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Original Research Article

Outcome of severe to critical COVID-19 patients with tocilizumab therapy

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ABSTRACT

Background: The inflammatory response plays a critical role in COVID 19 and inflammatory cytokine storm increases the severity of COVID-19. Tocilizumab, an IL-6 receptor monoclonal antibody, has been used for the treatment of patients with COVID-19. This study compared the outcome of tocilizumab therapy with other standard therapy in the management of severe to critical COVID-19 patients.
Methods: This observational prospective comparative study was conducted at the COVID-19 unit of Bangabandhu Sheikh Mujib medical university (BSMMU), for one year period following approval of this protocol. A total of 60 severe to critical COVID-19 patients were enrolled in this study and categorized into two groups: Tocilizumab along with standard therapy (n=30) and another group receiving standard therapy only (n=30). After taking written informed consent, a detailed history and thorough clinical examination were carried out along with relevant investigations. After the collection of all the required data, analysis was done by SPSS 24.0.
Results: The study's predominantly male patients (mean age 53.7±11 years) had high rates of hypertension (63.3%) and diabetes (48.3%), with most experiencing severe COVID-19 (76.6%). Initial similarities in both groups included socio-demographics and disease severity ($p>0.05$). After 2 weeks, the tocilizumab group had lower WBC counts (5.15±2.39 vs 7.56±1.47×10^9/l), lower CRP levels (2.7±0.93 vs 7.5±2.38 mg/l, $p<0.05$), shorter hospital stays (18.25±4.58 vs 25.4±2.70 days, $p=0.005$), reduced oxygen requirements (7.25±4.23 vs 12±7.29%, $p=0.005$), and lower mortality (40% vs 66.66%, $p=0.027$).
Conclusions: Tocilizumab therapy has better outcomes in severe to critical COVID-19 patients. However, a further larger study is recommended.

Keywords: COVID-19, Tocilizumab therapy, Standard therapy

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the zoonotic agent severe acute respiratory syndrome coronavirus 2.[1,2] The virus emerged in the human population in late December 2019 in Wuhan, central China, and has since spread across the globe. Owing to the rapid increase in the number of COVID-19 cases and

uncontrolled worldwide spread, it was declared by the WHO as a pandemic on March 11, 2020.[3] In Bangladesh, the first three known cases were reported on 8th March 2020 by IEDCR. Till then a total 2,014,887 of new cases were detected and 29,334 deaths occurred up to 12 September 2022.[4] A total of 603,711,760 confirmed cases and 6,484,136 deaths have occurred worldwide up to 7 September 2022.[5] According to Bangladesh's national guideline for clinical management of COVID-19, the country is suffering from the effects of this highly transmissible zoonotic illness, which is spreading across the country (at varying rates).

This novel coronavirus strain is continually evolving, leaving the entire world perplexed. The epidemic curve of this pandemic, which began in Wuhan, China, and spread throughout the world, followed a usual pattern of slow onset, steep rise in a few days, and then rapid upsurge, quickly collapsing the health system of the affected country. During this pandemic, both the number of affected cases and the number of deaths has increased. The clinical presentation of COVID-19 ranges from mild to critically ill. While most COVID-19 patients have a mild influenza-like illness and may be asymptomatic, a minority of patients are experiencing severe pneumonia, acute respiratory distress syndrome (ARDS), multiple organ failure (MOF), and even death.[6] It is estimated that around 10-15% of mild COVID-19 patients advance to severe, and 15-20% of severe cases progress to become critical, with many of the individuals in the critical category needing treatment in intensive care units (ICU).[3]

The inflammatory response plays a critical role in COVID-19 and inflammatory cytokine storm increases the severity of COVID-19.[7] The IL-6 and other components of the inflammatory cascade contribute to hosting defense against infections. These factors are significantly higher in severe cases than in moderate cases of COVID patients. In addition, levels of these cytokines are markedly elevated in deceased patients than in covid survivors. However, excessive synthesis of IL-6 can lead to a severe acute systemic inflammatory response known as a "cytokine storm," which increases risks of vascular hyperpermeability, multiorgan failure, and eventually death.[7] The IL-6 is an inflammatory interleukin mainly produced by macrophages and T lymphocytes in response to pathogens. In COVID-19, IL-6 has been positively correlated with disease stages and radiologic changes.[1] In the cytokine storm, immune cells and cytokines may be clustered in the pulmonary lesion resulting in a decrease in IL-6 levels in the peripheral blood. Then it subsequently raises to a peak level and declines gradually over 10-20 days of the clinical course.[7]

The IL-6 receptor (IL-6R) has two forms: membrane-bound interleukin-6 receptor (mIL-6R) and soluble interleukin-6 receptor (sIL-6R). IL-6 binds to sIL-6R to form a complex, which then binds to gp130 on the cell membrane to complete trans-signal transduction and play a pro-inflammatory role. As a recombinant humanized anti-human IL-6 receptor monoclonal antibody, tocilizumab can specifically bind sIL-6R and mIL-6R and inhibit signal transduction.[8] Study shows that there is an improvement in clinical status, improvement of oxygen saturation level, and improvement in changes in lung imaging after tocilizumab therapy in COVID patients. There was a decreased level of CRP, Procalcitonin and fibrinogen levels while lymphocyte and platelet count increased in tocilizumab therapy.[9] Few more well-designed studies are now time demanding for the recommendation of the use of tocilizumab in the management of COVID-19.

Objectives

General objective

General objectives were to compare the outcome of severe to critical COVID-19 patients with tocilizumab therapy and other standard therapy.

Specific objectives

Specific objectives were To compare the reduction of supplemental oxygen support with tocilizumab therapy with other standard therapy in severe to critical COVID-19 patients, to compare the survival rate of severe to critical COVID-19 patients with tocilizumab therapy with other standard therapy, to compare the impact of tocilizumab therapy with other standard therapy on the duration of their hospital stay, to compare changes in several blood parameters (CBC, CRP, S.LDH, S. ferritin, S. D-dimer, SGPT, S. creatinine, IL-6) of tocilizumab therapy with other standard therapy in severe to critical COVID-19 patients and to evaluate the predictors of death in severe to critical COVID-19 patients treated with tocilizumab or standard therapy.

METHODS

Study place

The study was conducted in the COVID-19 unit, at BSMMU.

Study period

Study conducted from August 2021 to July 2022.

Study population

Patients who were RT-PCR for COVID-19 positive severe to critical patients admitted to COVID-19 unit, BSMMU fulfilled the inclusion and exclusion criteria that constitute sample.

Sampling method

Non-probability sampling (consecutive sampling) method was used.

Study design

This study utilized an observational prospective comparative design to assess the outcome of severe to critical COVID-19 patients with tocilizumab therapy among hospitalized COVID-19 patients in BSMMU. Here, one group received tocilizumab with standard therapy and the other group received standard therapy only. Under these designs patients were selected according to inclusion and exclusion criteria. Data were collected from the patients attending in COVID-19 unit of BSMMU.

Sample size determination

The sample size was calculated by using the following formula:

$N=[Z\alpha_{/2+} Z\beta]^2 X [\pi_1(1- \pi_1) + \pi_2(1- \pi_2)]/ (\pi_1-\pi_2)^2$

Where,

n=Sample size, $Z\alpha_{/2}$=1.96, Zβ=0.84 (80% power).

π_1=Mortality of patients receiving standard therapy was 50% (0.50).

π_2 =Mortality of patients receiving tocilizumab was 7.7% (0.077).

$N=[1.96_{+} .84]^2 X [0.50(1-0.50) + 0.077(1- 0.077)]/ (0.50-0.077)^2=15$.

From the calculation, the sample size was obtained 15 in each group. At BSMMU there was a dedicated COVID unit and about 200 patients were remain admitted daily in the indoor and ICU during my study period. From them after exclusion, 30 patients were taken in each group, who fulfilled the inclusion criteria. Hence, total sample size was 60.

Sample size

Sixty patients fulfilling inclusion criteria.

Inclusion criteria

Patients admitted to the COVID ward at BSMMU with a positive RT-PCR for COVID-19 were included and age 18 to 80 of both sexes, willingness to provide informed written consent, and severe to critical disease status defined by ICU admission within the last 24 hours requiring invasive mechanical ventilation, non-invasive mechanical ventilation/ high-flow nasal cannula (oxygen needing >30 l/min) OR CRP >75 mg/dl were included.

Exclusion criteria

A history of recent use of other biologic immunomodulating drugs (within 1 month). Alanine transaminase (ALT) >5 times the upper limit of normal. An uncontrolled, serious bacterial (including tuberculosis) and fungal infection. Absolute neutrophil count <500 cells/µl. Platelet count <50,000 cells/µl were excluded (National guideline on clinical management of COVID-19 and national institute of health, USA treatment guidelines of COVID-19).

Data collection procedure

Adult COVID-19 patients admitted to BSMMU were enrolled voluntarily. Severe to critical cases (n=60) with positive RT-PCR were sampled with written consent. Demographics, comorbidities, and symptoms were recorded. Physical exams and oxygen saturation measurements were conducted. Patients were categorized by disease severity per WHO guidelines. Tocilizumab with standard therapy or standard therapy alone was administered. Initial clinical and biochemical assessments were done within 48 hours before tocilizumab. Assessments were repeated after 24 hours and on day 14 post-treatment. A control group receiving standard care without tocilizumab was included. Comparisons were made between tocilizumab and standard therapy groups. Data were recorded in a pre-designed sheet.

Data analysis

Statistical analysis was conducted using SPSS-24 software. Socio-demographic characteristics, comorbidities, clinical, and laboratory parameters were reported. Continuous data were presented as mean ± standard deviation, while categorical data as frequency and percentage. Chi-square test was used for categorical variables and independent t test for continuous variables when necessary.

Logistic regression was performed to predict COVID-19 outcome (death) using predictor variables (diabetes, hypertension, CRP, IL-6), with results presented as odds ratios (ORs) and 95% confidence intervals. Statistical significance was defined as $p<0.05$.

Data presentation

Different tables, graphs, charts, diagrams, etc were used to present data as necessary.

Ethical consideration

The research protocol was approved by the institutional review board of BSMMU, Dhaka. Voluntary informed written consent was obtained from patients or responsible family members after explaining the study's purpose and procedures. Patients had the right to participate or withdraw at any time without affecting their medical care. The patient privacy and the confidentiality were maintained throughout the study, ensuring no harm to the participants.

RESULTS

This observational prospective comparative study was conducted at the COVID unit, BSMMU, Dhaka. The study comprised 60 COVID-19 patients. A total of sixty patients were included in this study based on inclusion and exclusion criteria. The patients were categorized into two groups, one group receiving tocilizumab along with standard therapy (n=30) and the other group receiving only standard therapy (n=30). The main objective was to find out the outcome of severe to critical COVID-19 patients with tocilizumab therapy.

Table 1 showing, the distribution of COVID-19 patients according to age and gender. The highest number 27 (45%) of patients were in the age group of 51-60 years, followed by 14 (23.3%) in age 61 years and above. The mean age of the tocilizumab group was 50.2±11.5 years and the standard group was 57.3±9.5 years. The distribution of participants between the two groups was statistically not significant (p=0.096). Among the 60 patients, 61.6% were males and 38.3% were females. The gender distribution of COVID-19 patients in both groups was not statistically different (p=0.744).

Table 2 showing, the common clinical presentations were shortness of breath 60 (100%), fever 42 (70%) and cough 38 (63.3%) among the severe and critical cases of COVID-19 patients in both groups. Other clinical presentations are anosmia 30 (50%), sore throat 14 (23.3%) and chest pain 5 (8.3%). The mean BMI of the patients was 25.9±5.61 kg/m^2. The mean BMI of the tocilizumab group was 26.9±7.22 kg/m^2 and the standard group was 24.9±9.5 kg/m^2. Hypertension and diabetes mellitus were predominant co-morbidities in both groups. This table showing among hypertensive patients, the tocilizumab group was 18 (60%) and the standard group was 20 (66.6%). Among diabetes mellitus patients, the tocilizumab group was 17 (56.6%) and the standard group was 12 (40%). Among IHD patients, the tocilizumab group was 11 (36.6%) and the standard group was 9 (30%). Among CKD patients, the tocilizumab group was 5 (16.6%) and the standard group was 7 (23.3%). Among pre-existing lung disease patients, the tocilizumab group was 6 (20%) and the standard group was 5 (16.6%).

Table 1: Distribution of COVID-19 patients according to age, gender, clinical presentations, BMI and comorbidities (n=60).

Variables	Total, n=60 (%)	Tocilizumab, n=30 (%)	Standard therapy, n=30 (%)	χ^2 value	P value*
Age (in years)					
18-30	4 (6.6)	4 (13.3)	0	8.921	0.096
31-40	6 (10)	2 (6.6)	4 (13.3)		
41-50	9 (15)	7 (23.3)	2 (6.6)		
51-60	27 (45)	12 (40)	15 (50)		
>60	14 (23.3)	5 (16.6)	9 (30)		
Mean±SD	53.7±11	50.2±11.5	57.3±9.5		
Gender					
Male	37 (61.6)	20 (66.6)	17 (56.6)	0.635	0.744
Female	23 (38.3)	10 (33.3)	13 (43.3)		

*P value obtained by chi-square test.

Table 2: Distribution of COVID-19 patients according to clinical presentations, BMI and comorbidities, (n=60).

Variables	Total, n=60 (%)	Tocilizumab, n=30 (%)	Standard therapy, n=30 (%)
Clinical presentations			
Shortness of breath	60 (100)	30 (100)	30 (100)
Fever	42 (70)	24 (80)	18 (60)
Cough	38 (63.3)	20 (66.6)	18 (60)
Anosmia	30 (50)	11 (36.6)	19 (63.3)
Sore throat	14 (23.3)	9 (30)	5 (16.6)
Chest pain	5 (8.3)	3 (10)	2 (6.6)
BMI (kg/m^2)			
Mean±SD	25.9±5.61	26.9±7.22	24.9±9.5
Co-morbidities			
HTN	38 (63.3)	18 (60)	20 (66.6)
DM	29 (48.3)	17 (56.6)	12 (40)
IHD	20 (33.3)	11 (36.6)	9 (30)
CKD	12 (20)	5 (16.6)	7 (23.3)
Pre-existing lung disease	11 (18.3)	6 (20)	5 (16.6)

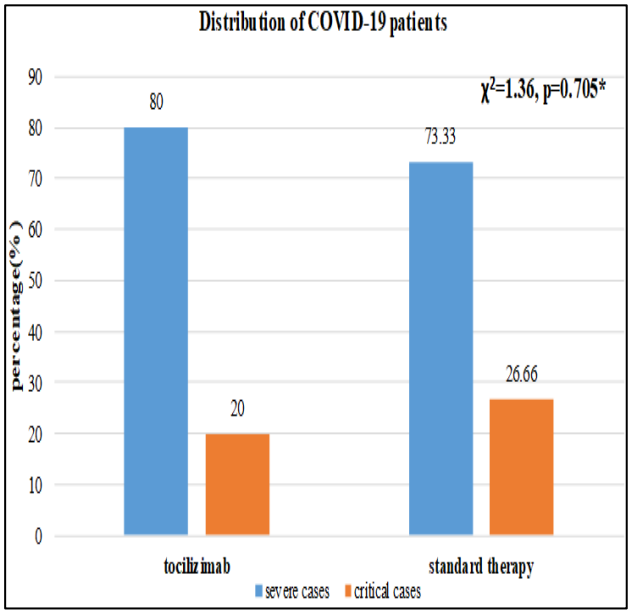

Figure 1: Distribution of COVID-19 cases among the study population according to the severity, (n=60).
*P value obtained by chi-square test.

Among 60 patients, 24 (80%) and 22 (73.33%) of the patients had severe COVID-19 in the tocilizumab and standard therapy groups respectively. Here, 6 (20%) and 8 (26.66%) were critical cases in the tocilizumab and standard therapy groups respectively.

The distribution of participants between the two group was statistically not significant (p=0.705).

Table 3 showing, there was no significant difference in hemoglobin, WBC count, lymphocyte count, platelet count, CRP, IL-6, LDH, SGPT, ferritin, D-dimer or serum creatinine in patients between two groups, 48 hours before tocilizumab or standard therapy.

Table 4 showing, the mean oxygen saturation of COVID-19 patient were below the normal range in both groups (tocilibzumab=76.1% and standard therapy=79.7%) and p=0.180. The mean oxygen requirement in tocilizumab group 51 (L/min) and standard therapy group 52 (L/min) and p=0.138. The difference in oxygen saturation and oxygen requirement between the two groups was not statistically significant.

Table 5 showing, after 2 weeks, it was observed that patients administered tocilizumab had significant reduction in WBCs ($5.15\pm2.39\times10^9$/L) compared to standard therapy patients ($7.56\pm1.47\times10^9$/L) (p=0.040). Mean CRP level significantly reduced in tocilizumab (2.7±0.93) compared to standard therapy (7.5±2.38). The mean IL-6 was significantly lower in patients treated with standard therapy (35.6±11.3) compared to patients with tocilizumab (61±21.2 mg/L) (p=0.020). There was no significant difference in LDH, SGPT, platelet count, ferritin, D-dimer, serum creatinine in patients between the 2 groups, after 2 weeks of tocilizumab or standard therapy.

Table 3: Baseline laboratory parameters among COVID-19 patients within 48 hours before tocilizumab or standard therapy, (n=60).

Variables	Tocilizumab, n=30, mean±SD	Standard therapy, n=30, mean±SD	T value	P value*
Hb (g/l)	11.4±0.98	11.3±0.88	0.679	0.627
WBCs ($\times10^9$/l)	8.15±2.39	8.15±2.19	-	0.813
Lymphocyte count (%)	15.6±2.23	16±2.30	0.684	0.836
Platelet count ($\times10^3$)	257.4±56.6	266.5±59.7	0.606	0.881
Ferritin (ng/ml)	833±164.6	874±167.9	0.955	0.773
CRP (mg/l)	84.1±8.76	85.7±10.5	0.641	0.414
LDH (IU/l)	620.6±120.3	633.3±108.3	0.430	0.494
IL-6 (pg/ml)	143.6±19.65	135.8±23.9	1.381	0.386
D-dimer (µg/ml)	2.68±2	2.59±2.3	0.162	0.623
SGPT (IU/l)	32.5±5.3	31.9±4.8	0.460	0.713
Serum creatinine (mg/dl)	1.1±0.2	1.12±0.17	0.417	0.836

*P value obtained by independent student t test.

Table 4: Baseline clinical parameters among COVID-19 patients within 48 hours before tocilizumab or standard therapy, (n=60).

Variables	Tocilizumab, n=30, mean±SD	Standard therapy, n=30, mean±SD	T value	P value*
Baseline SpO_2 (%)	76.1±4.28	79.7±3.17	1.720	0.180
Oxygen requirement (l/min)	51±13.2	52±10.7	0.226	0.138

Abbreviation: SpO_2-oxygen saturation. *P value obtained by independent student t test.

Table 5: Laboratory parameters among COVID-19 patients after 2 weeks of administration of tocilizumab or standard therapy, (n=47).

Variables	Tocilizumab, n=25, mean±SD	Standard therapy, n=22, mean±SD	T value	P value*
Hb (g/l)	12.4±1.11	12.1±1.20	0.136	0.996
WBCs (×10^9/l)	5.15±2.39	7.56±1.47	4.704	0.040
Lymphocyte count (%)	20.6±2.23	21.0±1.65	0.421	0.362
Platelet count (×10^3)	260±56.6	269±59.7	0.124	0.881
Ferritin (ng/ml)	619±164.6	587±107.9	0.258	0.773
CRP (mg/l)	2.7±0.93	7.5±2.38	10.28	0.001
LDH (IU/l)	257.2±89.8	333.3±108.3	0.452	0.355
IL-6 (pg/ml)	61±21.2	35.6±11.3	5.791	0.020
D-dimer (µg/ml)	0.78±0.48	0.99±0.57	0.292	0.124
SGPT (IU/l)	29±15.8	33.1±18.5	0.652	0.186
Serum creatinine (mg/dl)	1±0.15	1.1±0.17	0.141	0.863

*P value obtained by independent student t test.

Table 6: Clinical parameter among COVID-19 patients after 2 weeks of administration of tocilizumab or standard therapy, (n=47).

Variables	Tocilizumab, n=25, mean±SD	Standard therapy, n=22, mean±SD	T value	P value*
Oxygen requirement (l/min)	7.25±4.23	12±7.29	3.087	0.005

*P value obtained by independent student t test.

Table 6 showing, the mean oxygen requirement of COVID-19 patients in the tocilizumab group reduced from 51 (l/min) to 7.25 (l/min) after 2 weeks of administration of tocilizumab. Patients in standard therapy also showed a reduction of oxygen requirement from 52 (l/min) to 12 (l/min) and p=0.005. Difference in oxygen requirement between 2 groups was statistically significant.

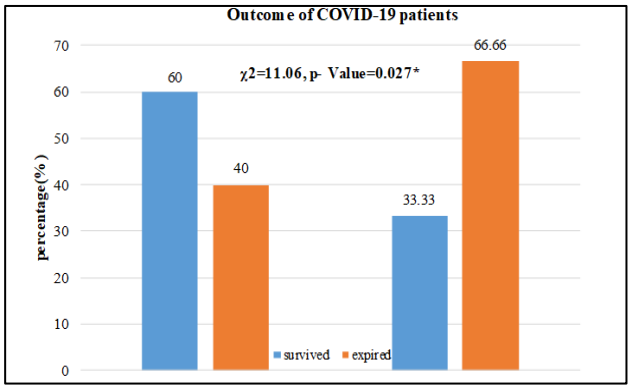

Figure 2: The outcome of COVID-19 patients receiving tocilizumab or standard therapy, (n=60).

*P value obtained by chi-square test.

During the hospital stay, it was observed that among patients administered tocilizumub 40% of the patient expired whereas in patients receiving standard therapy the percentage of expired patients was higher (66.66%). The in-hospital mortality was significantly less among patients administered tocilizumab (p=0.027).

Relative risk (RR): 0.40/0.66=0.60, relative risk reduction (RRR): 1-RR=0.40, absolute risk reduction (ARR): 0.66-0.40=0.26, number needed to treat (NNT): 1/ARR=1/0.26=3.8=4 (Rounded).

Therefore, we need to treat 4 patients with tocilizumab to prevent mortality in one additional patient.

Table 8 showing logistic regression analysis revealed that IL-6 was significantly associated with a high chance of mortality. Regression analysis reported that patients with higher IL-6 levels had 11.7 times the odds of non-surviving (OR, 95% CI: 11.7 (2.14-63.6), p=0.005). Patients with high CRP had more than twice the odds of non-surviving (OR, 95% CI: 2.78 (0.75-10.3), p=0.125) and diabetes mellitus and hypertension were not associated with mortality among patients with COVID-19.

Table 7: The number needed to treat for tocilizumab and standard therapy, (n=60).

Groups	Mortality, N (%)		Total	Risk
	Expired	Survived		
Tocilizumab	12 (40)	18 (60)	30	12/30=0.40
Standard therapy	20 (66.66)	10 (33.33)	30	20/30=0.66

Table 8: Logistic regression analysis for the predictors of mortality, (n=60).

Variables	B	OR	95% CI		P value
			Lower	Upper	
Age (>50 years)	0.38	0.69	0.17	2.64	0.582
Diabetes mellitus	0.51	0.60	0.17	2.16	0.435
Hypertension	0.51	0.60	0.17	2.16	0.435
CRP (>4 mg/l)	1.02	2.78	0.75	10.3	0.125
IL-6 (>37.7 pg/ml)	2.46	11.7	2.14	63.6	0.005

DISCUSSION

COVID-19 has spread around the world and is now a public health concern. Though the recovery rate among the COVID patient is higher the number of patients who died due to COVID is not so low. Disease severity depends on age and underlying health conditions. This observational prospective comparative study explores the outcome of severe to critical COVID-19 patients with tocilizumab therapy among hospitalized COVID-19 patients in BSMMU. A total of 60 patients aged 18 years or above were enrolled in this study from August 2021 to July 2022. There were two groups, tocilizumab and standard therapy. In each group, there were 30 in number. We assessed the outcome of severe to critical COVID-19 patients with tocilizumab and standard therapy and compare the outcome between the two groups. This study highlights the outcomes of tocilizumab therapy in severe and critical COVID-19 patients. Both tocilizumab and standard therapy groups were matched in terms of age, gender and disease severity to reduce the risk of selection bias. Tocilizumab administration was associated with a significantly lower in-hospital mortality rate, shorter hospital stays and greater clinical improvement than the standard of care. After 2 weeks of administration of tocilizumab the mean oxygen requirement of COVID-19 patients in the tocilizumab group reduced from 51 (l/min) to 7.25 (l/min). These findings reflect a substantial improvement and a high survival rate in patients who received tocilizumab for the treatment of COVID-19.

Another retrospective cohort study reported a male predominance (85.7%) with chronic illnesses such as hypertension (42.9%) and diabetes (23.8%) being more common among COVID-19 patients.[8] This result was similar to reports in this study (hypertension: 63.3% and diabetes mellitus: 48.3%). Tocilizumab-treated patients in our study showed a decrease in CRP level (2.7±0.93 mg/l) by 14 days and this decrease in the level of CRP was significantly lower than that of patients in the standard therapy group (p=0.001). In a study suggested that tocilizumab can exert its effects in patients whose COVID-19 illness is progressing to an inflammatory state (CRP >15 mg/dl).[10] Another study reported a speedy and constant response to tocilizumab among patients with COVID-19 pneumonia and hyper-inflammatory syndrome.[11] Also in a study showed that CRP levels were bought back to normal level in 84.2% of severe COVID-19 patients after tocilizumab administration.[8]

In the current study, among the tocilizumab group, we detected a decrease in D-dimer (0.78±0.48 µg/ml), LDH (257.2±89.8 IU/l) and ferritin (619±164.6 ng/ml) levels by day 14, which was consistent.[10] In a study established an association between elevated LDH levels and worse outcomes in COVID-19 patients.[12] The high ferritin levels in COVID-19 patients might be due to the IL-6 receptor blockade, increasing serum IL-6 levels, which contribute directly to ferritin synthesis.[13] In our study, it was reported the mean IL-6 was significantly higher in patients treated with tocilizumab (61±21.2 pg/ml, p=0.020) compared to a patients with standard therapy on the 14th day of treatment. This result was similar to a retrospective observational cohort study.[14]

This finding was expected because tocilizumab competitively blocks IL-6 receptors and leaves free IL-6 in plasma.[14] An Italian retrospective study among 544 severe COVID-19 patients reported a significantly lower death rate in the tocilizumab group than in the control group (7% vs. 20% respectively) but lesser than that reported by our study since the present study has reported a death rate of 40% in tocilizumab group and 66.66% in the standard therapy group.[14] Another retrospective cohort single-center study reported the tocilizumab group had a significantly lower 28-days in-hospital mortality rate than the standard-therapy group (21.6% vs. 42.3% respectively; p=0.015) and tocilizumab treatment was associated with an increased likelihood of clinical improvement compared to the standard therapy group.[15] A study shows 764 COVID-19 patients in the ICU reported a significant decrease in the mortality rate and risk of mechanical ventilation in the tocilizumab group compared to the control group.[10]

In this study, after 2 weeks of administration of tocilizumab, the mean oxygen requirement of COVID-19 patients was significantly reduced from 51 (L/min) to 7.25 (L/min) and the number of days in hospital was also decreased (18.25±4.58 days) compared to a standard therapy group. These findings reflect clinical improvement and a high survival rate in patients who received tocilizumab for the treatment of COVID-19. Contrary to the current study findings, a randomized, double-blind, placebo-controlled trial assessed the efficacy of tocilizumab among moderately ill hospitalized COVID-19 patients and revealed that tocilizumab was not effective in preventing intubation or death.[16] Also, a meta-analysis of seven retrospective studies presented that there is no

statistically significant difference between tocilizumab and standard therapy regarding all-cause mortality and ICU admission.[17] These inconsistencies in the findings between studies could be attributed to the variations in sample sizes, the control arm of the studies (i.e. comparator group) and the severity of COVID-19 in the study group. In a study suggests that IL-6 (>37.7 pg/ml) and CRP (>4 mg/l) is a predictor for COVID-19 outcome (death).[18,19]

In the present study majority of the patients were in the 5th decade of life (tocilizumab: 40% vs standard therapy: 50%), the mean age of the patient were 53.7±11 years and male predominance was observed in the study population (61.6%). A randomized, open-label trial conducted among 129 patients reported a male predominance (68%) with a mean age of 57 years.[20] In our study, logistic regression analysis revealed that among the predictors (Age>50 years, diabetes mellitus, hypertension, CRP, IL-6), interleukin-6 was independently predictor for death in severe to critical COVID-19 patients treated with tocilizumab or standard therapy. From our data, we determined that we need to treat four patients with tocilizumab to prevent mortality in one additional patient. Tocilizumab therapy for patients with severe or critical COVID-19 was significantly associated with better survival and clinical improvement compared to the standard of care.

Strength

We included patients with laboratory-confirmed for COVID-19 infection. Previous most of the study was done retrospectively. Data were collected on an electronic chart. In our study data was taken from the patient during hospitalization. So, no data was missing or wrong and there is less chance of biasness. Both group numbers are equal.

Limitations

This is a single center-based study. The pediatric group not included in this study.

CONCLUSION

In this study, the effectiveness of tocilizumab therapy was compared to standard therapy in the treatment of severe to critical COVID-19 disease. This study found that after 2 weeks of treatment, total WBC count and C-reactive protein were significantly lower in the tocilizumab group. Besides, patients who received tocilizumab had decreased oxygen requirement, decreased hospital stay and a lower in-hospital mortality rate compared to standard therapy only. Hence, early treatment with tocilizumab could be helpful to prevent excessive hyper-inflammation and death in COVID-19 pneumonia. With a few minor differences, these results are consistent with those of earlier studies in different countries. However, further large-scale multicenter research is warranted.

Recommendations

In our study, we found that patients receiving tocilizumab with standard therapy had more survival rate, less oxygen requirement and shorter hospital stay in comparison to standard therapy only so, we recommended to use tocilizumab in the management of severe to critical COVID-19 patients.

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