-19 patients when treated with TCZ. Particularly, critically ill patients with COVID-19 benefitted with TCZ treatment.[13] Other retrospective studies also provide evidence that early treatment with TCZ among critically ill patients with COVID-19 can help to reduce the mortality rate.[14,15]

Interestingly it was noted that the SpO_2 of all patients dramatically returned to normal on the first day after receiving TCZ and remained stable thereafter till discharge. These observations indicate effectiveness of TCZ in instant improvement of oxygen saturation and concentration of FiO_2. Observations from Xu *et al.*[11] study corroborate with these findings.

The present study reported acute respiratory distress syndrome and elevated transaminases as the most prevalent adverse events. Other adverse events were pneumonia, cardiac arrests, multiorgan dysfunction, acute renal shut down, septic shock, and dialysis. In previous studies, mild elevation in liver enzymes has been reported as one of most common lab abnormalities observed with TCZ. Few hospital-acquired infections were also reported.[5,10,16]

The present study also analyzed the death rate according to progressive time during the study to rule out whether there is any reduction in number of deaths with use of TCZ in later time. However, we could not observe any remarkable change in mortality rates during different time periods of the study.

There are several limitations to this study. First is the retrospective design of the study which has obstructed the possibility of real-time data collection and as a result lead to missing data for multiple parameters. This has considerably limited the result interpretation and indicates a need of well-designed prospective studies to validate these results. Second, this was a single-center, single arm study, and lack of control group restricts the overall inference in terms of safety and efficacy of TCZ to generalized population. And last, small sample size has restricted its applicability to a general population.

Conclusion

The disruption of the mechanisms that lead to hyperinflammatory state and subsequently to permanent lung injury and death is a vital aspect in identifying prognostic outcomes of the COVID-19 disease. Therefore, early diagnosis of the hyperinflammatory state and apt treatment are the two key strategies that will help in improving survival of these patients with cytokine storm syndrome wherein TCZ can be considered as a potential therapeutic agent. Overall results of this study suggest the potential role of TCZ, if administered during the earlier phase of cytokine storm syndrome, in reversal of abnormal oxygen saturation (SpO_2) and concentrations of FiO_2 to normal levels and rapid decline of elevated CRP levels to normal levels in patients with COVID-19. However, TCZ therapy need to be used vigilantly and cautiously in individual patients to avoid the risk

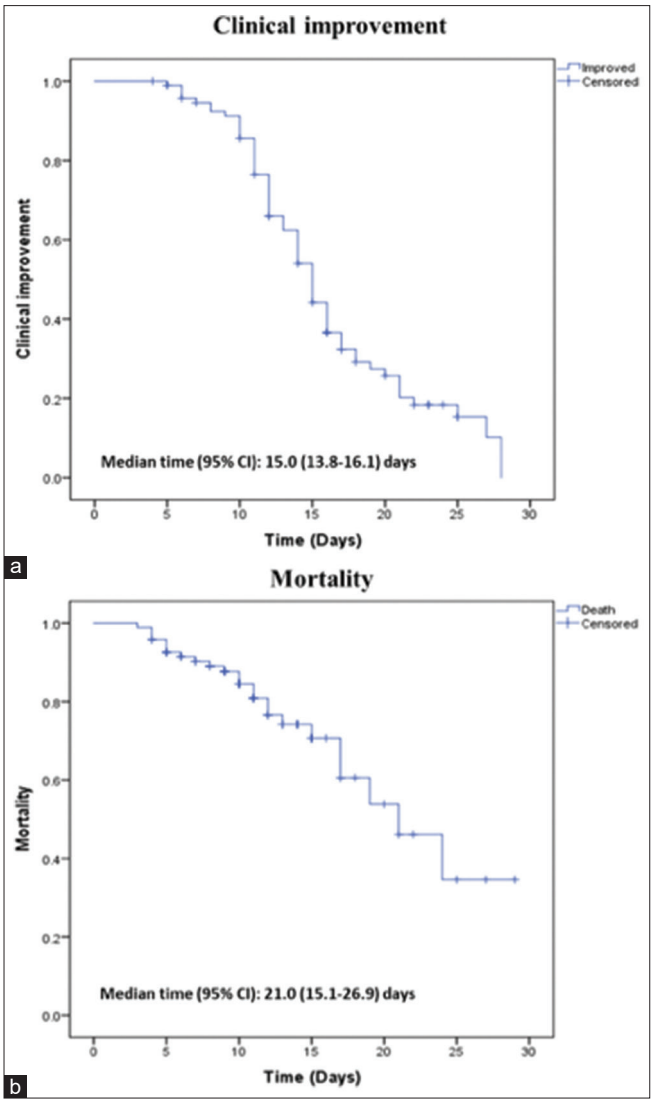

Figure 3: Kaplan-Meier plot for clinical improvement and mortality with TCZ

of severe adverse events. Future randomized clinical trials and real-world studies evaluating efficacy and safety of TCZ in patients with COVID-19 are required for validation of the available data.

Key points

- Early identification of cytokine storm and timely administration of TCZ can be advantageous in improving survival of patients with COVID-19.
- TCZ therapy helps in reversal of abnormal oxygen saturation (SpO_2) and rapid decline of elevated CRP levels to normal levels in patients with COVID-19.
- Vigilant use of TCZ therapy needs to be considered to avoid risk of severe adverse events.

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Conflicts of interest

There are no conflicts of interest.

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