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RESEARCH ARTICLE

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Tocilizumab for the treatment of severe coronavirus disease 2019

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Abstract

Tocilizumab, an interleukin-6 inhibitor, may ameliorate the inflammatory manifestations associated with severe coronavirus disease 2019 (COVID-19) and thus improve clinical outcomes. This was a retrospective review of patients with laboratory-confirmed severe COVID-19 who received tocilizumab and completed 14 days of follow up. Twenty-five patients were included, median age was 58 years (interquartile range, 50-63) and the majority were males (92%). Co-morbidities included diabetes mellitus (48%), chronic kidney disease (16%), and cardiovascular disease (12%). Fever (92%), cough (84%), and dyspnea (72%) were the commonest presenting symptoms. All patients received at least two concomitant investigational antiviral agents. Median oral temperature was on day 1, 3, and 7 was 38.0°C, 37.3°C ($P = .043$), and 37.0°C ($P = .064$), respectively. Corresponding median C-reactive protein was 193 and 7.9 mg/L ($P < .0001$) and <6 mg/L ($P = .0001$). Radiological improvement was noted in 44% of patients by day 7% and 68% by day 14. Nine patients (36%) were discharged alive from intensive care unit and three (12%) died. The proportion of patients on invasive ventilation declined from (84%) at the time of tocilizumab initiation to 60% on day 7 ($P = .031$) and 28% on day 14 ($P = .001$). The majority (92%) of patients experienced at least one adverse event. However, it is not possible to ascertain which adverse events were directly related to tocilizumab therapy. In patients with severe COVID-19, tocilizumab was associated with dramatic decline in inflammatory markers, radiological improvement and reduced ventilatory support requirements. Given the study's limitations, the results require assessment in adequately powered randomized controlled trials.

KEYWORDS

coronavirus, COVID-19, IL-6, SARS-CoV-2, tocilizumab

1 | INTRODUCTION

The identification in January 2020 of the novel betacoronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), in China was followed by worldwide spread.[1-3] On 11 March 2020, the World Health Organization (WHO) declared a SARS-CoV-2 pandemic.[4] As of 17 April 2020, the WHO has reported more than 2.1 million SARS-CoV-2 infections

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TABLE 1 Baseline characteristics of 25 patients treated with tocilizumab for severe COVID-19

Characteristic	Frequency or median (IQR)
Male gender, number (%)	23 (92%)
Age, median (IQR) y	58 (50-63)
Ethnic group, number (%)	
Arab	9 (36%)
Bengali	7 (28%)
Indian	3 (12%)
Caucasian	2 (8%)
Persian	2 (8%)
Tagalog	1 (4%)
Black African	1 (4%)
Independent functional status, number (%)	21 (84%)
Current or past smoker, number (%)	6 (24%)
Body mass index (kg/m^2), median (IQR)	29 (27-34)
Charlson co-morbidity score, median (IQR)	1 (0-3)
Cardiovascular disease, number (%)	3 (12%)
Diabetes mellitus, number (%)	12 (48%)
Chronic kidney disease, number (%)	4 (16%)
Malignant disease, number (%)	1 (4%)
Presenting symptoms, number (%)	
Fever	23 (92%)
Dry cough	13 (52%)
Productive cough	8 (32%)
Sore throat	7 (28%)
Dyspnea	18 (72%)
Rhinorrhoea	1 (4%)
Generalized pain	8 (32%)
Fatigue	14 (56%)
Diarrhea	2 (8%)
Nausea/vomiting	7 (28%)
Headache	3 (12%)
Altered consciousness	2 (8%)
Oral temperature, median (IQR) °Celsius	38 (38-39)
Chest radiological abnormalities	
Bilateral abnormalities	23 (92%)
Infiltrates and ground glass opacities	25 (100%)
Days from onset of symptoms to hospitalization, median (IQR)	5 (3-9)
Days from hospitalization to ICU admission, median (IQR)	1 (0-4)
Days from ICU admission to receipt of first dose of tocilizumab, median (IQR)	1 (1-3)

Abbreviations: COVID-19, coronavirus diease; ICU, intensive care unit; IQR, interquartile range.

globally, including nearly 140 thousand deaths.[5] Qatar reported the first COVID-19 case on 27 February 2020.[6] As of 17 April 2020, the total of laboratory-confirmed COVID-19 cases in Qatar was 4663 cases, including seven deaths.[7]

In the majority of patients, SARS-CoV-2 causes a mild to moderate illness characterized by fever and respiratory symptoms, with or without evidence of pneumonia.[8] However, up to 10% of patients with COVID-19 may develop severe pneumonia with hypoxia, acute respiratory distress syndrome, and multiorgan failure. Such patients may require admission to an intensive care unit (ICU) for critical support and mechanical ventilation.[8,9] Reported overall case fatality rates range from 0.9% in South Korea and 2.3 in China, to as high as 7.2% in Italy.[8,10,11] There are currently no approved therapeutic options for COVID-19 but a number of potentially useful antiviral agents are undergoing clinical evaluation.[12]

COVID-19 is associated with increased plasma concentrations of proinflammatory cytokines.[9] Moreover, histopathological examination of lung tissue from deceased patients with COVID-19 showed evidence of extensive alveolar oedema, proteinaceous exudate and patchy inflammatory cellular infiltration.[13,14] These findings suggest that severe SARS-CoV-2 infection is associated with a cytokine storm and pulmonary inflammation secondary to a dysregulated host immune response.[15] Tocilizumab is a humanized monoclonal inhibitor of the proinflammatory cytokine interleukin-6 (IL-6) and is licensed for use in the clinical management of cytokine release syndrome.[16] It has been postulated that tocilizumab may ameliorate the intense inflammatory manifestations associated with severe COVID-19 and thus improve clinical outcomes.[15] Peer-reviewed data on the clinical use of tocilizumab in severe COVID-19 are very limited.[17-21] We aimed to describe the clinical characteristics, laboratory findings and outcomes associated with the use of tocilizumab in patients with severe COVID-19 in Qatar.

2 | METHODS

We retrospectively included all patients in Qatar with laboratory-confirmed SARS-CoV-2 infection who received one or more doses of tocilizumab and completed at least 14 days of follow up.

SARS-CoV-2 infection was confirmed on respiratory samples using TaqPath COVID-19 Combo Kit (Thermo Fisher Scientific, Waltham, MA), a multiplex real-time reverse transcription polymerase chain reaction system targeting SARS-CoV-2 genomic regions encoding Orf-1ab polyprotein, N protein and S protein. Demographic and clinical data were retrieved from the patients' electronic records. Radiological findings were retrospectively reviewed and reported by a single radiologist. All patients received standard clinical care, as per the local COVID-19 management protocol. Accordingly, COVID-19 is classified as severe if any one or more of respiratory rate ≥30 per minute, $SpO_2 \leq 93\%$ while on room air, $PaO_2/FiO_2 \leq 300$ mm Hg, hypotension or any organ failure is present. Patients with severe COVID-19 were offered supportive care in addition to antiviral therapy with hydroxychloroquine, azithromycin, lopinavir/ritonavir, ribavirin, and/or interferon α2-a. The regimens are individualized based on the presence of

TABLE 2 Laboratory characteristics of 25 patients treated with tocilizumab for severe COVID-19 (median [IQR])

Characteristic	At the time of hospitalization	Highest follow up value	Lowest follow up value
Hemoglobin, g/L	13.6 (12.5-15.3)	13.3 (11.9-14.3)	9.9 (7.5-1.3)
Peripheral white cell count ($\times 10^9$/L)	6.0 (4.8-7.7)	14.4 (9.8-23.5)	4.9 (3.5-6.7)
Peripheral lymphocyte count ($\times 10^9$/L)	0.9 (0.7-1.1)	1.9 (1.3-2.5)	0.5 (0.4-0.9)
Peripheral absolute neutrophil count ($\times 10^9$/L)	5.0 (3.5-6.7)	12.3 (8.3-20.4)	3.0 (2.3-4.7)
Platelets count ($\times 10^9$/L)	208 (167-243)	439 (317-561)	185 (129-248)
Fibrinogen, g/L	4.6 (2.5-6.5)	5.0 (4.2-5.7)	1.7 (0.8-2.7)
ALT, IU/L	30 (21-44)	186 (78-225)	35 (21-49)
AST, IU/L	46 (34-60)	126 (78-206)	30 (24-42)
Serum creatinine, μmol/L	88 (82-109)	145 (103-272)	71 (62-84)
Serum lactate, mmol/L	1.6 (1.3-2.0)	1.8 (0.9-2.0)	0.8 (0.7-1.4)
Serum procalcitonin, ng/L	0.38 (0.12-0.83)	0.57 (0.36-5.10)	0.12 (0.04-0.46)
CRP, mg/L	95.2 (49.8-204.4)	231.5 (99.4-312.6)	<0.6 (<0.6-2.5)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; IQR, interquartile range.

contraindications, potential drug-drug interactions, and toxicities. The protocol allowed the use of tocilizumab for patients with COVID-19 who have elevated C-reactive protein (CRP) levels and require supportive care in ICU. Tocilizumab (Actemra, Roche Holding AG, Basel) was reconstituted with 100 mL 0.9% sodium chloride solution and administered by intravenous infusion over 60 minutes. Study day one is used to describe the day on which the first dose of tocilizumab was administered. Study days were thereafter counted sequentially to the 14th day of follow up.

The primary outcome was discharge alive from ICU by day 14. Additional outcomes were categorical ventilatory support status and inflammatory markers over the 14 days from the administration of the first dose of tocilizumab. Adverse events were grouped and graded according to the United States Department of Health and Human Service's Common Terminology Criteria for Adverse Events.[22]

Data were summarized using number (percentage) or median (interquartile range), as appropriate. The Wilcoxon signed-rank test was used to compare paired medians over time and McNemar test for paired proportions. Kaplan-Meier method and log-rank *P* value were used to compare time-to-discharge alive from ICU in those with baseline invasive ventilation status versus those without. Cox proportional hazards model was utilized to identify variables associated with the primary outcome. Variables with $P < 0.1$ in the univariate analysis were included in the multivariate model. All *P* values were two-sided with a threshold of <.05 for statistical significance. Statistical analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, Washington) and Stata (StataCorp LLC, College Station, TX).

The study was conducted according to the principles of the Declaration of Helsinki and the laws and regulations of the Ministry of Public Health in Qatar. Ethical approval was granted by Hamad Medical Corporation's Institutional Review Board (MRC-01-20-191), with a waiver of informed consent.

3 | RESULTS

The eligibility criteria were met by 25 individuals, all of whom were in ICU at the time of receipt of first dose of tocilizumab. The majority were males (23, 92%) and the median age was 58 years (interquartile range [IQR], 50-63). The most frequent ethnic backgrounds were Arab (9, 36%) and Bengali (7, 28%). Co-existing medical conditions included diabetes mellitus (12, 48%), chronic kidney disease (4, 16%) and cardiovascular disease (3, 12%). Notably, median body mass index was 29 kg/m^2 (IQR, 27-34).

Fever (23, 92%), cough (21, 84%), dyspnea (18, 72%), and generalized fatigue (14, 56%) were the most common symptoms present at the time of hospital admission. Median duration between onset of symptoms and hospitalization was 5 days (IQR, 3-9). Other baseline characteristics of the cohort are presented in Table 1.

All included patients had pulmonary infiltrates and ground glass opacities in their baseline chest radiographic images. The changes were bilateral in the majority (23, 92%).

Notable laboratory findings at the time of hospital admission include median CRP of 95.2 mmol/L (IQR, 49.8-204.4) and median peripheral lymphocyte count of 0.9×10^9/L (IQR, 0.7×10^9-1.1×10^9/L). Laboratory findings are summarized in Table 2.

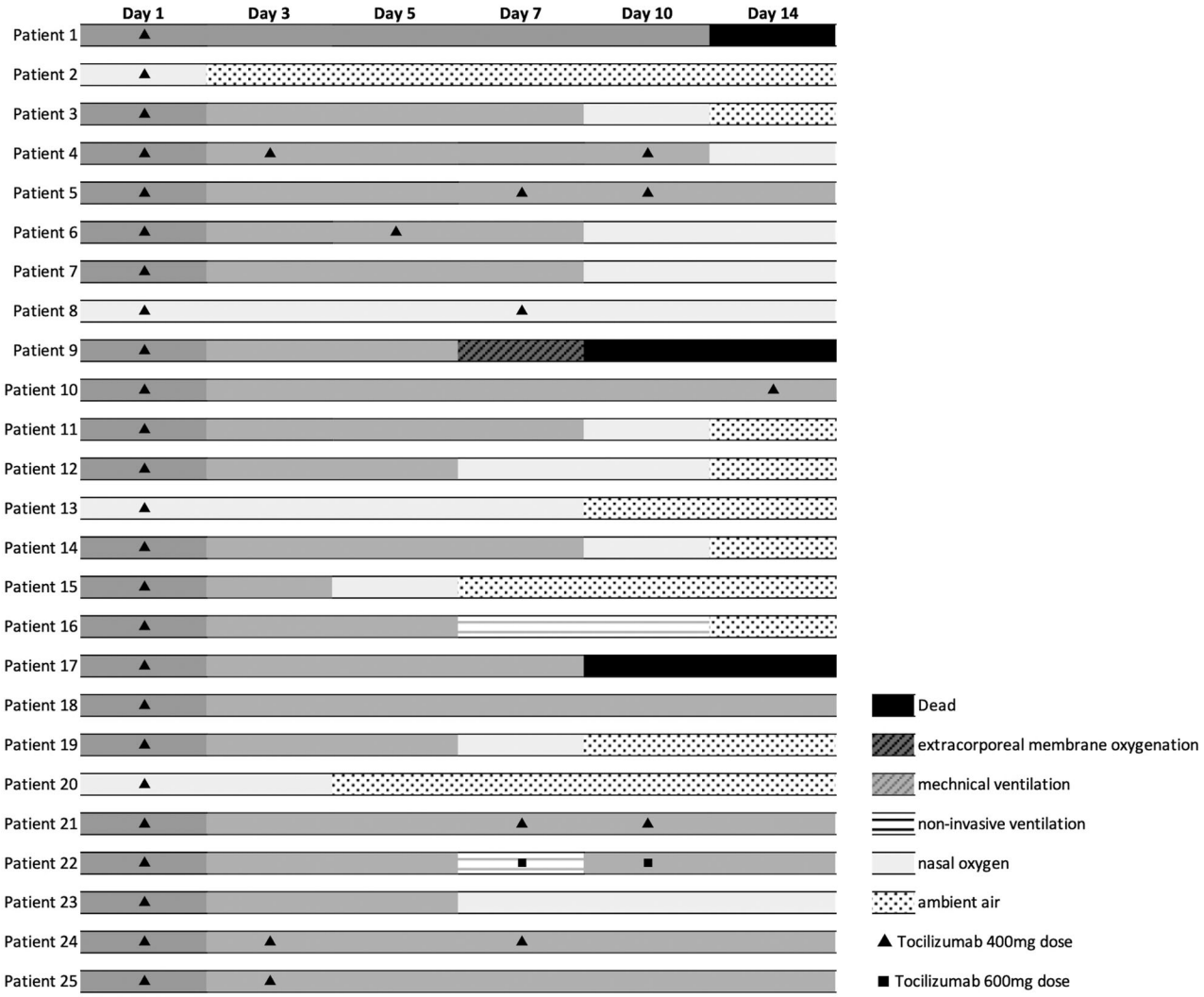

FIGURE 1 Individual patient's summary of ventilatory support status from first day of tocilizumab therapy through 14 days follow up. Each horizontal line represents a single patient's respiratory support category on the days shown at the top of the figure. The shading denotes type of ventilatory support on that day. The markers represent days of tocilizumab administration and the dose received

During the study period, four patients had secondary bacterial respiratory tract infections (two *Klebsiella pneumoniae*, one *Pseudomonas aeruginosa* and one *Staphylococcus aureus*). *Candida species* were isolated from respiratory cultures from eight patients (32%).

Included patients were transferred to ICU within a median of 1 day (IQR, 0-4) from hospital admission. Concomitant antiviral therapy included hydroxychloroquine (25, 100%), azithromycin (24, 96%), lopinavir/ritonavir (24, 96%), ribavirin (22, 88%), and interferon 1-α2a (15, 60%). The median number of antivirals received by individual patients was 5 agents (IQR, 2-5).

Tocilizumab was started within a median of 1 day (IQR, 1-3) of admission to ICU. Patients received a median of one tocilizumab dose (IQR, 1-3) and a median total dose of 5.7 mg/kg (IQR, 4.8-9.5) (Figure 1). Median oral temperature was 38.0°C (IQR, 37.2-38.5) on the day of tocilizumab initiation, 37.3°C (IQR, 36.9-37.9) on day 3 ($P = .043$) and 37.0°C (IQR, 36.8-37.3) on day 7 ($P = .064$). Median CRP declined from 193 mg/L (IQR, 121.6-302.4) on day 1 to 7.9 mg/L (IQR, 6-11.3) on day 7 ($P < .0001$) (Figure 2). Peripheral total white cell and lymphocytes count changes in association with tocilizumab therapy are shown in Figure 2. Significant radiological improvement was noted in 11 patients (44%) by day 7 and in 17 patients (68%) by day 14.

Nine patients (36%) achieved the primary endpoint of being discharge alive from ICU by day 14. Of the remaining 16, three (12%) patients died and 13 (52%) were still in ICU. The proportion of patients on invasive ventilation declined from 21 (84%) at the time of tocilizumab initiation to 14 (60%) on day 7 ($P = .031$) and 7 (28%) on day 14 ($P = .001$) (Figure 1 and Figure 3).

There was no statistically significant difference in the probability of being discharged alive from ICU between those who were on invasive ventilation at the time of initiation of tocilizumab (21, 84%) compared with those who were not (4, 16%) (log-rank $P = .218$). No baseline variables were independently associated with the primary outcome (Table 3).

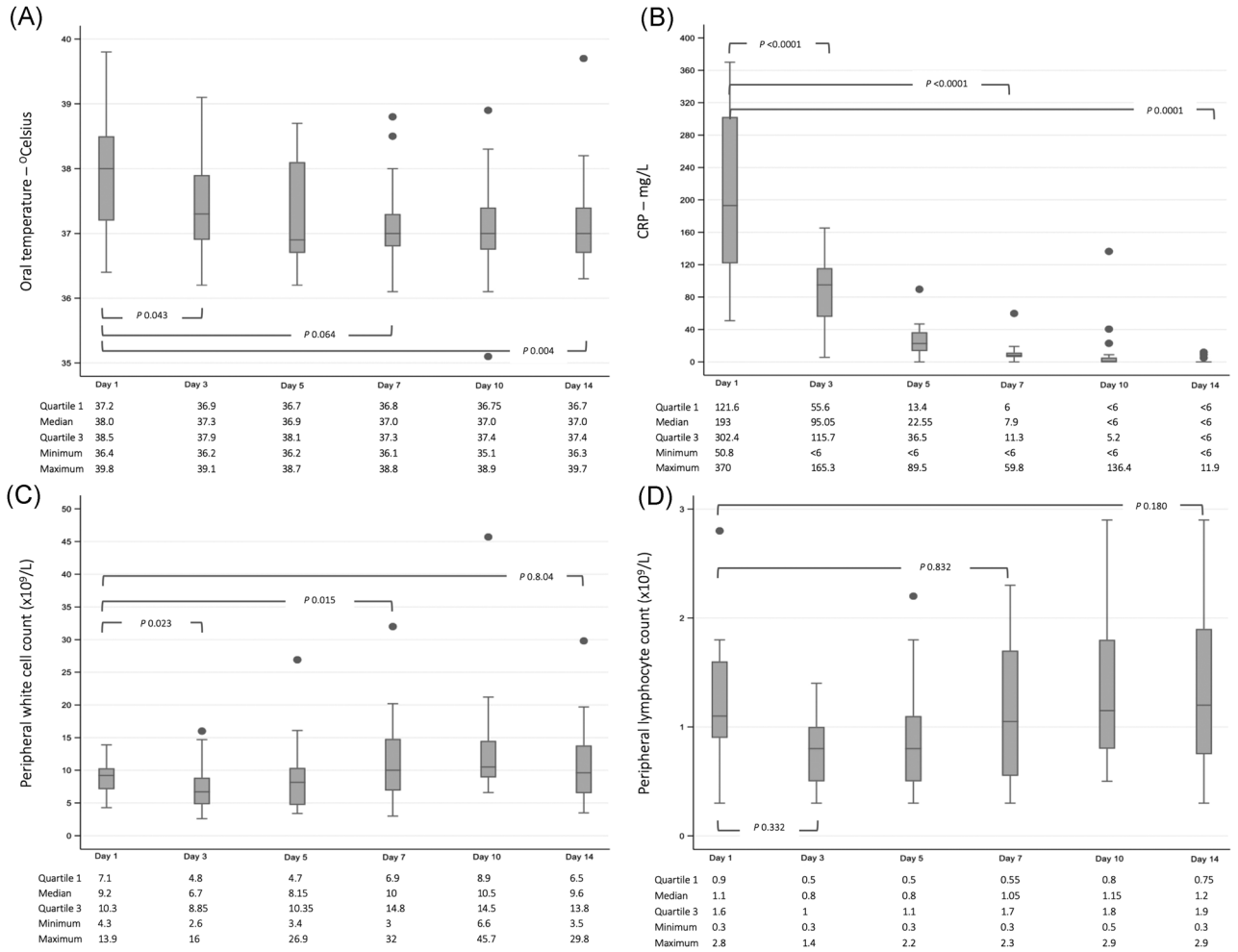

FIGURE 2 Selected serial inflammatory markers from first day of tocilizumab therapy through 14 days follow up. Study day 1 is the day of initiation of tocilizumab therapy. Serial observations on study days 1, 3, 5, 7, 10, and 14 are shown. The tables denote values corresponding to the time points. Panel A: oral temperature in degrees celsius. Panel B: CRP in mg/L. Panel C: peripheral white cell count in cells ($\times 10^9$/L). Panel D: peripheral lymphocyte count in cells ($\times 10^9$/L). The dataset for the shown timepoint is complete for all included patients. The Wilcoxon signed-rank test P values are shown for the comparisons indicated by the corresponding lines. CRP, C-reactive protein

Twenty three (92%) patients in this study experienced at least one adverse event. The median number of adverse events per patient was 2 (IQR, 1-3). The most frequent adverse events were anemia (16, 64%), alanine aminotransferase (ALT) rise (11, 44%), and QT interval prolongation (5, 20%). A breakdown of adverse events and their grades is shown in Table 4.

4 | DISCUSSION

We report the clinical characteristics and outcomes of 25 patients who received tocilizumab therapy for severe COVID-19. Unsurprisingly, all patients were in ICU at the time of tocilizumab initiation. Only three (12%) patients died during within 14 days of follow up. This is remarkably lower than all-cause mortality rates in critically ill COVID-19 cohorts reported elsewhere.[23,24] However, the median age in this cohort was 58 years with a median Charlson co-morbidity score of one. Older age and increased co-morbidities have been consistently associated with poorer COVID-19 outcomes.[11,25] It is likely that the lower mortality observed in this study is at least in part a result of those baseline characteristics.

Similar to other reports of tocilizumab use in patients with COVID-19, the most striking clinical change observed in association with the tocilizumab in this study was the rapid decline in oral temperature and serum CRP levels (Figure 2).[18-21] This is a likely reflection of tocilizumab's immune modulating effect. The proportion of patients in this study who were on invasive ventilation decreased from 84% at the time of initiation of tocilizumab therapy to 60% at 7 days and 28% at day 14. The changes were statistically significant at both of these time points compared with the baseline status. Furthermore, there was a corresponding radiological improvement in 44% and 68% of patients at day 7 and 14, respectively. Notwithstanding the multitude of potential confounders in this study, it is not unreasonable to propose that this positive response may have been

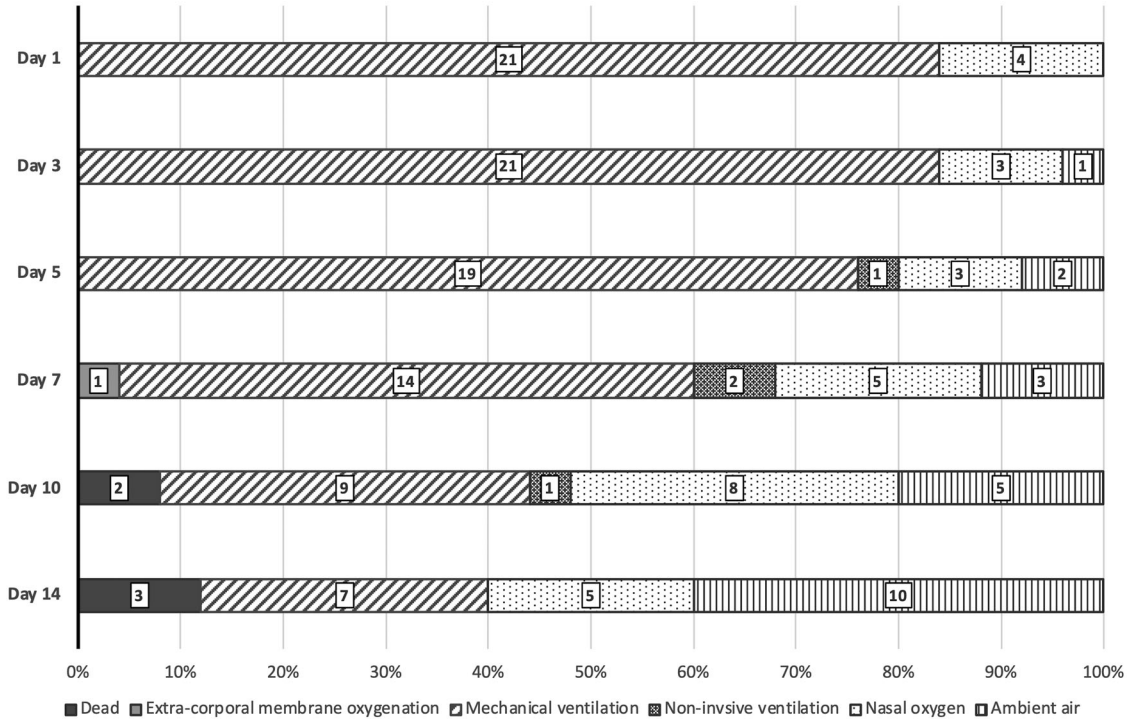

FIGURE 3 Summary of ventilatory support status from first day of tocilizumab therapy thru 14 days follow up (n = 25). Study day 1 is the day of initiation of tocilizumab therapy. Each horizontal line represents ventilation support categorization of the study cohort on the corresponding study day. The numbers indicate the count of individuals within each category at that time point

the result of tocilizumab's ability to ameliorate aberrant immune response-driven pulmonary manifestations of severe COVID-19.

Tocilizumab is licensed for use in certain patients with chronic inflammatory conditions such as rheumatoid arthritis, giant cell arteritis and polyarticular juvenile idiopathic arthritis.[16] Amongst its well described adverse events are upper respiratory tract infections, headache, hypertension, and ALT rise.[26] The majority of patients in this report experienced adverse events. However, all patients were

TABLE 3 Cox proportional hazards for discharge alive from ICU

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	*P* value	aHR	95% CI	*P* value
Age >60 y	0.319	0.037-2.762	.300	…	…	…
Independent functional status	0.048	0.003-0.780	.033	0.091	0.003-2.559	.159
Charlson co-morbidity score	0.986	0.723-1.344	.93	…	…	…
Cardiovascular disease	4.531	0.785-26.126	.091	2.050	0.211-19.944	.536
Diabetes mellitus	0.527	0.096-2.902	.462	…	…	…
Chronic kidney disease	0.898	0.104-7.744	.922	…	…	…
Baseline noninvasive ventilation status	2.778	0.501-15.409	.242	…	…	…
Baseline body mass index	0.917	0.770-1.091	.329	…	…	…
Baseline total peripheral white cell count	1.022	0.823-1.268	.845	…	…	…
Baseline peripheral lymphocyte count	1.950	0.205-18.579	.561	…	…	…
Baseline ALT	1.00	0.974-1.031	.876	…	…	…
Baseline CRP	0.998	0.989-1.007	.616	…	…	…
Total tocilizumab dose in mg/kg	0.649	0.379-1.111	.115	…	…	…

Abbreviations: aHR, adjusted hazard ratio; ALT, alanine aminotransferase; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; ICU, intensive care unit.

TABLE 4 Summary of adverse events in 25 patients treated with tocilizumab for severe COVID-19

	Grade 1	Grade 2	Grade 3	Grade 4	Total
Anemia	5	5	6		16
ALT rise	5	3	3		11
QT prolongation			5		5
AST rise	2	1			3
Acute kidney injury				2	2
Hypertriglyceridemia		1	1		2
Pancreatitis		2			2
Atrial fibrillation		1			1
Disseminated intravascular coagulation			1		1
Herpes simples virus reactivation			1		1
Hyperkalaemia		1			1
Lipase increase			1		1
Serum amylase increase			1		1
Total	**12**	**14**	**19**	**2**	**47**

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019.

critically ill and received concomitant investigational anti-SARS-CoV-2 therapies. With the exception of tocilizumab's association with ALT rise, some of the more frequent adverse events observed in this study are commonly associated with some of the concomitant agents. For example, anemia with ribavirin, QT prolongation with hydroxychloroquine.[26,27] Importantly, tocilizumab may be associated with opportunist infections.[16,26] One patient in this cohort experienced reactivation of oral Herpes Simplex infection and nearly one-third (8, 32%) had *Candida species* in their respiratory cultures. However, it is not possible to ascertain the extent to which the frequency, nature or severity of any of the adverse events observed in this study was related specifically to tocilizumab. Nevertheless, no scheduled tocilizumab therapy was discontinued as a result of concern over potentially related adverse events.

In this study, patients received one to three doses of tocilizumab. While the median total dose was 5.7 mg/kg (range, 3.7-20 mg/kg), the median individual dose was 4.8 mg/kg (range, 2.7-7.5 mg/kg). The standard recommended dose of tocilizumab for its approved indications is 4 to 8 mg/kg, while the proposed dosing regimen in the context of COVID-19 is 8 mg/kg, to a maximum of 800 mg per dose, with an additional dose 8 to 12 hours later if clinically required.[16,28] It is therefore not clear if any perceived benefits noted in this study could have been enhanced if tocilizumab dosing was consistently in line with the higher proposed investigational dosing schedules.

Limitations of this study include its retrospective nature, lack of a control arm and potential confounding from concomitant application of multiple interventions. Moreover, determination of serum IL-6 levels before and after tocilizumab therapy would have been useful to demonstrate the immune modulating effect. However, in the absence of high-level clinical evidence to guide therapeutic interventions in a such a rapidly growing pandemic, the wide off-label use of potentially beneficial agents is understandable.[29] While this report may offer some assessment of the possible role of tocilizumab in the management of patients with severe COVID-19, it cannot lead to any firm conclusions. The observed dramatic decline in inflammatory markers, coupled with radiological improvement and reduced ventilatory support requirements are encouraging. However, the results need confirmation in adequately powered randomized controlled trials, several of which are currently underway in different parts of the world.[30]

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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