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Safety and Efficacy of Tocilizumab in the Treatment of Severe Acute Respiratory Syndrome Coronavirus-2 Pneumonia: A Retrospective Cohort Study

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Original Article

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Abstract

Background: Cytokine release storm (CRS) in severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) is thought to be the cause for organ damage and death which is independent of the actual viral burden. Tocilizumab (TCZ), an interleukin-6 receptor antagonist, is approved for the treatment of CRS. We describe the efficacy and safety of TCZ in SARS CoV-2 pneumonia. **Methods:** This retrospective study was conducted at a tertiary care hospital from April 20 2020 to May 21 2020. The primary endpoint was the cumulative incidence of a composite of either need for admission to the intensive care unit (ICU) with invasive mechanical ventilation or death. Safety outcomes included an increase in liver transaminases and/or evidence of infection. **Results:** A total of 20 patients received TCZ during the study period. The median age was 54 years (95% confidence interval [CI] 47–63). About 85% of the patients were male. Nearly 70% of the patients had at least one comorbidity. About 55% required ICU admission. The median duration of ICU stay was 11 days (95% CI: 3–13 days). The cumulative incidence of the requirement for mechanical ventilation, clinical improvement and mortality was 11% (95% CI: 0.03%–1%), 74% (95% CI 37%–89%) and 25% (95% CI: 11%–63%), respectively. There was no difference in outcomes according to age, gender or computed tomography severity score. Asymptomatic transaminitis was the most common drug reaction (55%), and one patient developed bacteraemia. **Conclusions:** TCZ is likely a safe and effective modality of treatment for improving clinical and laboratory parameters of SARS CoV-2 patients with a reduction in ICU stay and ventilatory care need.

Keywords: Coronavirus, COVID-19, cytokine release storm, severe acute respiratory syndrome coronavirus-2, tocilizumab

Introduction

India reported the first case of severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) in January 2020. Since then, the number of positive cases has been increasing. As of 5 June 2020, more than 380,000 patients globally and 6300 people in India have died mainly due to bilateral pneumonia, respiratory failure and thrombotic complications attributed to immune-mediated inflammatory damage in SARS CoV-2 infection. SARS-CoV-2 and other viruses in the corona family (SARS CoV-1 and Middle East respiratory syndrome) infection induce a hyperinflammatory response resembling cytokine release storm (CRS) with secondary haemophagocytic lymphohistiocytosis or macrophage-activation syndrome (MAS), with markedly elevated pro-inflammatory interleukins (IL-1β and IL-6) and tumour necrosis factor.[1,2] Increased IL-6 blood level was identified as one of the laboratory markers associated with high mortality in the study by Zhou *et al*.[3] An overreacting immune system to viral infections including coronaviruses and influenza with CRS is thought to be the cause for

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pulmonary and other organ damage and dysfunction leading to death which is independent of the actual viral burden and is usually seen following the acute phase of the disease.[4] Researchers have used antiviral agents for controlling viral replication and found them to be beneficial when administered early, but once CRS has established, they seem to have little role.[5-7] In the absence of specific effective treatment to prevent progression of respiratory symptoms in patients with SARS CoV-2 pneumonia, researchers have tried different monoclonal antibodies to block IL-1 and IL-6 receptor for the management of CRS with some success.[2,8-11] IL-6 receptor antagonist, tocilizumab (TCZ), is the most common agent used for treatment of SARS CoV-2 pneumonia with evidence of CRS followed by anakinra in China, France and Italy and it has shown a survival benefit in these patients.

In this study, we describe the efficacy and safety of TCZ in a group of patients with moderate and severe SARS CoV-2 disease.

Methods

Settings and inclusion criteria

We performed a retrospective study at a tertiary care hospital in Western India. The study was approved by the Sterling Hospital Ethics Committee with reference number SH-CR/EC/AP/Academic/180–2020, dated 27 May 2020. All consecutive adult patients (>18 years) treated with TCZ between 21 April 2020 and 20 May 2020 for CRS associated with SARS CoV-2 pneumonia were eligible for inclusion.

The decision to administer TCZ was based on the presence of any or all three of the following: SPO_2 of ≤94%, laboratory indication of CRS as indicated by C-reactive protein (CRP) >10 times of (ULN) or double in the last 24 h, D-dimer >2500 ng/ml, worsening respiratory status or persistent high-grade fever.

TCZ was not considered in patients with active tuberculosis (TB), current or past exposure to TB or laboratory confirmed evidence of bacterial infection, serum glutamic pyruvic transaminase (SGPT) >5 times of ULN, absolute neutrophil count <1000 and platelets <50,000.

Treatment protocol

Patient received 1 intravenous (IV) infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose of 800 mg. Up to 1 additional dose was administered if clinical symptoms worsened or showed no improvement. All patients received the standard of care according to the current treatment protocol recommended by the Ministry of Health and Family Welfare in the state of Gujarat along with other necessary supportive measures. These included oral hydroxychloroquine 400 mg/day for 5 days after a loading dose of 400 mg twice a day on 1st day, oral azithromycin 500 mg/day for 5 days and IV ceftriaxone 1 g per day for 5 days. Anticoagulation with low-molecular-weight heparin or unfractionated heparin infusion was used if patient's D-dimer was >1000 ng/ml. Some patients also received single dose of 80 mg IV methylprednisolone before receiving TCZ.

Definitions

Mild infection

SARS CoV-2 patients have mild infections such as fever, myalgia, body pain, loss of taste, smell without radiological evidence of pneumonia and maintaining saturation on room air >94%.

Moderate disease

Moderate diseases are observed in patients with hypoxia with SpO2 <94 and complaining of shortness of breath with radiological evidence of pneumonia.

Severe disease

Severe disease includes all of the above (as in moderate

Table 1: Baseline characteristics of study patients

Characteristics	Number of subjects	*n* (%) / Median and 95% CI
Age (years)	20	54 (47-63)
Sex	20	Male 17 (85%)
		Female 3 (15%)
Comorbidities		
Diabetes	20	10 (50%)
Hypertension	20	10 (50%)
Ischemic heart disease	20	4 (20%)
Parkinsonism	20	1 (5%)
Hepatitis B	20	1 (5%)
Symptoms		
Fever	20	17 (85%)
Cough	20	12 (60%)
Shortness of breath	20	10 (50%)
Diarrhea	20	2(10%
Throat pain	20	2 (10%)
Anosmia	20	2 (10%)
Loss of taste	20	1 (5%)
Body pain	20	1(5%)
Myalgia	20	1 (5%)
Symptoms day at the time of admission days	20	8 (2-14)
CT severity score	16	11.06 (7-13)
Tocilizumab administered on day of Symptoms	20	9.5 (8-10)
Other Treatments		
Hydroxychloroquine	20	19 (95%)
One dose of Methyl Prednisolone	20	13 (65%)
Low Molecular weight Heparin	20	20 (100%)
Aspirin	20	17 (85%)
Baseline Oxygen Requirement		
Ambient air	20	4 (20%)
Nasal Prongs	20	3 (15%)
Face mask	20	3 (15%)
Non rebreathing mask	20	3 (15%)
Noninvasive ventilator/HFNC	20	7 (35%)

Table 2: Change in laboratory parameters after tocilizumab

Laboratory parameters (normal range)	Number of patients	Mean (95% Confidence intervals)			*P*		
		Baseline	Day 3	Day 7	Baseline versus day 3	Baseline versus day 7	Day 3 versus day 7
Neutrophil-Lymphocyte Ratio (1 - 3)	20	7.45 (5.17-9.73)	8.13 (3.01-13.25)	5.19 (2.30-8.06)	0.51	0.03	0.11
C-reactive protein mg/dL (<1 mg/dL)	20	17.2 (12.65-21.75)	2.59 (2.04-3.14)	0.28 (0.1-0.45)	0.0001	0.0004	0.0005
Serum Ferritin (21-274 ng/ml)	20	1020.35 (501.78-1538.92)	1289.22 (264.82-2313.62)	917.94 (128.30-1705.59)	0.96	0.07	0.02
D-dimer (0- 500ng/ml)	19	1613.7 (588.55-2668.92)	2791.22 (1064.92-4517.53)	3529.35 (1625.72-5432.98)	0.31	0.29	0.22
Serum glutamic-pyruvic transaminase (5-49 IU/L)	20	43.55 (32.56-54.54)	81.22 (46.12-116.32)	114.0 (61.61-166.38)	0.002	0.005	0.23

disease) and requiring high-flow nasal cannula or ventilatory assistance.

Outcomes

The primary endpoint was the cumulative incidence of a composite of either need for admission to the intensive care unit (ICU) with invasive mechanical ventilation or death.

The secondary endpoints were duration of ICU stay, time to hospital discharge, change in the neutrophil–lymphocyte ratio (NLR), CRP, D-dimer and serum ferritin after TCZ administration. Safety outcomes included an increase in liver aminotransferase enzymes (more than three times the upper limit of normal) and documented evidence of bacterial or fungal infection.

Data abstraction

Information on patient demographics, laboratory and radiology parameters were extracted from medical records and entered into an electronic database. Data were retrieved on patient demographics and medical characteristics including age, sex, presenting clinical symptoms, comorbidities (e.g., hypertension, diabetes and ischemic heart disease), radiological assessment, computed tomography (CT) severity score, relevant laboratory parameters performed during hospitalisation including NLR, CRP, SGPT, serum ferritin and D-dimer and outcomes were derived at from the medical charts. Clinical response was assessed using the World Health Organisation Modified Ordinal Scale for need for oxygen requirement. Scale 1 denotes patients not hospitalised or discharged; 2 denotes patients maintaining oxygen saturation on room air; 3 denotes patients requiring oxygen supplements with the following subgroups: 3a means nasal prong, 3b means simple mask and 3c means non-rebreathing mask; 4 denotes patients with high-flow nasal oxygen therapy, non-invasive mechanical ventilation or both; 5 denotes patients requiring invasive mechanical ventilation, ECMO or both and 6 denotes death.

Statistical analysis

Demographic and patient characteristics were described using descriptive statistics where categorical variables were summarised as rates or per cent and continuous variables as median along with 95% confidence intervals (CIs). The change in continuous variables across the time point was assessed using the paired non-parametric Wilcoxon Signed-Rank Test. The time-to-event outcomes were analysed using Kaplan–Meier analysis and summarised as proportions along with 95% CI. All analyses were performed using the NCSS 2020 Statistical Software (NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss).

Results

Patient characteristics

Between March 21 and May 20 2020, 65 confirmed SARS CoV-2 patients were hospitalised at the tertiary care private sector hospital. Of the hospitalised patients, 33 required supportive care only as they were either asymptomatic or mildly symptomatic. Twelve patients with moderate-to-severe disease with pneumonia and hypoxia received only corticosteroids, while 20 patients received TCZ for their moderate and severe SARS CoV-2 disease and were included in the study Baseline demographic features of patients who received TCZ are shown in Table 1, the median age was 54 years (95% CI: 47–63). Eighty-five per cent of patients (n = 17) were male and 15% were female (n = 3). The most common presenting symptoms were fever (85%; n = 17) and cough (60%; n = 12), followed by shortness of breath (50%; n = 10). Fifteen per cent (n = 3) of patients presented with all three symptoms of fever, cough and shortness of breath. Other presenting symptoms were body pain, diarrhoea, loss of taste, headache, sore throat, myalgia and back pain (n = 1). The median CT severity score was 10.5 (95% CI: 7–13). Fifty per cent of patients (n = 10) had diabetes and hypertension and 20% (n = 4) had ischemic heart disease. Seventy per cent of patients (n = 14) had at least one comorbidity of diabetes, hypertension or ischemic heart disease.

Baseline status and treatment characteristics

The median number of days patients who were symptomatic for SARS CoV-2 at the time of hospitalisation was 8 (95% CI:

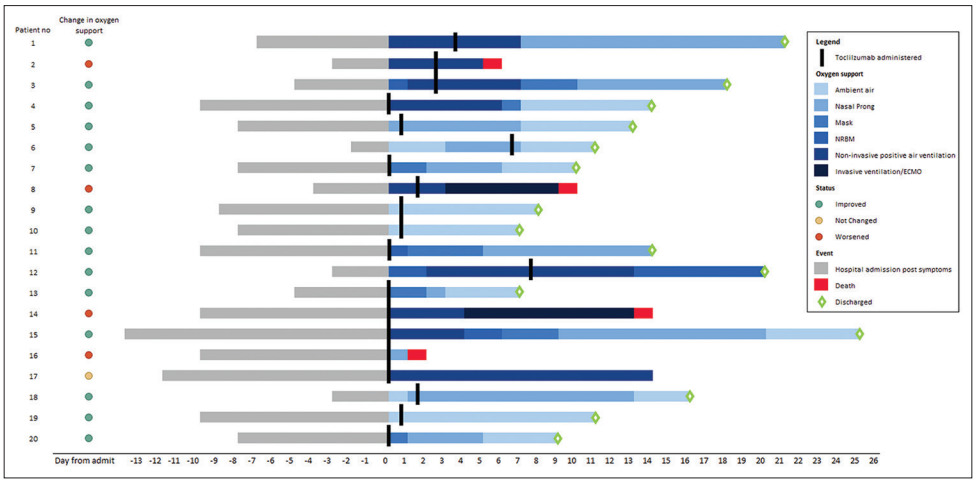

Figure 1: Progression and outcome of study patients

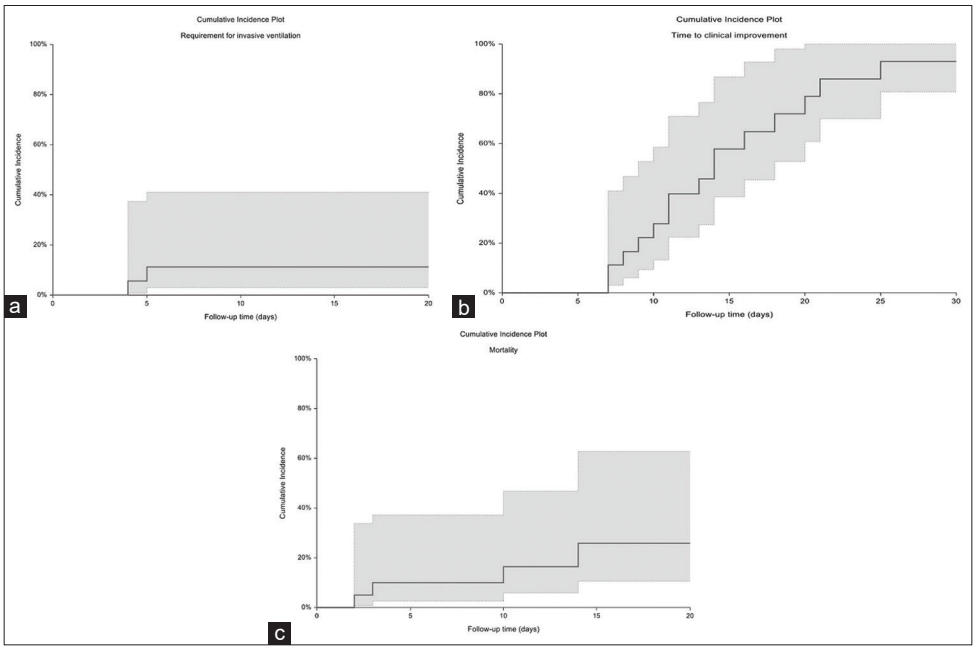

Figure 2: Cumulative incidence (a) requirement for ventilator; (b) time to clinical improvement; (c) mortality

5–10 days). Ninety-five per cent of patients (n = 19) received hydroxychloroquine. All patients received a combination antibiotic regimen of either azithromycin and ceftriaxone (65%; n = 13) or azithromycin and meropenem (5%; n = 1) or azithromycin alone (30%; n = 6). In addition, 65% of the patients (n = 13) also received at least one dose of corticosteroids before TCZ. The choice of corticosteroids was either methyl prednisone, dexamethasone or hydrocortisone. Steroids were discontinued in all patients once the patient received TCZ. All the patients received anticoagulation with either low-molecular-weight heparin alone (15%; n = 3) or in combination with aspirin (85%; n = 17). The median time to TCZ administration was 9.5 days (95% CI 8–10 days) from symptom onset.

At baseline, 20% (n = 4) of patients were on ambient air, followed by nasal prong (15%; n = 3), mask (15%; n = 3), non-rebreather mask (NRBM; 15%; n = 3) and non-invasive positive air ventilation (35%; n = 7), respectively. The progression and outcome of patients throughout the hospital stay is illustrated in Figure 1. The median time to follow-up from the day of illness was 12 days (95% CI: 9–16 days).

Outcomes

Of all the admitted patients, 55% (n = 11) (8 were admitted in the ICU, while 3 were shifted from the ward to the ICU) required ICU admission. The median duration of ICU stay was 11 days (95% CI: 3–13 days). As shown in Figure 2a, the cumulative incidence of requirement for mechanical ventilation was 11% (95% CI: 0.03%–41%). The first patient required ventilation on day 4 of admission and the second patient on day 5 of admission. The cumulative incidence of clinical improvement was 74% [95% CI: 37%–89%; Figure 2b]. The

cumulative incidence of mortality was 25% [95% CI: 11%–63%; Figure 2c]. The mean time to clinical improvement and mortality was 24 days (95% CI: 19–29 days). There was no difference in outcomes according to the age, gender or CT severity score. All patients, who had high-grade fever became afebrile within 24 h of TCZ. This clinical benefit was the most striking and rapid.

The change in laboratory parameters after TCZ is described in Table 2 (day 0 is the day of TCZ administration).

Neutrophil–lymphocyte ratio

The mean NLR was 7.45 (95% CI 5.17-9.73) on day zero, 8.13 (95% CI 3.01-9.73) on day 3 and 5.19 (95% CI 2.3-8.06) on day seven. The change in NLR levels from day 0 to day 7 was statistically significant ($P = 0.03$) but not for day 3 versus day 7 ($P = 0.11$).

C-reactive protein test

The mean CRP was 17.2 (95% CI 12.65–21.75) on day 0, 2.59 (95% CI 2.04–3.14) on day 3 and 0.28 (95% CI: 0.1–0.45) on day 7. The change in CRP values was a statistically significant from day 0 to day 3 ($P = 0.0001$) and day 7 ($P = 0.0004$) and between day 3 and day 7 ($P = 0.0005$).

Serum ferritin

The mean serum ferritin was 1020.35 (95% CI: 501.78–1538.92) on day 0, 1289.22 (95% CI: 264.82–2313.62) on day 3 and 917.94 (95% CI: 128.3–1705.59) on day 7. The change in serum ferritin levels from day 0 to day 3 ($P = 0.96$) and day 7 ($P = 0.07$) was not statistically significant. The change in serum ferritin levels from day 3 to day 7 was statistically significant ($P = 0.02$).

D-Dimer

The mean D-dimer was 1613.7 (95% CI: 588.55–2668.92) on day 0, 2791.22 (95% CI: 1064.92–4517.53) on day 3 and 3529.35 (95% CI: 1625.72–5432.98) on day 7. The change in D-dimer values from day 0 to day 3 ($P = 0.31$) and day 7 ($P = 0.29$) or from day 3 to day 7 ($P = 0.22$) was not statistically significant.

Serum glutamic-pyruvic transaminase

The mean SGPT was 43.55 (95% CI: 32.56–54.54) on day 0, 81.22 (95% CI: 46.12–116.32) on day 3 ($P = 0.002$) and 114 (95% CI 61.61–166.38) on day 7. The change in SGPT levels from day 0 to day 3 ($P = 0.002$) and day 7 ($P = 0.005$) was statistically significant. The change in SGPT levels from day 3 to day 7 was not statistically significant ($P = 0.23$).

Changes in radiological assessment

At baseline, 16 patients had CT scan of the thorax and 4 patients had X-ray of the chest. Follow-up CT scan was not performed to assess radiological improvement. X-ray of the chest was carried out in all patients before discharge which showed resolution. Figure 3 shows the X-ray of the chest at the time of TCZ, after 1 week and at the time of discharge of patient numbers 12 and 17 who stayed in hospital for 20 and 22 days, respectively, showing initial worsening followed by improvement.

Overall, the TCZ injection was well tolerated, and none of the patients had an infusion-related adverse drug events. Asymptomatic transaminitis was seen in 11 (55%) patients following TCZ and one patient had 8 times of ULN of SGPT. One patient had transient leukopenia and neutropenia and one

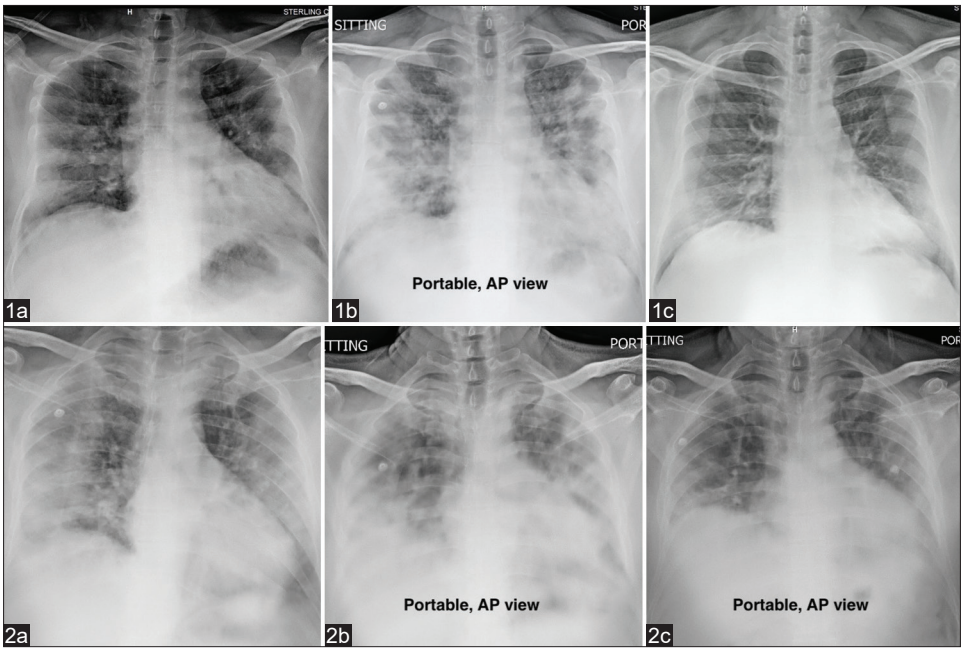

Figure 3: Serial Chest X-ray chest of patients after tocilizumab. Patient # 12: (1a) Day of Tocilizumab administration, (1b) After 1 week of Tocilizumab, (1c) At the time of Discharge. Patient #17: (2a) Day of Tocilizumab administration, (2b) After 1 week of Tocilizumab, (2c) At the time of Discharge

patient had enterococcal faeceum bacteraemia with raised serum-beta-D-glucan, possibly related to invasive candidemia or enterococcal bacteraemia.

Discussion

The findings from this single-arm retrospective cohort study shows that the use of TCZ is safe and is associated with reduced invasive mechanical ventilation requirement, ICU admission and mortality among patients with moderate and severe SARS CoV2. Asymptomatic transaminitis was the most common side effect and bacterial infection in one patient. In the absence of effective antiviral treatment, researchers across the world are trying various anti-inflammatory agents to control the cytokine storm resulting from hyperinflammation. A study by Ruan *et al*. reported elevated IL-6 and serum ferritin as an important predictor of mortality.[12] Short-term corticosteroids have been found to be associated with reduced need of ICU admission and ventilatory care in study by Fadel *et al*.[13] Anakinra also showed similar benefit while comparing with historic control from the same hospital.[11,14] There have been few case reports of success with TCZ, an IL-6 receptor blocker, in a patient with SARS CoV-2 pneumonia.[9,15-17] Similar to these reports, the findings from our study also showed a reduction in both the need for ICU care, invasive mechanical ventilation and mortality, suggesting that TCZ is possibly an effective treatment option for the SARS CoV-2-associated hyperinflammation. Indeed, all patients with fever had resolution within 24 h after receiving TCZ and remained afebrile thereafter along with a rapid decline in CRP levels.

Four patients, who deteriorated and died, had another coexisting pathology apart from hyperinflammation. Case 2 had pre-existing poor left ventricular function and had sudden cardiac arrest on hospital day 6. Case 8 had all the clinical features of SARS CoV-2 sepsis and encephalitis with progressive MAS despite TCZ and serum ferritin level of >10,000 pg/ml on the day before death. Case 14 had progressive intravascular coagulopathy as marked by persistent very high D-dimer values of >10,000 ng/ml, with normal platelets and fibrinogen degradation products and an elevated fibrinogen level. This patient received low-molecular-weight heparin followed by heparin infusion and recombinant tissue plasminogen activator but without any clinical improvement. Case 16 was admitted in the ICU with the features of pancarditis (pericarditis with elevated troponin levels), and his oxygen requirement sharply reduced and fever also subsided after 24 h of TCZ. However, the patient had a sudden cardiac arrest after 48 h of TCZ. Therefore, we suspect out of the four deaths, two deaths were related to cardiac pathology, one was related to severe viral sepsis and the fourth was related to ongoing vascular coagulopathy.

The results also show that TCZ rapidly reduces hyperinflammation but does not seem to have any significant effect on ferritin and D-dimer levels. Clinicians need to pay attention to control MAS and intravascular coagulopathy by using additional appropriate pharmacological interventions.

We suggest that timely use of TCZ as determined by fever, worsening hypoxia, high CRP and D-dimer in patients with SARS CoV-2 pneumonia can be a lifesaving. Notably, previous published studies with the use of TCZ in SARS CoV-2 have shown survival benefit with marked reduction in inflammatory markers. The results from one non randomised study also reported benefit with the use of a single low dose of tocilizumab, in patients with severe SARS CoV-2 pneumonia with significantly higher survival rates in treated patients compared to patients who did not receive Tocilizumab.[15] In addition, the positive treatment effect on survival with TCZ was independent from clinical comorbidities associated with poor outcomes such as age, diabetes, hypertension or heart diseases. This study also reported no infections in the TCZ group.[15,17,18]

A major limitation of our study is the lack of a comparator arm which was not possible in this acute setting due to unavailability of other regimen justifying equipoise without putting patients at additional risk for receiving any inferior treatment. Furthermore, given the life-threatening nature of the disease characterised by sudden worsening and rapid progression over few hours, a comparative arm cannot be justified. As the new treatments evolve over time, a randomised clinical trial in the future will be able to provide reliable evidence on the actual therapeutic benefit associated with the use of TCZ in CRS in SARS CoV-2. Until then, these findings validate the use of TCZ for the management of CRS in SARS CoV-2 safely.

In summary, TCZ effectively improves clinical and laboratory parameters with a reduction in the need for ICU and ventilatory care in patients with moderate-to-severe SARS CoV-2 disease.

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Conflicts of interest

There are no conflicts of interest.

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