

EFFECT OF TOCILIZUMAB IN TERMS OF HOSPITAL STAY AND MORTALITY PATTERN AMONG PATIENTS WITH SEVERE VERSUS CRITICALLY-ILL COVID-19 PATIENTS: A COMPARATIVE ANALYTIC STUDY

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Abstract

Background and Objectives: Most patients with mild and moderate COVID-19 infection recover with standard care therapy. Mortality in patients with severe illness and those critically ill is high. Tocilizumab acts by blocking interleukin-6 receptors and shows promising results in severe disease. Aim of this study was to assess the effect of Tocilizumab in severe and critically ill COVID-19 patients in terms hospital stay and reducing the risk of death.

Methods: In this comparative analytical, single-center study undertaken in DHQ university teaching hospital Gujranwala, forty-four patients were enrolled after an informed consent through non-probability consecutive sampling. The patients were categorized based on oxygen requirement as severe (oxygen requirement 10 L/min) and critically ill patients (oxygen requirement 15 L/min). All patients were treated with injection Tocilizumab (8mg per kg body weight) using criteria based on oxygen requirement (10L/min or more) and increased levels of any two of the laboratory investigations including CRP, D-Dimers, serum ferritin and LDH. Sociodemographic and clinical profile were collected using a semi-structured proforma. Outcome of interest was hospital stay and mortality. Comparison of effect of Tocilizumab was analyzed in regards to age, sex, laboratory investigations and stated outcome using Pearson's Chi-squared test. P-value of ≤ 0.05 was considered statistically significant. Data were analyzed using SPSS version 24.0.

Results: Of 44 COVID-19 patients, 26 (59.1%) had severe disease and 18 (40.9%) were critically ill. We did not observe any statistical difference between these two categories as regards age, sex, hospital stay or presence of co-morbid conditions. However, there were 17 (94%) deaths observed among critically ill patients, while one patient died with severe disease. This mortality difference was found statistically significant ($p < 0.001$).

Conclusion: Tocilizumab has shown significant effect to reduce mortality and minimizing hospital stay amongst COVID-19 patients with severe disease only with minimal effect in critically ill patients. Tocilizumab may be introduced early in treatment plan for severe COVID-19 patients.

Keywords: COVID-19, Pandemic, Severe COVID-19 disease, critically ill, Mortality, Survival, Tocilizumab, Hospital stay,

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COVID-19 pandemic has resulted in substantial mortality and morbidity worldwide. Several variants of SARS Cov-2 virus have been identified with each has its own unique course of disease, mainly

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affecting respiratory system. Cytokine storm is the hallmark of severe form of disease and attributed to secretion of interleukins.¹ The pathophysiology of the COVID-19 includes early viremia phase and late inflammatory phase. Multiple antiviral agents like Remdesivir and Favipiravir have been given trial to control viremia phase but with very little benefit.² Other treatment modalities involve using drugs that inhibit inflammatory phase. Efficacy of Dexamethasone is well established in this phase.¹

Inflammation in COVID-19 is mediated usually by Interleukin-6, which induces cytokine release syndrome after day seven of illness. Interleukin-6 demonstrates by animating helpful antibody production by immune cells that express membranous interleukin-6 receptors and co-stimulates undesirable pro-inflammatory cells that lack interleukin-6 receptors.³ In the later type trans-signaling needs dimerization of shed soluble interleukin-6 receptors with some other membrane protein, glycoprotein gp130.⁴

Tocilizumab acts by blocking interleukin-6 receptors. Multiple trials have been conducted to test the efficacy of Tocilizumab in treating severe to very serious disease. Some trials have shown beneficial results with this drug while others reported no difference in clinical results as comparing intervention and placebo groups.^{4,5} A report published in New England Journal of Medicine, Rosas et al. in a phase 3 trial (COVACTA Trial),^{2,3} reported that a single dose of Tocilizumab (8mg/kg body weight of body weight) had no significant clinical outcome compared with placebo at 28 days ($P=0.94$). Similarly, Salama et al.⁴ randomly assigned patients hospitalized with COVID-19 (ratio of 2 to 1) pneumonia who were not receiving mechanical ventilation to receive standard care plus one or two doses of either Tocilizumab (8mg per kilogram of body weight) or placebo. They concluded that the patients with COVID-19 pneumonia who were not receiving mechanical ventilation, Tocilizumab reduced the likelihood of progression to composite outcome of mechanical ventilation or death, but it did not improve survival. No new safety signals were identified ($P=0.04$). In another randomized, double-blinded, placebo-control-

led trial involving patients with confirmed severe COVID-19, Stone et al.^{5,6} randomly assigned patients (2:1) to receive standard care plus a single dose of either Tocilizumab (8mg per kilogram of body weight) or placebo. Their study showed that Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19. Some benefit or harm could not be ruled out because confidence interval for efficacy comparisons was wide. Stone et al. also reported that their multi-center cohort study involving 3924 critically ill-patients with COVID-19 showed that early administration of Tocilizumab was associated with prolonged survival.^{5,6} There is inconsistent evidence on effectiveness of Tocilizumab in studied population. This study aimed at assessing the effect of Tocilizumab in reducing hospital stay and mortality among COVID-19 patients with severe disease and those who are critically ill. Results will provide an evidence for clinicians to design treatment plan accordingly.

METHODS

Approval of current study was obtained from the institutional review board of Gujranwala Medical College (No. Admn. 377/GMC). We started the enrollment with effect from 11 January 2021 through 28 May 2021 in Divisional Headquarter University Teaching Hospital Gujranwala.

COVID-19 patients were received through medical emergency and were isolated in a separate ward (Pulmonary bay). After taking all baseline investigations and nasopharyngeal swab, patients requiring 2 to 10 liters of oxygen per minute were shifted to level one (Isolation). Patients requiring 11 to 50 liters of oxygen per minute were shifted to level two in High Dependency Unit settings (Severe disease category). Patients requiring more than 50 liters of oxygen per minute were shifted to level three Intensive Care Unit settings (Critically ill category).

A sample size of 44 (26 patients in severe disease category and 18 patients in critically ill category) patients was calculated by taking a confidence interval of 95%, with absolute precision of 10% and expected

reduction on events of clinical deterioration as 10%.

Inclusion criteria for COVID-19 patients included positive test on nasopharyngeal swab using RT-PCR, mechanical oxygen requirement of more than 10 liters per minute plus any two laboratory investigations: CRP level of more than 100 mg/dl or more than 70 mg/dl but rising trend, D dimers level of more than 1 mg/dl, LDH level of more than 450 mg/dl, serum ferritin level of more than 700 mg/dl. Patients with chronic kidney disease stage 4 and stage 5, chronic liver disease or liver enzymes of more than three times the upper limit of normal were excluded.

Patients in both categories were given intravenous Tocilizumab (8mg per kilogram body weight). Those with oxygen requirements of 10 l/min or more, chest X-ray, CBC, LFTs, RFTs, serum electrolyte along with specified inflammatory markers (CRP, D. Dimers, LDH, Serum Ferritin levels) were done daily. Use of experimental treatments and off-label marketed drugs intended to treat COVID-19 were not allowed.

The treatment protocols were set by Medicine Unit of the Hospital and were independently overseen by 'Corona Virus Patient Management Plan Committee'. The standard of care treatment comprised of steroids (Dexamethasone), anticoagulants (Clexane\ Enoxaparin\ Heparin), H2 receptor blockers (Ranitidine), vitamin C and D. The patient's clinical status was assessed using WHO Ordinal Scale⁶⁷ for clinical improvement (including: 1.No limitation of activities, 2.limitation of activities, 3. hospitalized but no oxygen therapy, 4. oxygen by mask or nasal prongs, 5. non-invasive ventilation or high-flow oxygen, 6.intubation and mechanical ventilation, 7.ventilation plus additional organ support). Deaths, adverse events during treatment in hospital were recorded according to grades of AE (Grade 1-5: Mild, moderate, severe, life-threatening or disabling, death respectively).

Treatment modality of a patient was decided on the basis of oxygen requirement and co-morbid conditions. Level one patient was given oxygen through simple face mask. Level two patients were given oxygen using a non-re breather mask, a high flow device or BIPAP machine. Level three patients were given oxygen using ventilators (both non-invasive and invasive).

Patients in each level were assessed thrice daily by medical specialist. Using WHO ordinal scale for clinical improvement, daily quantitative modifications were made in their treatment tickets. Clinical condition in terms of improvement and deterioration were recorded daily by on duty doctors. Treatment related adverse events and all hypersensitivity reactions were recorded daily.

Collected data was analyzed using SPSS 24.0. All baseline characters and variables were entered in database and coding was carried out to categorize age, sex, presence of co-morbidity, hospital stay days and whether discharged or died. Data were checked for normality assumptions and found to be non-normal, therefore analysis was conducted using frequency distribution and difference of proportion was examined using Pearson's Chi-Square test. A p-value of <0.05 was considered statistically significant. In case of cell values less than 5, we used exact test to compute p-value.

RESULTS

A total of 48 patients were invited for this study. Four patients did not fulfil the inclusion criteria and were excluded. Analysis of 44 patients (26 in severe disease category and 18 in critically ill category) was conducted after observing them from date of admissions to either date of discharge or deaths (Figure 1). Of 18 critically ill patients, 17(94%) died and only one patient died in severe disease category. Using WHO ordinal scale, all 26 patients in severe disease category were in class 4 (on high flow oxygen/non-invasive ventilation, whereas 16 out of 18 critically ill patients were classified as in class 6 (invasive ventilation. Comparing these COVID-19 patients, 17 (65%) and 16 (89%) were aged 50 years and above in severe disease and critically ill categories respectively; females (58%) dominated the severe disease category where as proportion of men were higher in critically ill category (57%). However, difference of proportion for age and gender was found to be statistically insignificant ($p>0.05$) (Table 1). About 14 (54%) patients in severe disease category and 10 (56%) critically ill patients had one or more co-morbid conditions (Diabetes Mellitus, Hypertension, Ischemic heart disease, Tuberculosis,

Chronic liver disease, Chronic Kidney disease). However, presence of co-morbid conditions among these categories of patients was not statistically significant ($p=0.91$). More than 80% critically ill patient remain admitted in hospital for two weeks compared to 61% patients in severe disease category. Nevertheless, difference of stay in hospital was not statistically significant ($p=0.15$) (Table 1). We found statistically significant difference of deaths among critically ill patients compared to the patients with severe disease ($p<0.001$).

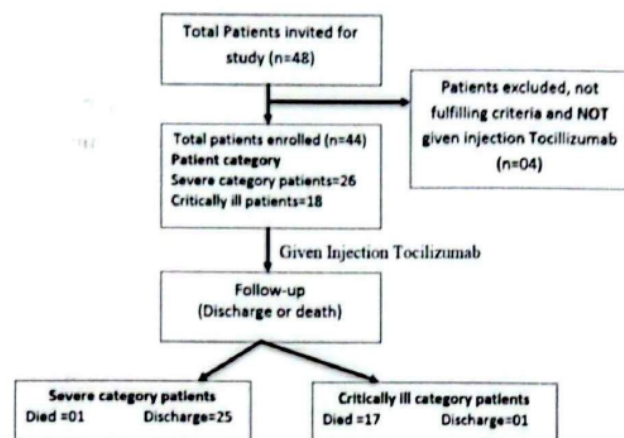


Figure 1: Flow Chart showing Patient's Participation and Outcome following Injection Tocilizumab

Table 1: Baseline characteristics of COVID-19 patient's and outcome in terms of hospital stay and death following injection Tocilizumab in DHQ Hospital Gujranwala ($n=44$)

Characteristics	Severe Disease Category (n=26)	Critically ill category (n=18)	p- value
	N (%)	N (%)	
Age			
< 50 years	09 (34.6%)	02 (11.1%)	0.16
50 years &above	17 (65.4%)	16 (88.9%)	
Sex			
Male	11 (42.3%)	10 (55.6%)	0.39
Female	15 (57.7%)	8 (44.4%)	
Comorbid conditions*			
Present	14 (53.8%)	10 (55.6%)	0.91
Absent	12 (46.2%)	8 (44.4%)	
Hospital stay (days)			
Two weeks	11 (61.1%)	21 (80.8%)	0.15
More than two weeks	07 (38.9%)	05 (19.2%)	
Outcome			
Discharged	01 (5.6%)	25 (96.2%)	<0.001
Died	17 (94.4%)	01 (3.8%)	

Footnotes: Comorbid conditions include Diabetes Mellitus, Hypertension, Ischemic Heart disease, Chronic liver disease, chronic kidney disease, Hepatitis C, Tuberculosis. Chi-Squared test was used to compute p-value. Percentages are column wise. Fisher's exact test was used when cell values are less than 5.

DISCUSSION

The results of this study showed that early intervention with Tocilizumab in severe disease category (as soon as inflammatory markers were raised) has considerable effect in reducing hospital stay and reduce the risk of death. Since the patients in severe category were already hospitalized and their inflammatory markers were being monitored. They received Tocilizumab as soon as the inflammatory markers reached the threshold for intervention and Tocilizumab was found to be proved efficacious. On the other hand, critically ill patients received Tocilizumab on day one of their admission and their actual duration of hyper-inflammatory phase were not known, therefore difference of Tocilizumab's effect in reducing mortality and hospital stay in these patients could not be established. It can be inferred that Tocilizumab may be more beneficial if given early in inflammatory phase since later with multi organ involvement it is not going to benefit in any way.¹³

Our results are consistent with the findings the COVACTA trial, which also showed that Tocilizumab is not effective in patients on mechanical ventilation. Both the studies showed that Tocilizumab has no efficacy in critically sick patients. Our study also supports the findings of Salama et al. which showed that Tocilizumab had survival benefit in only severe patients (not receiving mechanical ventilation).^{5,6,10}

The mean age of patients in severe disease category was 53 years and the mean age of patients in critically sick category was 63. It was seen that the patients falling in critically ill category were much older than the severe disease category. However, this difference in age was not significant in this study. When compared for co-morbidities, no significant difference was observed. It can be inferred that increasing age is a risk factor for negative outcomes.^{11,12}

We have also observed thromboembolic phenomenon complicating the disease course in many of the COVID-19 patients adding to mortality burden. It is possible that there are many other confounding factors adding to the mortality in COVID-19 critically ill patients.¹³ Results of this study should be interpreted after considering few limitations. The study is single centered, non-blinded with limited sample size. No founding effect was adjusted due to small sample size. Future studies should aim to conduct follow-up studies with blinding, including control group with standard care and using regressing modelling to predict the hospital stay and survival with either category. A large sample size and survival analysis would be more appropriate to provide concrete evidence on effectiveness of Tocilizumab in preventing the risk of deaths among Severe to critical COVID-19 patients.

CONCLUSION

Tocilizumab has shown significant effect to reduce mortality and minimizing hospital stay amongst COVID-19 patients with severe disease only with minimal effect in critically ill patients. Tocilizumab has limited role in critically ill patients in terms of mortality benefit and time to discharge from hospital. Tocilizumab may be introduced early in treatment plan for severe COVID-19 patients.

Conflict of Interest *None*

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