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Research Article

ROLE OF TOCILIZUMAB IN PATIENTS WITH MODERATE-TO-SEVERE COVID-19 PNEUMONIA

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ABSTRACT

Objectives: Cytokine release syndrome (CRS) is believed to be responsible for death in COVID-19. Tocilizumab is an interleukin (IL)-6 receptor antagonist, IL-6 being identified as a major component of the CRS cascade. The objective of the study was to determine if tocilizumab can prevent mortality and morbidity in moderate-to-severe COVID-19 pneumonia.

Methods: Patients admitted to the ICU between the time period of June 2020–August 2020 were included in this retrospective and cohort study conducted at GCS medical college, hospital and research center. Patients had to be more than 18 years of age and were required to have a positive reverse transcription polymerase chain reaction report for COVID-19. After applying the inclusion/exclusion criteria, 119 patients were considered for final analysis. Tocilizumab was administered as a single dose of 8 mg/kg in 22 patients. Rest of the patients received standard of care regime. The primary outcome was either discharge or death of the patients and the requirement of invasive mechanical ventilation during their hospital stay. The secondary outcome was the length of hospital stay. Appropriate demographic, clinical, and laboratory data were documented. Statistical analysis was done with appropriate clinical tests with significance set at $p<0.05$.

Results: Tocilizumab significantly reduced deaths in patients as well as the need for mechanical ventilation with NNT=3 and 5, respectively. The same held true even when the data were adjusted for age, gender, and number of comorbidities. Number of comorbidities had a negative association with mortality and need for mechanical ventilation irrespective of administration of tocilizumab as evidenced by multivariable logistic regression. There was no effect of tocilizumab in shortening the hospital stay in patients.

Conclusion: Tocilizumab seems to be a promising agent for the treatment of moderate to severe COVID-19 pneumonia and similar agents hold promise for any similar future emerging infections.

Keywords: COVID-19, Cytokine release syndrome, Interleukin-6, Mortality, Tocilizumab.

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INTRODUCTION

The world got introduced to the worst pandemic, it has ever seen, in March 2020 and till now, it has not emerged out of it. So far, close to 535 million cases of COVID-19 and 6.3 million deaths have been reported worldwide as this is written [1]. India so far has seen approximately 43 million cases and 5.24 lakh deaths which accounts for about 10% of total global case burden. The mortality arising from COVID-19 might have come down with the advent of various vaccines but still it remains a stark reality in a good number of cases. While we have been close to 2 years into the pandemic, we do not have a definitive treatment against COVID-19. The only treatments shown to benefit severely ill COVID-19 patients have been steroids as shown by the RECOVERY trial [2] and anticoagulation.

The leading cause of death in severely ill COVID-19 patients is refractory respiratory failure. In a study which analyzed causes of death in COVID-19 patients, 45% of ICU patients died due to refractory respiratory failure and 30% died due to sepsis with multiorgan failure [3]. It has been suggested that this high mortality is due to increased inflammatory markers. Several inflammatory mediators including cytokines and chemokines have found to be raised in severely ill COVID-19 patients, interleukin-6 (IL-6) being one of the most important among them. These inflammatory mediators eventually lead to the cytokine release syndrome (CRS) which is thought to be the cause of high mortality among COVID-19 patients [4]. It has been mentioned that while bacterial sepsis is characterized by monocyte deficiency and inability to produce cytokines, patients with severe COVID-19 exhibited markedly elevated levels of IL-6 and C-reactive protein (CRP) [5]. A study conducted by the department of microbiology at Mount Sinai showed that there was an imbalanced host response to the SARS-CoV-2 virus. There was a reduced interferon-I and interferon-III response to SARS-CoV-2 virus as compared to other respiratory viruses such as influenza-A and respiratory syncytial virus. They also found that IL-6 and IL1RA were uniquely elevated in patients infected with SARS-CoV-2 thus suggesting that the CRS may be a distinct feature of COVID-19 infection and thus may pave the path for agents such as tocilizumab and anakinra in the treatment of severe COVID-19 disease [6].

Tocilizumab is a humanized antihuman IL-6 receptor antibody. It binds to both the soluble as well as membrane bound IL-6 receptor thus inhibiting the signaling cascade and subsequent effects of IL-6 [7]. It is approved for treatment of rheumatoid arthritis, Castleman's disease, polyarticular and systemic juvenile idiopathic arthritis, giant cell arteritis, and chimeric antigen receptor T cell therapy-induced CRS [8]. Its efficacy in severe COVID-19 disease is still controversial with conflicting data available from around the globe so far. However, there are very few studies from India regarding the efficacy of tocilizumab on severe COVID-19 pneumonia. We have humbly attempted to shed some light in this area and contribute to the ever-growing medical literature while the world continues its combat with the deadly virus.

Aims and objectives

The primary objective of the study was

1. To determine whether the use of tocilizumab was associated with increased survival in COVID-19 patients with moderate-to-severe pneumonia
2. To determine whether administration of tocilizumab was associated with a reduced requirement of invasive ventilatory support.

The secondary objective was to determine whether tocilizumab was associated with a reduced length of hospital stay in COVID-19 patients.

Patients were followed up from the time; they were received in the ICU till the time of either discharge or death whichever occurred earlier during their hospital stay.

METHODS

Study setting and design

This was a retrospective and single center study in adult (>18 years) patients with reverse transcription polymerase chain reaction (RT-PCR) confirmed COVID-19 with moderate-to-severe pneumonia (Fig. 1). The study was carried out at GCS Medical college, hospital, and research center which is a tertiary care teaching hospital at Ahmedabad. The severity of the pneumonia was decided as per the prevailing definitions at the time as given by the Ministry of Health and Family Welfare, Government of India [9]. The study was approved by the Institutional Ethics committee vide no. GCSMC/EC/Proj/Approve/2020/168 and was registered with the Clinical Trials Registry of India vide no.CTRI/2020/08/027246. Since patients admitted or received to the ICU were the ones to most likely receive tocilizumab, patients admitted to the ICU between the time period of June 2020–August 2020 were enrolled in the study. The inclusion criteria were adult (>18 years) with a positive RT-PCR report for COVID-19. The following exclusion criteria were implemented so as to avoid bias and as many confounders as possible:

1. Patients who did not have a positive RT-PCR report for COVID-19
2. Patients who were seriously ill and unlikely to survive for >48 h
3. Patients who required intubation within 24 h of admission to hospital
4. Patients who received remdesivir
5. Patients who got transferred out to another hospital before the outcomes could be achieved
6. Patients in whom tocilizumab was contra-indicated (Active tuberculosis, sepsis, malignancy, on immunosuppressive agents, pts. on dialysis and liver enzymes more than 3 times upper limit of normal).

All patients received standard of care treatment which included hydroxychloroquine 200 mg PO BD per day with Azithromycin 500 mg PO OD, Ceftriaxone 1 gm BD intravenously, intravenous fluids and intravenous methylprednisolone 40 mg BD. All patients also received anticoagulation in the form of enoxaparin 60 mg subcutaneously BD. All patients required some form of respiratory support. Patients who received tocilizumab received a single dose of 8 mg/kg intravenously. The dose was not repeated owing to limited availability of tocilizumab. All patients enrolled in the study showed signs of CRS with respect to clinical and laboratory parameters.

Data collection

Data were retrospectively collected from the health records of all admitted patients. demographic data as in age and gender, clinical data in the form of vital signs and various laboratory parameters such as complete blood count, liver and renal function tests, inflammatory markers such as CRP, ferritin, LDH, and D-dimer were collected from the health records. Other data such as SPO_2 on admission, need and form of respiratory support, number and type of comorbidities, number of days of respiratory support, and length of hospital stay were also recorded.

Data analysis

Categorical data were expressed as numbers and percentages while continuous data were expressed as means and standard deviation. Chi-square test was utilized to test significance for categorical data while Students t-test was utilized to analyze continuous data. Multivariable logistic regression analysis was undertaken to evaluate the effect of tocilizumab after adjustment of confounders such as age, gender, number of comorbidities on mortality and age, gender, and oxygen saturation on presentation was utilized to evaluate the effect of tocilizumab on the need for invasive mechanical ventilation. Odds ratios (ORs) and estimates with 95% confidence intervals (CIs) were reported for the associations, as deemed appropriate. We assessed model fit using the Hosmer–Lemeshow goodness-of-fit test.

Absolute and relative risk reduction was also estimated to determine the magnitude of the effect of tocilizumab.

Statistical significance was set at $p<0.05$ with 95% CIs. Analysis was done using SPSS 20 software.

RESULTS

During the timeframe of June 2020–August 2020, 189 patients were admitted in the ICU, out of which 119 patients met the eligibility criteria to be included in the study. Twenty-two patients received tocilizumab while the rest were treated as a control group (Fig. 1).

Patient demographics

There were 38 (31.9%) females and 81 (68.06%) males in the study population, the M: F ratio being 2.13:1 (Fig. 2).

There were 77 (64.70%) deaths in total and 52 (43.69%) patients required invasive ventilatory support. The mean age of the study population was 60.78 years with the greatest number of patients, 61, between the age group of 61–80 years. However, while the control group had the greatest number of patients in the same age group, the treatment group had maximum patients in the age group of 41–60 years indicating that younger patients were more likely to receive tocilizumab. However, this difference in the age groups was not found to be statistically significant. It was observed that patients who received tocilizumab had significantly longer duration of illness, higher respiratory rates, lower SPO_2 and higher CRP, D-dimer, and IL-6 values as compared to those in the control group (Table 1).

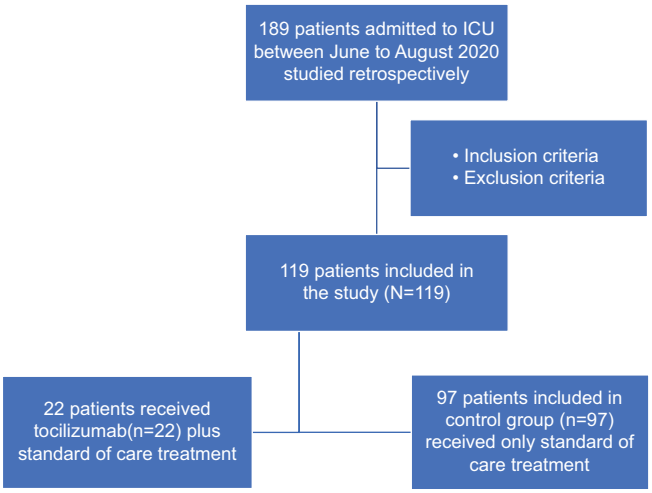

Fig. 1: Flowchart showing selection of study patients

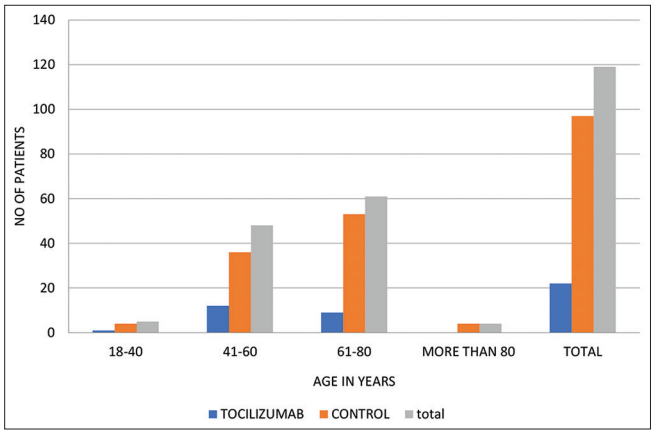

Fig. 2: Graph showing age distribution of study population

It was also observed that patients in tocilizumab group had a higher percentage of patients with three comorbidities and those having both pre-existing diabetes mellitus and hypertension. Tocilizumab group also had higher percentage of patients with severe pneumonia compared to the control group.

Primary outcomes

Primary outcomes were measured in terms of death versus discharge irrespective of the duration of hospitalization as well as the need for invasive ventilation while hospitalized. We observed that the number of deaths that occurred in the treatment group was significantly lower than those in the control group. There was a 41% absolute risk reduction and 56% relative risk reduction for death when patients were administered tocilizumab [NNT=3, unadjusted OR=6.9231, CI (2.4285, 19. 7361), p=0.0003]. However, on multivariable logistic regression with respect to age, gender, and number of comorbidities, the odds of survival increased with decreasing number of comorbidities. The number of comorbidities was found to have a significant effect on the outcome along with tocilizumab (Table 2).

In terms of invasive ventilation, we observed that patients who received tocilizumab were less likely to require intubation and subsequent invasive ventilatory support as compared to the control group. There was a 20% absolute risk reduction and 42% relative risk reduction in requirement of invasive ventilatory support when patients were treated with tocilizumab [NNT=5, unadjusted OR=2.8308, CI (0.9616, 8.3333), p=0.0589]. The multivariable logistic regression done with respect to nuber of comorbidities, age, and the oxygen saturation on presentation revealed that the odds of not requiring invasive ventilation increased with decreasing comorbidities (Table 3). There was no effect of the oxygen saturation on presentation with the requirement of invasive ventilation.

Hence, we observed a positive impact of tocilizumab on both primary outcomes in our patients considering that patients who received tocilizumab were in general sicker as compared to those in the control group.

Secondary outcome

The secondary outcome in our study was evaluated in terms of the duration of hospital stay between both groups. We found that patients treated with tocilizumab had a statistically significant higher hospital stay by almost a week as compared to those who were not treated. However, when only survivors were taken into account from both groups, it was seen that the duration of hospital stay was not statistically different between the patients who survived (t=0.96, p=0.34) and those who succumbed. This leads to an extrapolation that patients who succumbed might have lived longer if they were administered tocilizumab. This reinforces our primary outcome finding that tocilizumab does indeed impact survival of covid-19 patients.

DISCUSSION

A number of retrospective and prospective studies have been conducted till date to study the effects of tocilizumab in COVID-19 pneumonia. So far, we still do not have a clear answer as to whether tocilizumab is effective

Table 1: Demographic, clinical, and laboratory parameters of study patients

Parameters	Tocilizumab (n=22) Mean±SD (%)	Control (n=97) Mean±SD (%)	p-value (<0.05 is significant)
Age (years)	59.5±10.06	61.08±11.68	0.65
Gender (M:F ratio)	2.7:1	1.9:1	
Symptom duration (days)	6.2±2.8	4.76±3.25	0.046
No. of comorbidities			
1	6 (27.27)	31 (31.95)	
2	9 (40.90)	33 (34.02)	
3	3 (13.63)	11 (11.34)	
>3	1 (4.54)	0 (0)	
Comorbidities			
Hypertension	5 (22.72)	20 (20.61)	
Diabetes mellitus	3 (13.63)	22 (22.68)	
Both	9 (40.90)	31 (31.95)	
Respiratory rate (breaths/min)	28.04±5.5	25.04±4.89	0.01
SPO_2(%)	83.95±9.71	87.67±7.39	0.04
CRP	85.24±83.96	64.30±63.10	0.19
D-dimer	2633.64±3246.32	977.6±1509.01	0.0004
LDH	764.46±313.77	734.22±227.86	0.52
S.ferritin	865.19±641.17	728.81±469.94	0.25
IL-6	179.50±303.4	50.80±59.44	0.0003
Type of pneumonia			
Mild	2 (9)	10 (10.30)	
Moderate	3 (13.63)	27 (27.83)	
Severe	17 (77.27)	58 (59.79)	
No. of days of respiratory support	16.5±9.08	13±8.25	0.07
Hospital stay (days)	21.27±10.23	14.52±8.73	0.0019
No. of deaths (%)	7 (31.8)	71 (73.19)	
Invasive ventilation	6 (27.27)	46 (47.42)	

CRP: C-reactive protein

Table 2: Multivariable logistic regression for effect of tocilizumab on mortality

Variable	β-Co-efficient	Std. error (Wald)	p-value	Odds ratio	95%CI
Tocilizumab	2.3786	0.6180	0.0001	10.78	(3.2134, 36.2299)
No. of comorbidities	−0.8115	0.2622	0.002	0.44	(0.2657, 0.7427)
Age	0.3895	0.4589	0.3959	1.4763	(0.6006, 3.6287)
Gender	−0.1456	0.4764	0.7599	0.8645	(0.3399, 2.1991)
Constant	−0.0331	0.7812	0.9662		

Chi-square=29.39, df=4, p=0.0000 for this Model fit

Table 3: Multivariable logistic regression for effect of tocilizumab on the need of invasive ventilation

Variable	β-Coefficient	Std. error (Wald)	p-value	Odds ratio	95%CI
Tocilizumab	1.1345	0.5760	0.0489	3.1097	(1.0057,9.6156)
No. of comorbidities	−0.3846	0.2129	0.0708	0.6807	(0.4485,1.0331)
Age	0.4126	0.4046	0.3078	1.5107	(0.6836,3.3384)
SPO_2	−0.1070	0.4106	0.7946	0.8986	(0.4019,2.0092)
Constant	0.6262	0.7134	0.3801		

Chi-square=9.8191, df=4, p=0.0436 for this Model fit

in reducing mortality in COVID-19. There are little data from India in this regard considering the size of its population and diverse ethnicity.

Our study results demonstrated a significant reduction in mortality as well as the need for invasive mechanical ventilation in critically ill patients. Furthermore, the number of comorbidities had a statistically significant effect on mortality as well as the need for invasive ventilation. Similar findings have been demonstrated in multiple studies. In a study by Nasa *et al*. [10] which had similar number of patients as ours, patients treated with tocilizumab had a mortality of only 9.1%. They also required less escalation of treatment as compared to the control group. Another study conducted by Shastri *et al*. [11] showed that increasing number of comorbidities had an adverse effect on survival of patients. Fifty-nine (59%) of patients in the treatment group and 43.36% patients in the control group had two or more than two comorbidities in our study. Despite the higher percentage of comorbidities in the tocilizumab group, these patients showed better survival as compared to the control group. A recent systematic review by Tleyjeh *et al*. [12] analyzed five randomized and controlled trials (RCTs) and 18 cohort studies where it was inferred that tocilizumab decreases the need for mechanical ventilation. However, while the RCTs showed that there was no effect of tocilizumab on short-term mortality, the cohort studies demonstrated low certainty evidence of the association between tocilizumab and lower mortality. The RCTs, however, did not consider mortality as a primary end-point and hence were not adequately powered to do so. In another meta-analysis by Aziz *et al*. [13] involving only observational studies and a pooled data of more than 6000 COVID-19 patients, it was observed that an addition of tocilizumab to standard of care could reduce mortality and the need for mechanical ventilation in COVID-19 patients more so in those having severe illness. A propensity score matched retrospective study conducted by Biran *et al*. [14] across 13 hospitals in USA also showed a positive impact of tocilizumab on in-hospital mortality. It was also seen that patients younger than 65 years fared better with tocilizumab a finding similar to our own study where patients receiving tocilizumab were younger than those in the control group; however, this might be a result of patient selection bias considering the limited availability of tocilizumab at the peak of the pandemic.

Out of the various international RCTs conducted REMAP-CAP trial concluded that tocilizumab improved 90-day survival when administered to severely ill patients requiring organ function support [15]. This was in contradiction to the EMPACTA and COVACTA trials which evaluated patients at 28 days where the survival impact of tocilizumab was not statistically significant [16,17]. The trial published in Lancet by the recovery collaborative group showed that there was an additional benefit of tocilizumab when given to hypoxic patients with systemic inflammation. The mortality observed in the tocilizumab group in this study was 31% which is close to the 27% mortality that we observed in our study [18]. A study by Salvarani *et al.* conducted on 126 patients also showed that tocilizumab did not prevent disease progression when given to patients who had a PAO_2/FiO_2 ratio between 200 and 300 mmHg [19]. This reiterates the suggestion that tocilizumab may not be useful for patients who remain clinically stable and may be reserved only for moderate to critically ill patients. This is in contradiction to the RECOVERY trial stated above where they observed the benefit of tocilizumab among all patients requiring any form of respiratory support, provided that they were hypoxic and they had systemic inflammation.

Regarding the secondary outcome of the study which was length of hospital stay, we observed that patients in the tocilizumab group had a mean hospital stay of 21.27 days while the control group had a mean stay of 14.52 days. The difference was found to be highly significant statistically (p=0.0019); however, when the same comparison was done taking the survivors in both groups, the mean hospital stay did not have any significant difference. Most trials mentioned above demonstrate a decrease in hospital or ICU stay for patients treated with tocilizumab. This was not seen in our study perhaps due to severity of illness in these patients, diverse ethnicity, and local guidelines regarding discharge as well as possibly delayed administration of tocilizumab as compared to other studies.

Study limitations

The limitation of our study was a small sample size besides being a retrospective single-center study. The strength of our study was that we tried to eliminate the effect of confounders by having implicit inclusion and exclusion criteria and utilizing logistic regression. We have been able to answer our objectives with much clarity.

CONCLUSION

Tocilizumab does show promise in severely ill COVID-19 patients and we recommend that it should be made a part of guidelines for COVID-19 treatment. We also conclude that patient selection and time of administration of tocilizumab remains crucial and clear guidelines need to be set for selection of patients from the vast array of data which is now available for tocilizumab and other similar agents. Till date, many lives across the globe have been lost to pandemics caused by emerging viruses and these agents shed a light of hope for mankind in the fight for survival against present as well as future viral diseases.

AUTHOR CONTRIBTIONS

Conceptualization of research, data analysis was done by Dr Shaila Jay Shah and Dr Jay H. Shah. Dr. Ravi Patel did most of the data collection and data entry. All three authors have contributed to the preparation and revision of the manuscript.

CONFLICT OF INTERESTS

None.

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