

Response of Tocilizumab in Treating Severe to Critical COVID-19; Single-Centre Experience at a Tertiary Care Centre

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ABSTRACT

Objective: To study the effectiveness of Tocilizumab in reducing mortality in severely or critically ill patients.

Study Design: Quasi-experimental study

Place and Duration of Study: Mayo Hospital, Lahore Pakistan, from Dec 2020 to May 2021.

Methodology: The participants meeting the inclusion criteria of the study were allocated to an Experimental and a Control Arm based on age and oxygen requirements. The Experimental-Group was given Tocilizumab plus standard care, while the Control- Group received standard care only. Primary outcome was death, while secondary outcomes were the need for invasive ventilation and length of hospital stay. Results were analyzed after 28 days.

Results: Among 81 patients, 60(74.1%) were males, 21(25.9%) were females. Of these, 44(54.3) received Tocilizumab plus Standard Care, while 37(45.7%) received Standard Care only. Out of 44 patients from the Tocilizumab-Group, 21(47.7%) survived, whereas, from 37 in the Standard Care-Group, 15(40.54%) survived at the end of 28 days. However, the difference in survival distributions between the two groups was not statistically significant ($p=0.41$).

Conclusion: Tocilizumab was found to have no significant impact on improving the chances of survival and reducing the risk of Invasive Ventilation in COVID-19 patients. A wider confidence interval, however, cannot rule out the possibility of some benefit or harm. Hence, further studies are needed on this subject.

Keywords: Efficacy, Tocilizumab, Severe COVID-19, Standard Care, Survival

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INTRODUCTION

Management guidelines for COVID-19 include prevention and control of spread besides medical treatment and supportive care. Medical treatment of COVID-19 involves oxygen supplementation and mechanical ventilation, administration of steroids, antiviral agents such as Remdesivir and anti-inflammatory agents such as Tocilizumab(TOC) as needed.^{1,2} FDA has approved Remdesivir for COVID-19 treatment, whereas the National Institute of Health (NIH) recommended Dexamethasone for hospitalized COVID-19 patients.^{3,4}

Tocilizumab (TOC) is a monoclonal antibody acting as an IL-6 receptor inhibitor. It has been used to treat many inflammatory diseases.⁸ It appeared to be effective against COVID-19 because of the suggested mechanism that CRS caused by COVID-19 might be prevented or even reversed by targeting IL-6 receptors, and hence, detrimental effects of the disease can be avoided.^{5,6} Multiple observational studies have shown improved outcomes in COVID-19 patients treated with Tocilizumab. However, different randomized control

trials have shown conflicting results within different regions and different population backgrounds, along with varying degrees of standard of care (SoC) and disease severity.^{7,8} CRS caused by COVID-19 can lead to ARDS that might be fatal.⁹ With the lack of definite treatment and mixed results of existing trials, the potential benefit of Tocilizumab in COVID-19 based upon the pathogenesis of the disease and mechanism of action of the drug necessitates further investigation into this subject.¹⁰ However, in Pakistan, only a few studies have been done on the clinical benefits of Tocilizumab in COVID-19 patients, and among those, only some are experimental. Hence, this study aims to determine the efficacy of Tocilizumab in treating severe and critical COVID-19 and its impact on improvement in the outcome of patients with severe COVID-19.

METHODOLOGY

The quasi-experimental study was conducted at Mayo Hospital, Lahore, from December 2020 to May 2021 after The Institutional Bioethics Review Committee (IBRC) approved the study protocol (443/RC/KEMU). The sample size was calculated by taking a expected percentage of mortality events as 5% in the Tocilizumab-Group and 27.5% in the non-Tocilizumab

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Group.¹¹ Patients were selected through a simple random sampling technique.

Inclusion Criteria: Patients with severely or critically ill COVID-19 were included who were at least 18 years old, had significantly raised biomarkers for COVID-19 (CRP, ferritin, D-Dimers), did not have septicemia prior to Tocilizumab administration, and met the criteria of eligibility for Tocilizumab administration as per SOPs of Hospital.

Exclusion Criteria: All those patients who were already on immunosuppressants due to any chronic illness, had ESRD being on dialysis or had any pre-existing lung pathology (asthma, ILD, fibrosis, etc.), had any severe disease that affected the survival (metastatic disease, blood diseases, active bleeding, HIV/AIDS etc.) or active tuberculosis, had thrombocytopenia (<50,000), absolute neutrophil count (ANC) <1000 or LFTs 5 times higher than upper limit were excluded.

Data collection was started after obtaining patients' or their legal guardians' informed written and verbal consent. International conference on harmonization E6 guidelines for good clinical practice were followed during this process. Patients meeting inclusion criteria were allocated to an experimental and a control arm based on age and oxygen requirements following the predefined protocols of the study. Severe COVID-19 was defined as Positive PCR, any respiratory rate greater than 30/minute, oxygen saturation of less than 93% at room air, or radiological progression of 50% or more within 48 hours. In contrast, critical COVID was defined as positive PCR with the above-mentioned characteristics and/or having shock, MODS, extracorporeal life support (ECMO) or mechanical ventilation.

The treatment group received SoC plus one or two doses of intravenous Tocilizumab (8 mg per kilogram of body weight, to a maximum of 800 mg per dose). In contrast, the control group received a standard of care per protocol. Progress was monitored by serial investigations. The primary endpoint was death by any cause 28 days post-randomization. Secondary endpoints were the need for invasive mechanical ventilation at 28 days and the length of hospital stay.

Statistical Package for Social Sciences (SPSS) version 24.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency & percentages. Kaplan Meier Curve was drawn with the outcome being death, survival time in days, and exposure being

administration of Tocilizumab. Median survival times were calculated, and the log-rank test was used to test significant differences in survival distributions. Cox regression analysis was also conducted with Tocilizumab, age and gender as covariates. The *p*-value of ≤0.05 was considered as significant.

RESULTS

Ninety patients were enrolled in our study, with 45 in each Group. Nine patients were excluded from the final analysis because of loss of follow-up. Out of 81 patients, 44(54.3%) were given Tocilizumab. Sixty participants were male, and 21 were female. As for the type of ventilation provided to these 81 patients, 30(37%) were provided with noninvasive positive pressure ventilation (NIPPV). Twenty-four patients (29.6%) were given high-flow oxygen with a non-rebreathing mask (NRM), and 24(29.6%) were given mechanical ventilation. Nine of the participants (20%) expired on the first day after the administration of Tocilizumab. The mean length of hospital stay was 8.284±6.31 days. It was 7.46±5.67 days in the SoC group and 8.97±6.78 days in the Tocilizumab group. Five (11.1%) expired on the second day, seven (15.6%) on the third, five (11.1%) on the fourth, one (2.2%) on the fifth, six (13.3%) on the sixth, eight (17.8%) on seventh, two (4.4%) on eighth and two (4.4%) on the tenth day after the drug administration (Table-I).

Table-I: General characteristics of patients given and not given Tocilizumab (n=81)

Characteristics	Patients given Tocilizumab n=44	Patients not Given Tocilizumab n=37	<i>p</i> -value
Age Mean±SD in years	58.68±13.32	54.85±13.31	0.01
Gender			
Male	36(81.8%)	24(64.9%)	0.64
Female	8(18.2%)	13(35.1%)	
Survived till end of study period n(%)	21(47.8%)	15(40.5%)	0.14

The median survival of patients not given Tocilizumab was eight days (2.9-13.1), whereas the median survival of patients given Tocilizumab was seven days (4.1-9.9). However, the survival distributions between the two groups were not statistically significantly different, (*p*=0.41). Regression analysis was significant, as revealed by the Omnibus test ($\chi^2=8.12$, *p*=0.04). Tocilizumab had no significant bearing on survival at *p*=0.14 (Figure), and neither did gender (*p*=0.64). Only old age was a significant predictor of death at *p*=0.01 (Table-II).

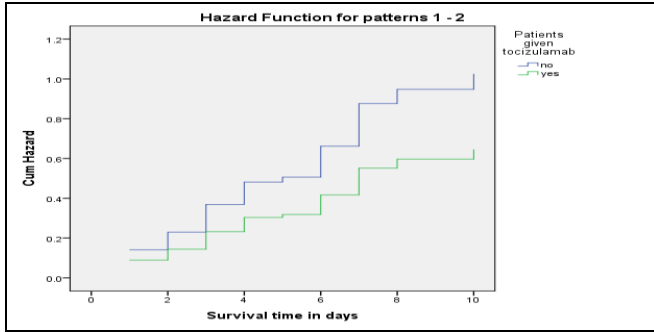


Figure: Comparison of Hazard Ratio between Patients given and not given Tocilizumab (n=81)

Table-II: Cox Regression Analysis

Risk Factors	p-value	Odds Ratio	95.0% Confidence Interval
Male gender	0.64	0.84	0.41-1.74
Treatment with Tocilizumab	0.14	1.59	0.85-2.95
Age in years	0.01	1.03	1.01-1.06

DISCUSSION

In our study, 47.77% Tocilizumab-treated patients survived till the end of the study, whereas 40.54% from standard care survived till the end, showing improved outcomes in patients treated with Tocilizumab. However, these results were not statistically significant ($p=0.14$). A previous study also showed similar results, reporting no significant effect of Tocilizumab treatment on mortality and the length of ICU stay.¹² However, CRP levels were markedly reduced after Tocilizumab administration. Markedly reduced levels of cytokines after TCZ treatment might be attributed to the pharmacological effect of TCZ. Another study also reported similar results, showing no significant 30-day mortality benefit with TCZ.¹³

Several observational studies showed improved outcomes in patients of COVID-19 treated with Tocilizumab. A study in California reported that mortality in patients treated with Tocilizumab was significantly lower 8/55 (15%) than those under standard care 15/41 (37%) [$p=0.02$]. This difference was even more marked for patients on mechanical ventilation, as 9/15 (60%) died in the standard-care Group compared to 6/44 (14%) Tocilizumab-treated patients ($P= 0.001$).¹⁴ Another study in India showed that Tocilizumab-treated COVID patients had less mortality than standard-care treated patients (HR 0.621, 95% CI 0.427-0.903, $P0.013$). Median survival was also higher in the tocilizumab-treated Group (18 vs nine days).¹⁵ Strikingly, more patients treated with Tocilizumab underwent Invasive Ventilation in both studies. Another study in Wuhan reported a lower

mortality rate (21.54% against 32.31%) and shorter ICU stay in patients treated with Tocilizumab.¹⁶

COVACTA (a multi-centre, global trial) demonstrated 19.7 % mortality in Tocilizumab-treated patients against 19.4% mortality in the placebo group ($p=0.94$). However, in this study, ICU stays in TOC treated patient was found to be shorter (9.8 compared to 15.5) than in the Placebo Group, a finding suggestive of morbidity benefits of TOC administration.¹⁷ Another trial in Boston, USA, reported more mortality and increased risk of invasive ventilation among those receiving TOC treatment than those with standard therapy. Only old age was a bad prognostic factor, as observed in our study. Unlike some studies suggesting that early administration of TOC to those who do not have severe disease will significantly improve the outcome, this study showed that even in moderate disease, there was no significant effect of TOC on the risk of intubation or death or disease worsening.¹⁸ Our study also demonstrates similar results showing neither significant mortality benefit nor improved survival period. However, some studies from different regions of the world reported improved outcomes in COVID-19 patients treated with TOC.^{19, 20, 21}

These studies show promising results of TOC in COVID-19. However, these are single-centred, observational studies with small sample sizes, and the results of these studies were not supported by RCTs worldwide. Our study, however, showed that TOC has no remarkable effect in improving morbidity and mortality of COVID-19 patients. Many RCTs across the globe have also shown similar results, asserting that TOC might not be the breakthrough we had been looking for, and our study also strengthens this notion. Our study also entails additional studies involving multi-centre settings and having a larger sample size to contribute to formulating universally accepted management guidelines.

LIMITATIONS OF STUDY

Our study has, however, certain limitations. It was a single-centre study with a small sample size and had very little participation of female patients. Moreover, the impact of Co-morbidities on outcome could not be analyzed as we had no previous record of how well the control of those conditions was before randomization. Further, as we only included severely or critically ill COVID-19 patients, the impact of Tocilizumab on moderate disease could not be validated in this study. As there are different studies indicating Tocilizumab to be more effective in the early phase of the disease, further research is indicated.

CONCLUSION

Tocilizumab does not cause any significant morbidity or mortality benefit in COVID-19 patients. Further studies, especially RCT, are recommended to explore the effectiveness of the drug and to establish a standard treatment protocol for COVID-19.

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

SK: & MMA: Conception, study design, drafting the manuscript, approval of the final version to be published.

SA: & UM: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

SZ: & SF: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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