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TIMING OF ADMINISTRATION OF TOCILIZUMAB AND ITS EFFECT ON OUTCOME IN CRITICALLY ILL COVID-19 PATIENTS. A RETROSPECTIVE ANALYSIS.

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Abstract

Background: COVID-19 infection has been implicated in millions of deaths worldwide. The respiratory distress occurs with cytokine storm around 2ndweek of symptom onset. Tocilizumab, a humanized monoclonal antibody directed against the interleukin 6(IL-6) receptor has been used at varying extents in suppressing it, however, limited literature exists about the timing of its administration. We contemplated this study with the primary objective to establish whether tocilizumab favourably affected the outcome when given in the early stages of complication. The secondary objectives were to assess the importance of ROX score and the effect of age on outcome.

Methods: We conducted a retrospective study in a tertiary care hospital. Patients who received tocilizumab were divided into two groups depending on whether they received the drug in ≤ 10 days (Group 1) or≥ 11 days (Group 2) of onset of symptoms. The patient's demographic data and co-morbidities, on- admission vitals, ROX score, and laboratory parameters, outcome etc. were collected from the electronic health records.

Results: Both groups were comparable with regard to demographic and baseline parameters on admission. The outcome was significantly better in patients of Group-1(P=0.01) with better survival. The outcome was also significantly higher in ages ≤ 50yrs age(P=0.02) who received tocilizumab. Failure to improve ROX score after 24hrs. of administration of tocilizumab was associated with poor outcomes (p=0.001).

Conclusion: Tocilizumab when given in the early stages of COVID-19-related complications may be associated with decreasing mortality. Age may be an indicator of favourable effect, and failure to improve ROX score after tocilizumab is associated with poor outcomes

Keywords:COVID-19،COVID-19-mortality, Cytokine storm syndrome, Tocilizumab,ROX Score

Introduction:

COVID -19 infection caused more than 5 million deaths worldwide as of end January 2022, as per the WHO Coronavirus dashboard, however the true mortality might be far higher. The virus has been isolated, and genetic sequencing was done as early as January 2020,[1] promoting much research work to prevent the disease, stop the spread, decrease severity, cure, and prevent mortality with varying success. With limited time and knowledge about the risk factors related to the progression of the disease, much of the initial efforts were aimed to treat the patients with drugs which have proven beneficial for virus infection and managing the respiratory distress associated with COVID-19 pneumonia. The cytokine storm has been identified to be the major causative factor for rapidly progressive respiratory failure, often requiring ventilatory support. Pathogenesis of such respiratory deterioration includes the destruction of alveolar epithelial cells, dysregulated immune response with release of a plethora of proinflammatory cytokines, and release of inflammatory mediators, ultimately culminating in the dreaded cytokine storm. [2&3] Tocilizumab, a humanized monoclonal antibody directed against the Interleukin (IL-6) receptor, has been reported to improve clinical outcomes in critically ill COVID patients, [4-7] whereas a few studies are sceptical about its beneficial effects. [8-10] Usually the cytokine storm onset to progression occurs within day5 to day10 of onset of symptoms, hence, timing of administration of tocilizumab may play a role in overall outcome. However, limited literature exists regarding the timing of administration of this drug. [11] Hence, we contemplated this study with an aim to analyse the benefit of tocilizumab in our centre, with regard to timing of administration. The primary objective of this study is to see when there is an early cytokine storm in the course of illness, would administration of tocilizumab, provide any benefit in preventing progression of the disease. Secondary objectives being to find the effect of age on outcome of the disease and

ROX index before and after Tocilizumab administration.

Methods:

This is a retrospective, observational, cohort study at a tertiary care centre which managed severe COVID-19 patients in the critical care unit from June to October 2020. Data was derived from the electronic health records of COVID-19 patients who received ICU care. All the patients who received Tocilizumab were divided into two groups depending on whether they received the drug in the first ten days of onset of symptoms (Group-1) or ≥11 days (Group-2). Demographic and baseline variables were collected in both groups. In view of advanced disease states, patients who were already intubated and on ventilator support outside before shifting to our critical care unit were excluded from the study group. During the course of hospitalisation, the patients were treated according to the institutional protocol of 3 level of care. Level-I being mild symptomatic and asymptomatic patients admitted for isolation or observation. Level-II being patients who were hypoxic but managed with oxygen through mask. All the patients who were not maintaining oxygen saturation with oxygen mask or in respiratory distress with respiratory rate of more than 30 were shifted to Level-III of care for non-invasive ventilation or ventilator support if needed. Patients were treated with Remdesivir for five days if presented to hospital within first five days of illness. The standard care with regard to azithromycin, hydroxychloroquine, corticosteroids, low molecular heparin and antibiotics followed as per institutional guideline for all the patients. The Clinical criteria like ROX index which is defined as the ratio of oxygen saturation as measured by pulse oximetry/FiO2 to respiratory rate,[12] used to monitor the patient's wellbeing. Patients who required Fio2 of 0.8 or more to maintain spo2 of 92%, or sustained respiratory rate> 30 even with non-invasive ventilation were given tocilizumab 8mg/kg with a maximum of 400mg over one hour duration. A repeat dose of tocilizumab of same strength was administered If the condition of the patient was not improved after 12 hours of first dose. Patients were followed up for hospital discharge and death within 90 days after drug administration.

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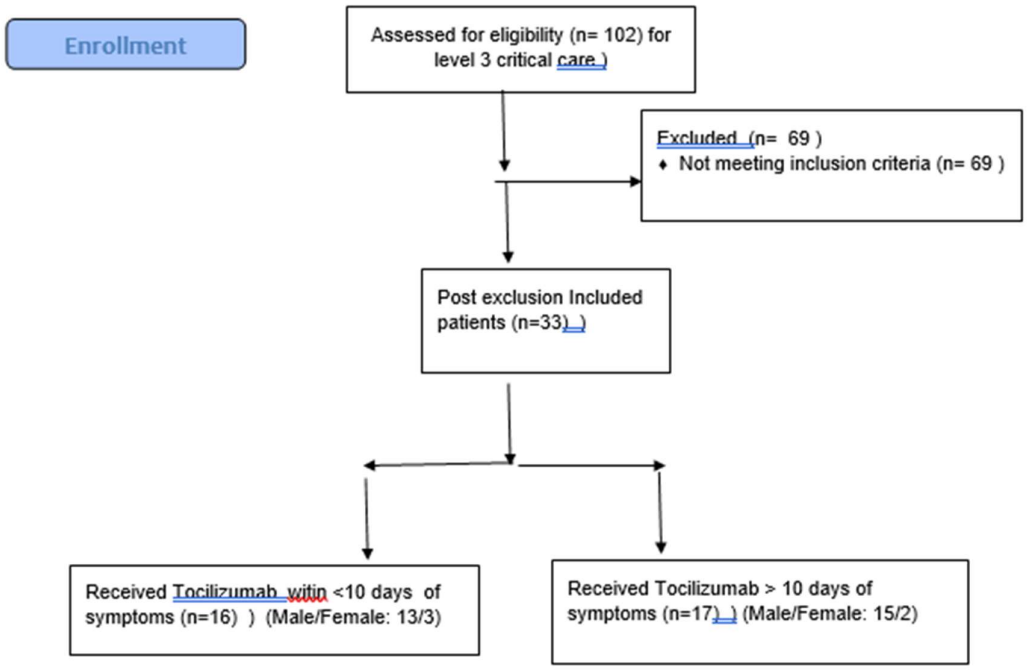

Figure 1: Flow diagram for inclusion and exclusion of patients

Results:

A total of 102 patients admitted to the designated level-3 for critical care management. After the due exclusions 33 (32.3%) patients were included in the study (Figure 1). Both the early and late tocilizumab administered groups (Group-1 and Group-2) were comparable with respect to age, gender, BMI and associated co-morbidities (Table-1).

Table:1- Demographic parameters of the groups

Parameter	Group-1 (≤D10 of symptoms)	Group-2 (≥D11 of symptoms)	P value
Age (years)	52.75±11.5	51.65±13.9	0.24
Gender M/F	13/3	15/2	0.65
BMI	27.3±5.2	25.8±3.7	0.58
Comorbidity	8/8	11/6	0.49
Multiple	4/12	7/10	0.45
Remdesivir	12/4	10/7	0.46

Age of the patient was found to be strongly associated with mortality among the tocilizumab administered patients with 83% patients expired were above 50 years of age Table II.

Table II: Age-related outcomes in tocilizumab- treated group

Age	Survived	Expired	P-value
<50 years (n)	13	2	0.02
>50 years (n)	8	10	

The critical care admission vital as well as lab parameters were comparable in both the groups. Though the SGOT (Serum glutamic oxaloacetic transaminase) was statistically of higher value in Group-2 still both the groups were in normal laboratory range (Table III).

Table III: Admission parameters

Variables		**Group-1**	**Group-2**	**P-value**
ROX score		5.12±1.5	4.93±1.8	0.692
HR (Beats/min)		98±16	96±17	0.812
MAP (mm Hg)		93.6±13	92.6±13	0.729
Urea		32±7.8	33.4±11.8	0.340
Liver enzyme	SGOT	34±14	50±27	**0.008**
	SGPT	28±15	48±19	0.079
	ALP	68±29	80±26	0.86
Inflammatory markers	N/L Ratio	10.6±6.6	15.6±13.2	0.321
	Ferritin	733±557	852±728	0.421
	Serum.LDH	393±123	471±139	0.55

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The average ROX scores before and for the first 24hr after Tocilizumab administration was found to be significantly better (P=0.001) in those who survived (Table IV).

Table IV: Average ROX scores

Outcome	Average ROX scores before tocilizumab	24-hour average ROX score after tocilizumab	P value
Survived	5.27±1.67	7.5±1.87	0.001
Expired	4.93±1.23	4.40±1.10	0.22

Survival in the Group-1 was significantly higher than in Group-2 (P=0.01). Table V

Table V: Outcome of Tocilizumab administration: (n= number of patients)

Outcome	**≤10days**	**≥11days**	**P value**
Survived (n)	14	7	0.01
Expired (n)	2	10	

Discussion:

In our study we have observed timing of administration plays a role in tocilizumab administration, with better survival rate among those who were administered tocilizumab early in the course of illness. The first ten days of onset of illness is important in COVID-19 like illness as it has been proposed the cytokine storm starts in second week of illness and the hyperinflammation phase is pronounced during day-5 to day-10 of onset of illness.[13&14]

Our finding is in contrast to the study finding of moreno et.al. [11] which can be due to different age group of the enrolled patients. Also, we followed only the clinical criteria for tocilizumab administration, whereas the study by they used both clinical and laboratory values like IL-6, and D-dimer. The accuracy of test result especially IL-6 affected by many parameters like sample collection, storage etc. which many a times make the test result unreliable. [15] Also the critical review of studies on the biomarkers by Giulia et. al suggests, study findings on the potential usefulness of CRP, PT, and D-dimer levels as biomarkers of COVID-19 severity are promising yet clinical usefulness remains to be established.[16] Limited literature about usefulness of the markers in predicting treatment responses necessitates confirmatory studies. The waiting period for the test results where critical time lost for decision making and timely availability of test was an issue for which we relied mainly on clinical criteria for tocilizumab administration. In a metanalysis by Emmanuel et al., they analysed 9 RCTs out of which 7 RCTs are exclusive on Tocilizumab.[17] The indication of tocilizumab varied in most of the studies where seven studies required a specific hypoxia threshold, four studies required a CRP threshold, and six studies required a pre-defined radiographic change. They have not found patient level factors predicting effectiveness of IL-6 inhibition however we found age of less than 50 years is an important factor to predict effectiveness of IL-6 inhibition (p=0.01). This probably attributed to the higher mean age of the patients enrolled in the studies making the impact of patient level factor played minor role. The RECOVERY trial which was single large study which contributed over three quarter of the overall study weighting in the analysis, mean age of the patients were 63 years where as our study the average age group being 51 years.[18]

In our study, though the baseline vital parameters on critical care admission were comparable in both the groups, the ROX scores average before tocilizumab administration and 24 hour average ROX scores following tocilizumab administration was significantly better in the survivor group (P=0.001). ROX score has been shown to help in assessment of progress and the risk of intubation in COVID-19 patients with pneumonia. However, failure to improve ROX score after Tocilizumab administration also seems to predict poor prognosis of COVID-19 patients.

Our study has some limitations too, which may be enumerated. A) The sample size is

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less, so future prospective studies with bigger sample size as well as retrospective studies can analyze collected data taking in to these parameters may help in providing complete insight to our study finding. B) Though all the patients admitted in critical care unit with severe COVID-19, still many patients must have in different grades of severity with regards oxygenation, and laboratory and radiological parameters which could have affected the outcome. C) laboratory and radiological parameters were not compared at the time of administration of tocilizumab.

D) The study subjects belonged to level 3 critical care only, there may be patients in level 2 also having higher IL-6 but clinically stable in the early stages of presentation and later shifted to level 3 care during which cytokine storm would have worsened, so going alone by clinical method, adding those patients would have improved our sample size and thereby generalisability.

Conclusion:

Tocilizumab, when given in the early stages of clinical worsening of COVID-19 related illness may be associated with better outcome.

Age may be an indicator of favourable outcome of IL-6 inhibitor therapy.

Failure to improve ROX Score within 24 hours after Tocilizumab administration is associated with poor outcome.

Limitations: This study was conducted in a single centre and hence cannot be extrapolated to the the general population

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Each author believes that the manuscript represents honest work and certifies that the article is original, is not under consideration by any other journal, and has not been previously published.

Availability of Data and Material:

The corresponding author is prompt to supply datasets generated during and/or analyzed during the current study on wise request.

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