Microbes, Infection and Chemotherapy

ORIGINAL RESEARCH

https://doi.org/10.54034/mic.e1251

Impact of three consecutive intravenous doses of tocilizumab in severe COVID-19 pneumonia: a retrospective cohort study

Authors: Raihan Rabbani[1], Md. Jahidul Hasan[2], Ahmad Mursel Anam[3], Shihan Mahmud Redwanul Huq[4]

Abstract

Background. Acute respiratory distress syndrome (ARDS) in severe COVID-19 pneumonia is mostly responsible for high mortality rate. Tocilizumab, an interleukin-6 (IL-6) inhibitors, down-regulates the progression of cytokine storm leading to ARDS. **Objectives**. The study aimed to assess the clinical outcomes of three consecutive intravenous doses of tocilizumab in patients with severe COVID-19 pneumonia. **Methods**. This retrospective observational study was conducted on severe COVID-19 pneumonia patients in a single-center who were treated with three intravenous dose of tocilizumab (8 mg/Kg of body weight, max 800 mg per dose × 3) along with intravenous dexamethasone. Three doses of tocilizumab-associated changes in respiratory function, clinical outcomes and mortality rate were analyzed. **Results**. Seventy-four patients (N) received intravenous tocilizumab therapy. After third intravenous dose of tocilizumab (48-72 h apart from the second dose), SpO_2 (blood oxygen saturation) was increased and the requirement of supplemental oxygen (RSO) was decreased more than after the second dose [Median: 96.5% (IQR: 96-98%) and Median: 0 (IQR: 0-1 L), respectively versus Median: 92% (IQR: 91-92%) and Median: 6 L (IQR: 5-7.2 L, respectively] ($P < 0.05$). SpO2 was normalized in 78.4% of patients ($P=0.001$) treated with three doses of tocilizumab. Further RSO and demand of invasive mechanical ventilation support were increased in 21.6% (58/74 patients) and 14.8% (11/74 patients) of patients, respectively with a 30-day mortality rate of 4% (3/74 patients). Tocilizumab therapy was well tolerated in all patients. **Conclusions**. An additional third intravenous dose of tocilizumab improved clinical outcomes and reduced mortality rate in patients with severe COVID-19 pneumonia.

Key word: severe COVID-19 pneumonia, tocilizumab, third dose, IL-6 inhibitor, cytokine storm, ARDS, SpO_2.

[1]MD, Consultant, Internal Medicine and ICU, Square Hospitals Ltd., 18/F Bir Uttam Qazi Nuruzzaman Sarak, West Panthapath, Dhaka-1205, Bangladesh.
Phone: +8801754544689.
drraihan@squarehospital.com
https://orcid.org/0000-0001-5173-5793

[2]M. Pharm., Clinical Pharmacist (ICU and Infectious Diseases), Clinical Pharmacy Services, Department of Pharmacy, Square Hospitals Ltd., 18/F Bir Uttam Qazi Nuruzzaman Sarak, West Panthapath, Dhaka-1205, Bangladesh.
Phone: +8801911011167.
jahidrj@gmail.com
https://orcid.org/0000-0001-7038-6437

[3]MRCP, Associate Consultant, High Dependency Unit (HDU), Square Hospitals Ltd., 18/F Bir Uttam Qazi Nuruzzaman Sarak, West Panthapath, Dhaka-1205, Bangladesh.
Phone: +8801911010841.
murselanam@gmail.com
https://orcid.org/0000-0001-9673-9704

[4]MRCP, Associate Consultant, Internal Medicine and ICU, Square Hospitals Ltd., 18/F Bir Uttam Qazi Nuruzzaman Sarak, West Panthapath, Dhaka-1205, Bangladesh.
Phone: +8801713401761.
shihan.huq@gmail.com
https://orcid.org/0000-0002-1122-5606

Corresponding author:
Md. Jahidul Hasan
Address: M. Pharm., Clinical Pharmacist (ICU and Infectious Diseases), Clinical Pharmacy Services, Department of Pharmacy, Square Hospitals Ltd., 18/F Bir Uttam Qazi Nuruzzaman Sarak, West Panthapath, Dhaka-1205, Bangladesh. Mobile: +8801911011167.
E-mail: jahidrj@gmail.com

Submitted: october 07, 2021
Reviewed : october 12, 2021
Approved : november 30, 2021

How to cite: Rabbani R, Hasan MJ, Anam AM, Huq SMR. Impact of three consecutive intravenous doses of tocilizumab in severe COVID-19 pneumonia: a retrospective cohort study. Microbes Infect Chemother. 2021; 1: e1251

Introduction

A sudden pneumonia outbreak in Wuhan, China in December 2019 within a couple-of-month, through a declaration of World Health Organization (WHO) on 11 March 2020, was introduced to world population as "COVID-19 (coronavirus disease-2019) pandemic" caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and rapidly spread to more than 200 countries around the world (1). As of 15 August 2020, more than 20 million confirmed COVID-19 cases and 7,55,786 deaths were reported worldwide, and Bangladesh with 3,591 mortality cases was standing at the third highest position in COVID-19-associated mortality at that time among all the affected countries in

South-East Asia (2).

The initial replication-phase of SARS-CoV-2 can be followed by a second inflammation-phase where a host hyperimmune response is developed. In response, excessive release of proinflammatoy cytokines, including IL-2 (interleukin-2) leads to cytokine storm in host body that may results in bilateral pneumonia and acute respiratory distress syndrome (ARDS). Patients with ARDS in severe COVID-19 pneumonia may progressively develop critical COVID-19 pneumonia while respiratory failure, septic shock, and multiple organ dysfunctions are associated with severe COVID-19 infection (3, 4). ARDS in severe COVID-19 is the leading cause of mortality worldwide and over production of proinflammatory cytokines prominently contributes to poor outcomes in severe COVID-19 infection (5, 6).

Several studies reported that IL-6 (interleukin-6) is the key proinflammatory cytokine that significantly contribute in the rapid progression of cytokine storm in COVID-19, and elevated IL-6 level is associated with increased severity of COVID-19 infection with worse clinical outcomes (4, 6-9). Possible IL-6 inhibitors in COVID-19 are still under clinical investigation. IL-6 receptor is composed of membrane-bound interleukin-6 receptor (mIL-6R) and soluble interleukin-6 receptor (sIL-6R). Tocilizumab (TCZ) is a humanized recombinant anti-human IL-6 receptor monoclonal antibody that specifically blocks the two forms of IL-6 receptor: membrane-bound interleukin-6 receptor (mIL-6R) and soluble interleukin-6 receptor (sIL-6R). It is a popular drug for the treatment of refractory rheumatoid arthritis and was approved by the Food and Drug Administration (FDA) of the United States (US) (7, 10). Currently, TCZ is an investigational drug in COVID-19 and has been included in the seventh version of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia by the National Health Commission of China (10). However, inadequate clinical data on the TCZ-associated clinical outcomes of patients with severe/critical COVID-19 pneumonia is the major limitation in its comprehensive use as an IL-6 inhibitor in COVID-19. Moreover, maximum two dosages of intravenous TCZ at a maximum of 8 mg/kg of body weight (up to 800mg) at 12 h apart (within 24 h) with or without steroidal therapy has been used in patients with severe COVID-19 pneumonia in multiple studies where the mortality rate ranges from 20% to 29% and intensive care unit (ICU) admission rate (for increasing severity of the disease) ranges from 10% to 45% (7, 10-15). Though tocilizumab was not included in the national COVID-19 treatment guideline in Bangladesh up to 30 July 2020, due to rapid increasing trend of confirmed COVID-19 cases and associated mortality (16), this drug was intended to use in the treatment of severe COVID-19 pneumonia in some tertiary care hospitals in some megacities in Bangladesh. However, the increased mortality rate, increased ICU and mechanical ventilation support, and high supplemental oxygen demand even after 2 consecutive dosages of TCZ within a short time in patients with severe COVID-19 pneumonia is still indicating inadequate therapeutic response of TCZ in severe COVID-19 treatment. The main objective of this study was to evaluate the clinical outcome of three consecutive intravenous doses of tocilizumab in Bangladeshi patients with severe COVID-19 pneumonia.

Materials and methods

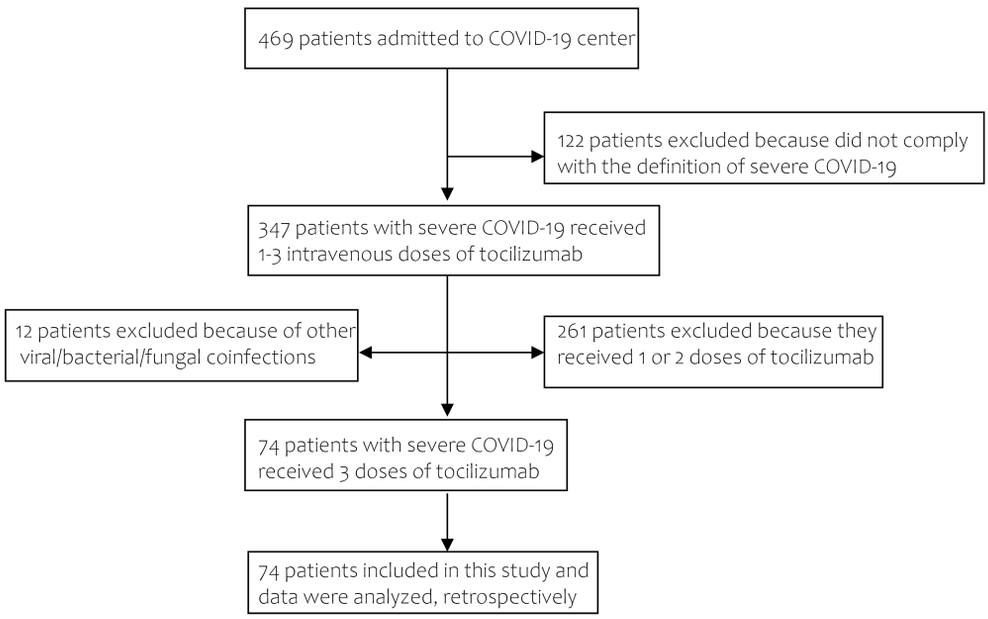
Study design and patients

This retrospective cohort study was conducted on 347 adult patients (⩾ 18 years) admitted with confirmed severe COVID-19 pneumonia from May 15, 2020 to September 30, 2020 at the Square hospital, Dhaka, Bangladesh, and received interleukin-6 inhibitor TCZ for the treatment of severe COVID-19-associated pulmonary hyperinflammation. Among them, 74 (N) patients met the study's sample inclusion and exclusion criteria, received three consecutive doses of tocilizumab for the treatment of COVID-19 pneumonia, and completed the study (Flowchart 1). Rest of the patients excluded from the study due to leaving hospital against the medical advice and disagreeing to take TCZ more than one dose. All the data of participated patients and medications of the study were collected from the electronic patient database of the hospital and manually from patients' prescriptions by a dedicated multidisciplinary clinical team consisting of five doctors and one clinical pharmacist. They also charged for the monitoring of drug-associated adverse event in patients. Lab investigations and day-to-day clinical assessment of all the patients were performed routinely. COVID-19 infection was confirmed by a positive reverse transcriptase polymerase chain reaction (RT-PCR) assay (instrument/device: Rotor Gene-Q/Cobas z480, and QIAGEN kits for real-time PCR, QIAGEN GmbH, Germany) of two specimens (nasal and oral swabs) in the Molecular laboratory of the hospital. Clinical assessment of all patients' condition and the progression of the disease were performed by the team before the first dose, after the first dose, after the second dose of TCZ, and continued up to 72 h after the third intravenous dose of TCZ. The study was approved by the Research Ethical Committee of Square hospital in July 25, 2020. Informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research ethical committee.

Sample inclusion and exclusion criteria

Inclusion criteria:

I. SARS-CoV 2 is present in the nasal/oral swabs
II. no previous history of COVID-19 infection
III. having at least two additional signs of severe COVID-19 pneumonia with confirmed pneumonia lesions (bilateral ground-glass opacities) (>50%) in the chest computerized tomography (CT) scan images at the time of admission: (1) dyspnoea; (II) oxygen saturation in blood (SpO_2) level ⩾ 93% on room air; and (III) respiratory rate ⩽30 breaths/min
IV. Onset of symptom(s)-to-hospitalization no more than 10 days
V. No history of taking any anti-inflammatory drugs within last 3 months of hospital admission



Flowchart 1. Overview of participants included in this study

Exclusion criteria

I. patient with pregnancy
II. any history of trauma or surgical procedure within the last 3 months of hospital admission
III. any history of acute/chronic autoimmune disease
IV. history of hospital stay for >3 days for any purpose with the last 3 months
V. current evidence of bacterial or fungal coinfection
VI. coming from another hospital or healthcare facility

Treatment of severe COVID-19 and tocilizumab administration

All patients with severe COVID-19 pneumonia found dexamethasone 0.25 to 0.5 mg/kg of body weight (max 20 mg per day) in two divided doses in the early stage of COVID-19 pneumonia diagnosis. Patients with severe COVID-19 pneumonia having SpO2 of less than 94% with a PaO2/FiO2 ratio of less than 300 mmHg or a 30% fall in the PaO2/FiO2 ratio on ambient air over a period of 24 h, extensive lung infiltrates on chest HRCT scan, and elevated serum inflammatory biomarkers (either ferritin: >400 ng/mL or C-reactive protein: >2 g/dL) were considered as right candidates for the administration of intravenous tocilizumab (Actemra® 20 mg/mL, concentrate for solution for infusion, F. Hoffmann-La Roche Ltd, Switzerland). In case of other confirmed viral or bacterial, or fungal coinfections, platelet count <100,000/mm3, neutrophil count <2000/mm3, and elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level more than five times the upper normal limit (ALT: 50 U/L and AST: 40 U/L), TCZ therapy was contraindicated. Lab facility to do serum IL-6 level was not available in the hospital at that moment. The multidisciplinary clinical team evaluated the eligibility of the patients to receive TCZ therapy based on inclusion and exclusion criteria of the study. Recently used dosing systems of TCZ in different studies (7, 17) were followed by the team. The intravenous dose of TCZ used in the study was 8 mg per kg of body weight (max 800 mg). The second dose of TCZ was administered within 12–24 h after the first dose. The additional third dose of TCZ was administered within 48–72 h after the second dose. Each intravenous dose was infused to patient over 60 min. The current SpO2 and corresponding demand of supplemental oxygen in all patients after each dose of TCZ was recorded by the team.

Statistical Analysis

IBM SPSS Statistical software (version 22) was used for the analysis of the data. Continuous variables were expressed as median with interquartile range (IQR) and student's t-test was performed. Categorical variables were expressed as numbers (%) and compared by the χ^2 test across the groups. The level of significance was considered at P 0.05.

Results

The number of male patients was higher than the females (54 and 20, respectively, N = 74) and the median age was 62 years (IQR: 52-68.3 years). The median day of taking admission to hospital was 7 days (IQR: 6-8 days). As the symptoms of COVID-19, the median body temperature was 100.5°F (IQR: 100-101) (P <0.05). Other symptoms, including dry cough, shortness of breath, weakness, diarrhea, anosmia, and sore throat was common (95.9%, 78.4%, 100%, 36.5%, 82.4% and 75.7%, respectively) (P <0.05). Chronic diseases, including diabetes (86.5%), hypertension (71.6%), and cardiovascular diseases (CVD) (63.5%) were mostly common in more than fifty-percent of patients (N = 74) (P=0.001) (Table 1).

The median SpO2 was 86.5% (IQR: 84.7-88%) (P=0.220) and PaO2/FiO2 (the ratio of arterial oxygen partial pressure to fractional inspired oxygen) was 245 mmHg (IQR: 193-260 mmHg) (P=364) in the patients at the time of hospital admission. The median values of infection markers, including C-reactive protein (CRP) and procalcitonin were 57.1 mg/L

Table 1: Baseline demographic information, symptoms of COVID-19, comorbidity and laboratory findings in patients on admission

Characteristics	Values (N = 74)
Male/female, n (%)	54/20 (73/27)
Age (year), median (IQR)	62 (52-68.3)
Days from onset of symptoms-to-hospitalization, median (IQR)	7 (6-8)
Fever (°F), median (IQR)	100.5 (100-101)
Dry cough, n (%)	71 (95.9)
Shortness of breath, n (%)	58 (78.4)
Weakness, n (%)	74 (100)
Diarrhea, n (%)	27 (36.5)
Anosmia, n (%)	61 (82.4)
Sore throat, n (%)	56 (75.7)
Diabetes, n (%)	64 (86.5)
Hypertension, n (%)	53 (71.6)
CVD, n (%)	47 (63.5)
Bronchial asthma, n (%)	36 (48.6)
CKD, n (%)	27 (36.5)
COPD, n (%)	14 (18.9)
Severe obesity, n (%)	9 (12.1)
CLD, n (%)	3 (4)
Malignancy, n (%)	3 (4)
PD, n (%)	1 (1.3)
SpO_2 (%), median (IQR)	86.5 (84.7-88)
PaO_2/FiO_2 (mmHg), median (IQR)	245 (193-260)
Respiratory rate, (breaths/min), median (IQR)	24 (20-26)
Heart rate (beat/min), median (IQR)	98 (86-105.25)
CRP (mg/L), median (IQR)	57.1 (40-204.3)
Procalcitonin (ng/mL), median (IQR)	0.12 (0.07-0.3)
WBC (K/µL), median (IQR)	7.8 (5.11-10)
Neutrophils (%), median (IQR)	86.9 (78.4-89.6)
Lymphocytes (%), median (IQR)	13.1 (11.6-14.6)
Platelet (K/µL), median (IQR)	164 (127.2-201)
D-dimer (mg /L FEU), median (IQR)	4.3 (2.4-6.6)
Serum Ferritin (ng/mL), median (IQR)	717 (525.2-964)
LDH ((U/L), median (IQR)	607.5 (388-830.7)
Creatinine (mg/dL), median (IQR)	1 (0.8-1.3)
ALT (U/L), median (IQR)	51 (34-63.2)
AST (U/L), median (IQR)	35 (28-45.2)
MEWS, median (IQR)	3 (2-3)

(IQR: 40-204.3 mg/L) and 0.12 ng/mL (0.07-0.3 ng/mL), respectively (P <0.05). The median level of serum D-dimer [4.3 mg /L FEU (IQR: 2.4-6.6 mg /L FEU) (P=0.038)] and ferritin [717 ng/mL (IQR: 525.2-964 ng/mL) was significantly high in the patients. Kidney and liver functions were within the normal range. The median score of the Modified Early Warning Score (MEWS) in the patients was 3 (IQR: 2-3) (P <0.05) (Table 1). The median value of SpO2 and the requirement of supplemental oxygen (RSO) 72 h apart from the third dose of TCZ [96.5% (IQR: 96-98%) and 0 L (IQR: 0-1 L), respectively] was significantly lower than that after the first [89% (IQR: 88.7-90%) and 8 L (IQR: 8-10 L), respectively] and second dose of TCZ [92% (IQR: 91-92%) and 6 L (IQR: 5-7.2 L), respectively] (Table 2). Table 2 descriptively demonstrated individual patient-wise comparison of SpO2 and RSO following the intravenous administration of first, second and third dose of TCZ. Three patients developed mild elevation in serum CRP and alanine aminotransferase level as adverse events (AEs) associated with TCZ, but therapy was continued. No moderate-to-serious AEs were evidenced. Patients received other routine medications, including remdesivir, low-molecular-weight heparin, moxifloxacin, and vitamins.

All the patients received intravenous dexamethasone concomitantly with TCZ for their severity of disease. After the third intravenous dose of TCZ, ARDS was resolved through stabilizing the SpO2 (⩾ 95%) at room air within 72 h in approximately 78.4% of patients (N = 74) (P <0.05) with declined supplemental oxygen requirement. In contrary, among the 74 patients received the third intravenous dose of TCZ, RSO was further increased in 21.6% of patients (N = 74) (P <0.05) and 14.8% of patients were managed with invasive mechanical ventilation (IMV) in ICU setup (P <0.05) for the deterioration of their clinical condition. Within 30 days after the third dose of TCZ therapy, 4% of patients (N = 74) were died from different complications following COVID-19 infection such as respiratory failure, heart failure, sepsis, and brain stroke (P <0.05) (Figure 1).

Discussion

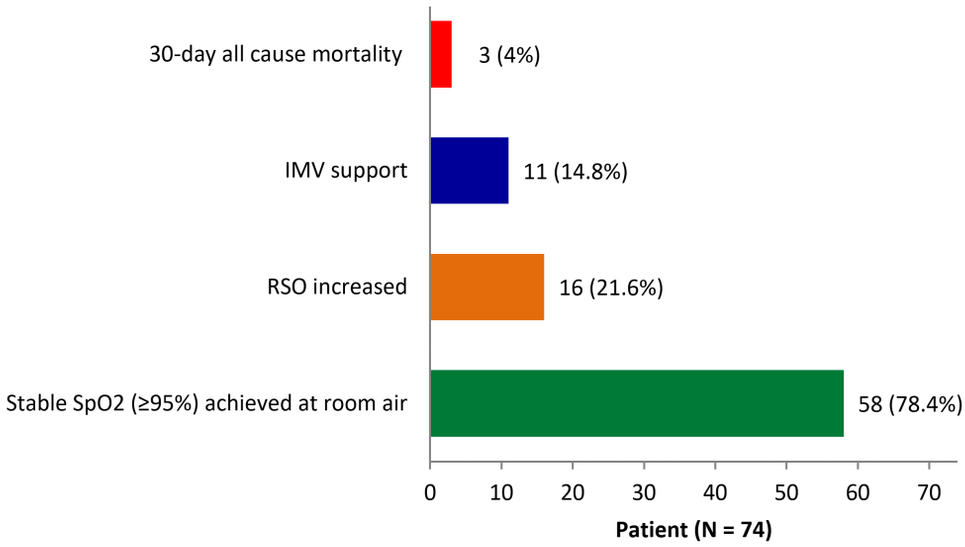
In this study, we found that an additional third intravenous dose (up to 800 mg) of tocilizumab in addition to intravenous dexamethasone treated ARDS effectively by restoring the normal SpO2 level (>94%) and reducing the demand of supplemental oxygen to zero level within 48 h after the administration of third dose of TCZ's in 78.4% of patients with severe-to-critical COVID-19 pneumonia. A study in the United States found that among the patients with severe COVID-19 received one dose of TCZ, 46% of patients was weaned-off the critical phase of the diseases and 27% of patients died (12). Similarly, another study in Spain on 82 patients with severe COVID-19 pneumonia receiving a single dose of TCZ developed ARDS and respiratory failure in 54.9% and 75.6% of patients, respectively with a mortality rate of 26.8% within 7 days (11). In contrary, a study in Wuhan, China found that after receiving two doses of TCZ (at daily, every other day, or every third-day dosing regimen) with methylprednisolone, CRP level dropped significantly from 126.9 (10.7-257.9) to 11.2 (0.02-113.7) mg/L and up to 90-time higher IL-6 level than the normal level reduced remarkably with a better clinical outcome in patients with moderate to critically COVID-19 infection (15). In the present study, after receiving the third dose of TCZ, less than fifteen-percent of patients remained on IMV in ICU with a 30-day all cause

Table 2. Differences in blood oxygen saturation level and requirement of supplemental oxygen before and after the three doses of tocilizumab in patients with severe COVID-19 pneumonia

Patient	Tocilizumab intravenously												P value
	Before first dose			After first dose			After second dose			After third dose			
	SpO_2 (%)	RSO (L)	SpO_2 (%)/ RSO (L), Median (IQR)	SpO_2 (%)	RSO (L)	SpO_2 (%)/ RSO (L), Median (IQR)	SpO_2 (%)	RSO (L)	SpO_2 (%)/ RSO (L), Median (IQR)	SpO_2 (%)	RSO (L)	SpO_2 (%)/ RSO (L), Median (IQR)	
1	88	7	86.5	90	8	89	92	5	92	96	0	96.5	
2	86	12	(84.7-88)/	89	10	(88.7-90)/	91	8	(91-92)/	96	2	(96-98)/	
3	84	8	10 (10-12)	88	6	8 (8-10)	91	4	6 (5-7.2)	95	1	0 (0-1)	
4	89	6		90	5		92	4		96	0		
5	88	10		90	8		91	6		97	1		
6	86	12		89	8		92	6		96	0		
7	88	10		90	8		93	5		96	1		
8	89	7		90	6		93	5		96	1		
9	79	15		86	10		92	8		95	0		
10	87	9		89	7		93	5		97	0		
11	85	12		90	10		92	8		98	0		
12	82	10		89	8		92	6		96	2		
13	88	8		90	6		92	4		96	1		
14	88	9		90	8		91	6		98	0		
15	86	10		89	9		90	6		96	0		
16	86	10		89	8		91	6		97	0		
17	81	12		87	10		91	8		96	2		
18	84	14		90	10		92	6		95	0		
19	83	12		89	10		91	7		95	0		
20	89	10		90	8		93	6		96	2		
21	84	10		88	8		90	6		98	1		
22	89	12		90	9		92	5		97	0		
23	88	8		89	6		92	5		96	0		
24	88	7		90	5		91	4		98	0		
25	85	12		89	10		92	8		97	0		
26	87	12		89	10		93	8		96	0		
27	89	10		89	8		92	6		96	0		
28	85	15		89	12		91	8		95	2		
29	86	12		89	10		91	8		97	0		
30	88	10		90	8		92	5		98	1		
31	89	12		91	12		92	8		96	0		
32	79	14		87	10		92	8		99	2		
33	90	12		92	10		91	6		98	1		
34	89	14		90	12		93	8		95	2		
35	82	12		88	10		92	8		96	1		
36	89	10		91	8		92	6		97	0		
37	84	10		88	8		92	5		97	0		
38	89	8		90	7		92	4		98	0		0.001
39	84	10		90	8		91	6		99	2		
40	87	10		89	8		92	6		96	2		
41	82	14		86	10		91	6		98	1		
42	89	10		90	8		91	6		97	0		
43	83	10		88	8		91	5		98	0		
44	88	12		89	8		91	5		96	1		
45	86	10		89	8		92	6		95	1		
46	86	10		88	7		91	5		97	0		
47	89	10		90	8		92	5		98	2		
48	89	12		90	8		93	6		96	0		
49	85	12		89	8		92	6		98	1		
50	85	14		88	10		92	8		99	0		
51	86	10		89	6		92	5		97	1		
52	88	12		90	8		93	4		97	1		
53	89	10		89	8		91	5		98	0		
54	79	10		87	8		92	5		98	0		
55	87	10		89	8		92	4		96	0		
56	87	12		90	9		92	4		96	0		
57	82	14		88	10		91	7		98	0		
58	88	12		90	10		92	8		97	0		
59	88	10		90	8		91	6		95	1		
60	86	10		88	8		92	5		96	0		
61	86	12		89	10		92	8		96	0		
62	81	12		86	10		92	4		97	0		
63	84	10		88	10		91	6		95	1		
64	89	12		91	8		92	5		96	0		
65	85	10		88	8		92	8		98	0		
66	87	10		89	8		92	5		97	0		
67	89	12		90	10		93	6		98	0		
68	88	12		91	8		93	5		96	0		
69	86	12		89	8		92	6		96	0		
70	89	14		90	10		92	6		97	1		
71	79	14		86	12		91	9		96	1		
72	88	10		90	8		92	5		98	0		
73	85	14		89	10		90	8		97	0		
74	86	12		90	8		92	7		96	0		

IQR = interquartile range; % = percentage; SpO2 = peripheral blood capillary oxygen saturation; RSO: requirement of supplementary oxygen; L = liter

Figure1. Stabilization of respiratory function, further deterioration in blood oxygen saturation level, invasive mechanical ventilation support and 30-day mortality in patients with severe COVID-19 received three doses of tocilizumab



IMV: invasive mechanical ventilation; RSO: requirement of supplementary oxygen; SpO2 = peripheral blood capillary oxygen saturation

mortality rate of approximately 4%.

Before the pandemic COVID-19, world faced outbreaks of other coronavirus, including severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012. A strong cytokine storm due to excessive release of proinflammatory cytokines, including IL-6, IL-12, and tumor necrosis factor-α (TNF-α) was reported in SARS pneumonia (18). IL-1β, IL-6, and IL-8 levels were found high in MERS pneumonia leading to a profuse cytokine storm (19). Similarly, in COVID-19, a massive cytokine storm due to excessive release of proinflammatory cytokines, including IL-2, IL-6, IL-7, IL-10, TNF-α, interferon-γ (IFN-γ)–inducible protein, granulocyte-macrophage colony stimulating factor (GM-CSF), monocyte chemoattractant protein, and macrophage inflammatory protein 1α has been detected in COVID-19 (3, 6). Impaired oxygen diffusion occurs in COVID-19 pneumonia due to the dysfunction of alveolar–capillary blood–gas exchange system due to excessive release of proinflammatory cytokines, mostly including IL-6 leading to ARDS and respiratory failure (17). A study in Wuhan, China found that approximately 67.3% of patients developed ARDS with increased level of IL-6 and 71.2% of patients required IMV in severe COVID-19 pneumonia (20). TCZ can specifically inhibit IL-6 receptor-mediated signal transduction by blocking sIL-6R and mIL-6R (21). Chinese studies observed high IL-6 level in severe COVID-19 pneumonia and found encouraging results with tocilizumab in the suppression of cytokine storm through down-regulation of IL-6 level, significantly (17, 22). Italian scientists considered Chinese experience and started the off-label use of TCZ in the treatment of severe COVID-19 pneumonia in their populations and found better clinical outcomes (23). Based on the recent evidences worldwide, Directorate General of Health Services, Bangladesh included TCZ in the national COVID-19 clinical management guideline for its use in local COVID-19 patients with a maximum of two doses (24). In this study, while improved clinical outcome was not achieved with two doses of TCZ, medical decision went to the use a third dose which improved blood-oxygen saturation and reduced the rate of ICU admission, IMV in severe COVID-19 pneumonia patients.

In a prospective study, after the first dose of TCZ with steroid in severe COVID-19, 91% of patients required a second dose of TCZ, and 11.5% of patients died within the first week of receiving the second dose of TCZ (mean: 5± 1.5 days) (25). Another study in Italy found a mortality rate of 27% in COVID-19 pneumonia patients after receiving two doses of TCZ while disease clinically worsened further in 33% of patients (14). Campochiaro and colleagues (26), found that 13% of patients with severe COVID-19 pneumonia required IMV after receiving two TCZ doses and the 28-day mortality rate was 16%. After receiving second dose of TCZ, RSO was increased (flow: 13 L/min) with a mortality rate of 25% in a retrospective study (27). Thus, a second dose of TCZ within 12-24 h apart from the first dose may not be capable enough to improve clinical outcomes and to reduce mortality rate (below 10%) in severe COVID-19 pneumonia treatment. In the present study, an additional third dose of TCZ within 72 h after second dose reduced RSO [SpO2/ RSO: after second dose: 92 (IQR: 91-92)/6 (IQR: 5-7.2) versus after third dose: 96.5 (IQR: 96-98)/0 (IQR: 0-1)], significantly with a significantly reduced IMV support requirement (below 15%) and mortality rate (below 5%) in severe COVID-19 pneumonia.

Experience with three doses of tocilizumab is limited. An Italian study used a third intravenous dose of TCZ, optionally (in 13% of patients) in patients with severe COVID-19 pneumonia in ICU where 26% and 24% of patients were not clinically improved (remained on IMV) and died within 10 days, respectively (28). In contrast, our study found that with a third intravenous dose of TCZ, IMV support was limited to 14.8% of patients with a mortality rate of 4% (3/74 patients). Moreover, only three patients (N = 74) developed adverse events. Respiratory failure secondary to ARDS is the most common

cause of death in patients with severe COVID-19 pneumonia worldwide. Early and adequate inhibition of inflammatory cascades by using anti-IL-6 drugs may attribute prompt stabilization in respiratory function, improved clinical outcomes and low mortality rate in severe-to-critical COVID-19 pneumonia (29). Tocilizumab in COVID-19 pneumonia has revealed a potent inhibition of IL-6 leading to improved clinical outcomes and reduced mortality rate in multiple studies (25-29). More than twenty clinical trials are investigating the impact of TCZ in COVID-19 pneumonia and no standard dosing guideline of TCZ has still been developed (25, 29). The recent update of the their first global, randomized, double-blind, placebo-controlled phase III COVACTA clinical trial of tocilizumab in hospitalized patients with severe COVID-19 pneumonia revealed that at week four, the primary endpoint of improved clinical outcomes with tocilizumab was not statistically significant compared to placebo (control group), and the mortality rate-difference among the groups was very minimum [0.3% (95% confidence interval) (P=0.941)] (30). In our study, significantly improved clinical outcomes with reduced mortality rate were found with three consecutive doses (12 to 72 h apart) of intravenous tocilizumab in the management of severe-to-critical COVID-19 pneumonia. Though tocilizumab is a drug of huge cost-burden especially for the patients in Low-and Middle-Income countries, including Bangladesh (31), but its use in COVID-19 has created tremendous hope (12-15, 17). In the present study, an additional third intravenous dose of TCZ in Bangladeshi patients with severe COVID-19 pneumonia improved blood oxygen saturation through stabilization of the respiratory function and reduced the requirement of invasive mechanical ventilation in ICU, significantly which improved clinical outcomes and reduced 30-day all cause mortality rate. Other than few mild AEs in three patients (N = 74), tocilizumab therapy was well tolerated in all patients. The results of ongoing trails are highly important to establish its efficacy and safety in COVID-19 pneumonia. Small sample size, no comparative or control group, and no IL-6 level comparison in regard of dosages of tocilizumab in patients were the major limitations of this study.

Conclusion

Hyperinflammatory response leading to ARDS in severe COVID-19 pneumonia is a serious life-threatening stage of the disease. This study found a good response with an additional third dose of tocilizumab in stabilizing respiratory function, reducing the demand of supplemental oxygen, and minimizing the risk of mechanical ventilation support with a declination in 30-day all cause mortality.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the research ethical committee of Square Hospital Ltd., Dhaka, Bangladesh (No. 2007SH-OR027).

Human and animal rights

No Animals were used in this research. All human research procedures were followed in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

Consent for publication

Informed consent was taken from all the participants when they were enrolled.

Availability of data and materials

The data that support the findings of this research are available from the corresponding author upon request with permission from Ethics Committee of Square hospital.

Funding

No external funding source.

Conflict of interest

All authors have no conflicts of interest to disclose.

Acknowledgements

The authors are grateful to all participants of this study and to the authority of Square hospital for their permission to conduct this study.

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