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Tocilizumab in severe Covid-19 patients (clinical and laboratory outcome): A single centre retrospective observational study

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Abstract

Background: Severe covid 19 disease is associated with multiorgan damage and mortality which is associated with dysregulated immune system with hyperactive inflammation, called as cytokine - release syndrome, for which IL 6 is considered to be the main culprit for the severity of the disease. Here we are observing the use of Tocilizumab, a monoclonal antibody against the IL 6 receptor in the treatment of severe COVID 19 patient.

AIM: The aim of this study was to assess the role of tocilizumab in severe COVID -19 patients, clinical and laboratory outcome.

Method: We did a retrospective, observational study on patients who were admitted in ICU with severe COVID-19 pneumonia who met the severity criteria were given Tocilizumab. Severity grading according to MoHFW were graded. The primary objective was to evaluate the effect of tocilizumab on mortality, length of hospital stay, trends of inflammatory markers and clinical progression of disease on day 10 of admission, compared with the similar group how were treated with standard treatment alone.

Results: Out of (50 in tocilizumab group and 49 controls) patients, mortality was analysed showed 24% in tocilizumab group, 42.9% in control group. Mean length of hospital stay in tocilizumab and control group were compared i.e., 13.3 days and 14.27 days respectively. And there was significant reduction in inflammatory markers LDH, S FERRITIN, D DIMER, and CRP in tocilizumab group.

Interpretation: Treatment with tocilizumab, might reduce the mortality in severe COVID-19 pneumonia patients. Since our study sample being small, a study with larger sample size may require predicting the outcome.

Keywords: Tocilizumab, Covid-19, patients, retrospective, observational

Introduction

In December 2019, A newly discovered coronavirus, SARS-CoV- 2, in Wuhan city which caused global threat emerged from china, caused the novel coronavirus disease (COVID-19) [1]. Which is an enveloped single stranded positive-sense RNA virus of zoonotic Pathogenicity. That spread rapidly to become a pandemic by WHO on March 11, 2020 [2]. This pandemic is associated with high mortality and burden mainly on developing countries like India. ACCORDING TO WHO, GLOBALLY AS OF 21 September 2021, there have been 228,807,631 confirmed cases of COVID-19, including 4,697,099 deaths, reported. As of 19 September 2021, a total of 5,776,127,976 vaccine doses have been administered [3].

To date there are more than 3.31cr infected cases were reported, while the death toll reached 4.41 Lakhs patients in India [4]. COVID-19 associated critical illness was characterized by acute respiratory failure, sepsis shock, thromboembolism, and multi organ system failure. Pathophysiology include dysregulated immune response causing higher proinflammatory cytokines [4]. Management of these cases is on-going challenge in this pandemic surge.

Since no appropriate therapy was approved against COVID-19, but current clinical approach towards the immunomodulatory drugs, such as selective cytokine inhibitor such as tocilizumab, a humanized monoclonal antibody against IL-6 receptor is suggested in treatment of severe COVID-19 patients [5].

Materials and Methods

Study design and participants

This is a retrospective, observational study done on severe COVID 19 patients admitted in our centre. The study population who were confirmed by RT-PCR on nasopharyngeal swab, and evidenced by bilateral chest infiltrates on chest radiography or CT.

Eligible patients

1. Adults >18 years old
2. MoHFW [6], severity grading respiratory rate >30/min, spo2 <90% on room air) presence of severe disease preferably with in 24 -48 hours of onset of disease).A Ratio of the partial pressure of oxygen to the fraction of inspired oxygen (pao2/fio2) of less than 300 mm of Hg.

Exclusion criteria

1. Immunosuppressive status
2. Active bacterial /fungal /latent tubercular infection.
3. Neutropenia, thrombocytopenia

The data of both tocilizumab group and control group were obtained from medical records.

Procedure

Both the patient groups has received standard treatment (oxygen supply to target Spo2 more than 90%, antibiotics in case of critical condition, hydroxychloroquine, ivermectin,

low molecular weight heparin, anti-virals, steroids, Prone ventilation was also supported.

In addition to standard treatment, tocilizumab group received two consecutive intravenous dose of 6mg/kg tocilizumab 12hours apart intravenously.

Statistical Analysis

We are comparing the mortality and length of hospital stay who received tocilizumab with the control group, and comparison of Data before and after tocilizumab was analysed using SPSS version 21. Categorical data was presented as frequencies and percentages. Continuous data was presented as mean and standard deviation. Chi square test was used as test of significance for categorical data for comparing the mortality percentage in the two groups. Un paired T test was used as test of significance for continuous data for comparing length of hospital stay in tocilizumab and control group. WILCOXON SIGNED RANK test was used as test of significance for continuous data for comparing lab parameters before and after tocilizumab skewed data). P value less than 0.05 was considered as statistically significant.

Results

1. Among cases, 24% were dead after drug intervention with tocilizumab, whereas in controls without drug intervention 42.9% were dead. On performing chi square test, this difference was found to be statistically significant (P value <0.05).

Table 1: Show the Tocilizumab Group and Control Group

			Group		Total
			Tocilizumab Group	Control Group	
Death	Alive	Count	38	28	66
		%	76.0%	57.1%	66.7%
	Dead	Count	12	21	33
		%	24.0%	42.9%	33.3%
Total		Count	50	49	99
		%	100.0%	100.0%	100.0%

CHI SQUARE = 3.960, P VALUE = 0.047 (S)

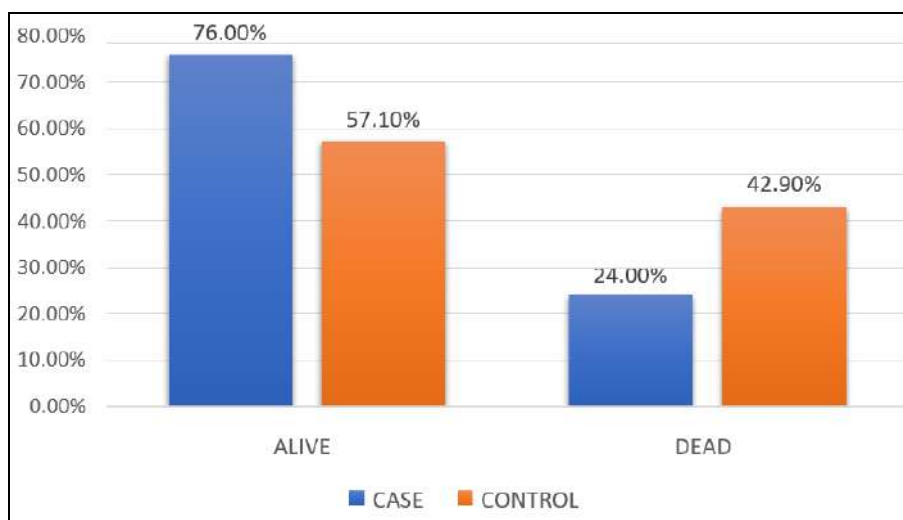


Fig 1: Frequency of Live and dead ratio in controls and cases after and before drug administration

2. Mean length of hospital stay was 13.3 days in those who received tocilizumab which is low when compared to controls where length of stay was 14.27 days. On

performing unpaired t test, this difference was found to be statistically significant (P value <0.05).

Table 2: Mean Length of Hospital stay

	Group	N	Mean	Std. Deviation	P Value
Length of hospital stay	Tocilizumab group	50	13.30	1.681	.044
	Control Group	49	14.27	2.885	

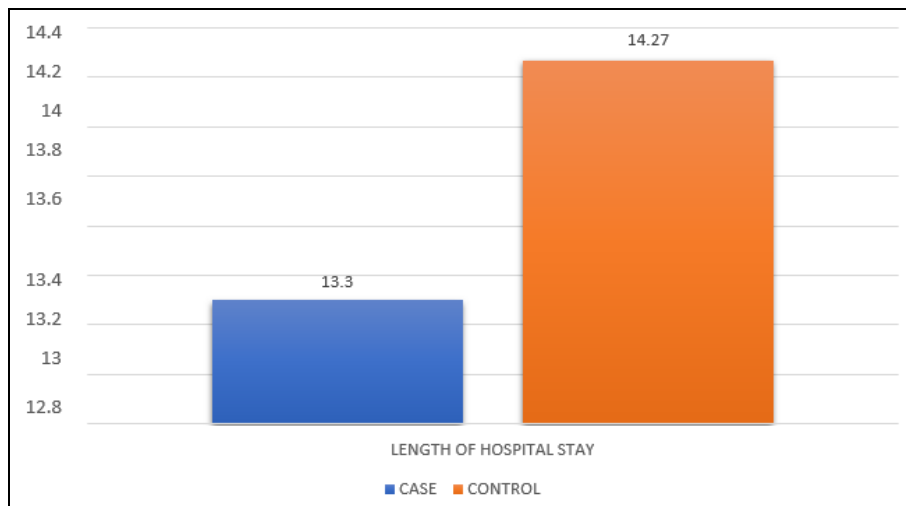


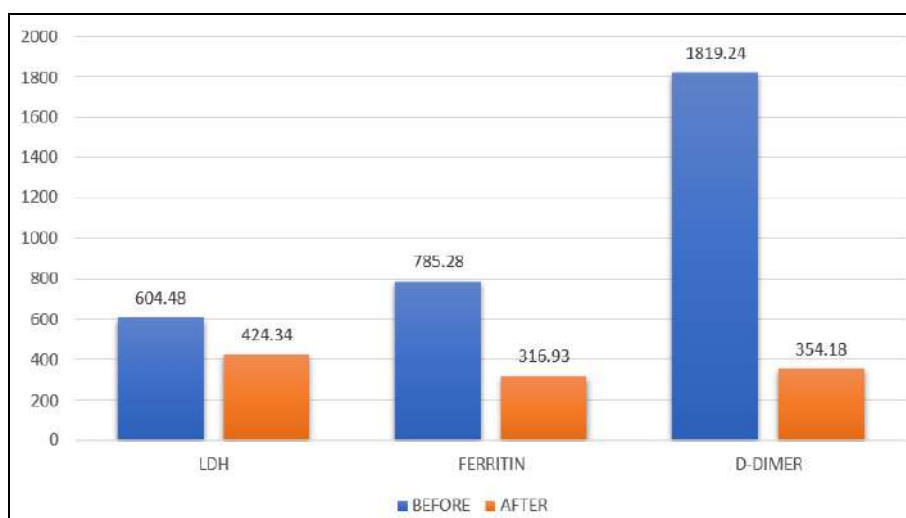
Fig 2: Mean length of Hospital stay

3. As shown in the below table, mean values of all lab parameters have decreased after giving tocilizumab drug.

On performing Wilcoxon signed rank test this difference was found to be statistically significant (p value <0.05).

Table 3: Lab Parameters

	Mean	Std. Deviation	P Value
LDH before	604.48	237.165	.001
LDH after	424.34	224.188	
Ferritin before	785.280	434.3997	.001
Ferritin after	316.936	241.7037	
D-dimer before	1819.24	1980.063	.001
D-dimer after	354.18	286.846	
CRP before	35.56	17.107	.004
CRP after	25.90	12.122	



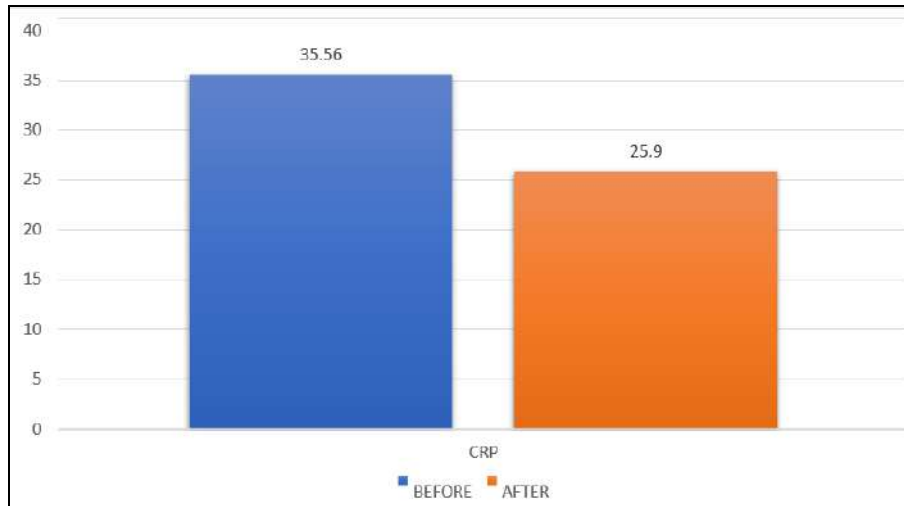


Fig 3: Lab parameters before and after Giving Tocilizumab Drug

4. Severity of Disease in Tocilizumab Group after Day 10 of Injection

Table 4: Show the frequency and percent

	Frequency	Percent
Mild	13	26.0
Moderate	20	40.0
Severe	5	10.0
Death	12	24.0
Total	50	100.0

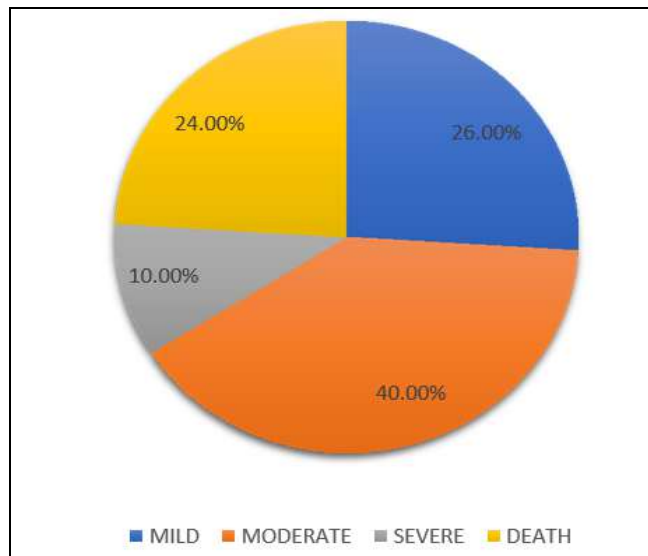


Fig 4: Severity of disease in tocilizumab group after day 10 of injection

Discussion

In this small retrospective, single centre study we found a significant decrease in mortality and length of hospital stay in Tocilizumab group compared with those treated with standard care alone. Reported 24% mortality in Tocilizumab group, 42.9% mortality in control group.

Our study are in consistent with those of similar, retrospective study by Yojana Gokhale, [7] done at tertiary care centre Mumbai, India in which median survival in the tocilizumab group was significantly longer than in control group 18 days versus 9 days, log rank p 0.007.

A study by Prashant NASA *et al.*, [8] a similar small retrospective study showed tocilizumab can improve

outcome by reducing the need for invasive ventilation and mortality when used timely with CRS.

The COVINTOC [9] is a Indian an open label multicentre randomised controlled phase 3 trial, this study showed routine use of tocilizumab is not suggestive, however their might be a role for it in patients with severe COVID 19.

EMPACTA [10] is the first global phase 3 trial to show efficacy with tocilizumab, demonstrated reduction in need of mechanical ventilation in covid 19 pneumonia.

No other Indian randomised controlled trails on tocilizumab in patients with severe covid 19 has been reported in India at the time of this study.

Overall, a large number of studies done globally, available on the effectiveness of TCZ on the mortality of patients with severe COVID-19 presenting conflicting reviews.

Conclusion

From the following study it showed, that the mortality rate was significantly lower in patients treated with Tocilizumab than the control group who were treated with only standard treatment, and there was a significant trend towards a decreased length of hospital stay in the Tocilizumab group, even the inflammatory markers showed improvement in majority of patients treated with tocilizumab.

The severity of COVID 19 pneumonia is thought to be driven by so called cytokine strome.in our study IL-6 levels remained stable after tocilizumab but decreased in control group, this can be due to tocilizumab competitively block il6 receptors and not free IL 6 in plasma. The longer and larger sample sizes are needed to better understand the prognostic role of IL- 6 levels in COVID 19 treated with tocilizumab.

As there were many limitations in the following study, control group with multiple co morbidities many being on mechanical ventilator support, which showing favourable outcome among tocilizumab group, it is inconclusive in view of the retrospective nature of study with a small sample size to determine the efficacy.

There seems to be a lot of differences in the outcome of trials from different studies done at different geographical locations. In consistent with our study, The COVINTOC is a Indian an open label multicentre randomised controlled phase 3 trial, this study showed their might be a role for it in patients with severe COVID 19.

Obviously, more data with large sample size would be needed to establish the efficacy of TCZ-treated patients with COVID-19, particularly from RCTs.

In this pandemic with no confined effective drug treatment against COVID pneumonia, Tocilizumab could be used as effective in battling against cytokine storm.

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