Tocilizumab in Patients of Covid Pneumonia: A Comparative Study of In-Hospital Outcomes in a Medical College of Lucknow

Jalees Fatima[1], Vaibhav Shukla[2], Sunny Malde[3], Ruman Kugashiya[4], Amir Ansari[5], Aseem Yadav[6]

ABSTRACT

Introduction: Coronavirus disease (COVID-19) infection, an illness caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), has spread rapidly worldwide resulting in a pandemic. Aim: To study the "in-hospital outcomes of COVID 19 pneumonia", in patients who received or didn't receive tocilizumab.

Material and methods: This retrospective analytical study was conducted in the Department of Medicin at Era's Lucknow Medical College & Hospital, Lucknow, India between July 15,2020 to May 15,2021. Moderate and severe cases who received or didn't received tocilizumab were selected as case subjects having raised inflammatory markers & absence of any absolute contraindication for administration of tocilizumab. The inflammatory markers were evaluated twice; first on baseline of symptoms onset & Second 14±2 days of symptom onset or At least 48 hours after tocilizumab administration whichever is later in either group. We have applied WHO ordinal scale for assessment of clinical improvement in COVID 19 patients of both groups.

Results: Total 90 consecutive patients of Moderate & Severe COVID pneumonia were included in the study. There were 45 patients in both tocilizumab receiving and not receiving group. Both the had raised baseline inflammatory markers and there was a significant decrease in CRP, IL-6 & S. Ferritin levels in Tocilizumab receiving group post administration. Important side effects observed after administration of Tocilizumab were sepsis with MODS (11 patients), & thrombocytopenia with ecchymosis. There was a statistically non-significant difference (p-value-0.120) in mortality in both the groups.

Conclusion: Tocilizumab, a recombinant monoclonal antibody has been used as a rescue therapy in patients of COVID-19 having hyperinflammation. In the above study tocilizumab has demonstrated significant reduction of inflammatory markers post administration as compared to the group which has not received the drug.

Keywords: Covid Pneumonia, Tocilizumab, Cytokine Storm

INTRODUCTION

Coronavirus disease (COVID-19) infection, an illness caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), has spread rapidly so much so that WHO on 11 March 2020, the World Health Organization (WHO) declared it as a pandemic[1]. As of 17st January 2022, SARS-CoV-2 , has caused 32.8 Cr cases around the world, of which 55.4L people have died & rest have recovered so far. The clinical presentation of COVID 19, is highly varying with ranging from asymptomatic to severe pneumonia presenting with respiratory failure requiring mechanical ventilation to death [2]. India is recently faced third wave of COVID 19. The virus has mutated itself over last 2 years presenting with new variants like "Delta" and "Omicron". The population was naive to this variants which has resulted in increased virulence of organism combined with excessive hyperinflammatory response (Cytokine Release Syndrome) of the host immunity.

The immune mechanism behind this viral infection revolves around the production of α-interferon, TNF-α and secretion of IL-6 & IL-12. Due to this mechanism, there is formation of CD8+ specific cytotoxic T- cells, which along with CD4+ helper T-cells are involved in the production of antigen specific B-cells and antibody production [3]. Hence, when body is unable to carry an adequate immune response against the virus, this state of persistent inflammation results into Cytokine Release Syndrome (CRS) or Cytokine storm [4]. Since a patient having categorized as severe pneumonia due to COVID-19 develop clinical and laboratory features of CRS (high fever, intense fatigue & myalgia, and elevated serum inflammatory markers such as C-reactive protein (CRP), ferritin, D-Dimer & IL-6 levels). Due to CRS, there is apoptosis of epithelial cells and endothelial cells, and vascular leakage which finally results to ARDS, multiorgan dysfunction and even death [5].

Tocilizumab is a recombinant humanised monoclonal antibody of the IgG1 class, which is directed against both interleukin-6 (IL -6) receptors [6,7]. It is currently recommended for the treatment of rheumatological and immune mediated disorders [8,9]. Recently, tocilizumab has become one of the therapeutic options for the management of CRS or Cytokine storm in COVID 19 infection with variable effects on morbidity and mortality. Current literature has shown conflicting result of this drug on the outcome of COVID 19 pneumonia. The aim of this study was to assess in-hospital

[1]Professor and Head , Department of Medicine, Era's Lucknow Medical College, [2]Professor, Department of Medicine, Era's Lucknow Medical College, [3]Junior Resident Department of Medicine, Era's Lucknow Medical College, [4]Junior Resident , Department of Medicine, Era's Lucknow Medical College, [5]Junior Resident, Department of Medicine, Era's Lucknow Medical College, [6]Junior Resident, Department of Medicine, Era's Lucknow Medical College, India

Corresponding author: Dr. Jalees Fatima, Professor and Head , Department of Medicine, Era's Lucknow Medical College, India

How to cite this article: Fatima J, Shukla V, Malde S, Kugashiya R, Ansari A, Yadav A. Tocilizumab in patients of covid pneumonia: a comparative study of in-hospital outcomes in a medical college of Lucknow. International Journal of Contemporary Medical Research 2022;9(6):F1-F7.

outcomes in COVID 19 patients with pneumonia who received Tocilizumab.

MATERIAL AND METHODS

This retrospective analytical study was conducted in the Department of Medicine at Era's Lucknow Medical College & Hospital, Lucknow, India which is a dedicated 400 bedded COVID Centre with full equipped ICU. All moderate & severe COVID Pneumonia cases admitted between July 15,2020 to May 15,2021 were included. The main objective of study was to determine the effect of tocilizumab in patients of moderate and severe COVID 19 pneumonia in terms of clinical parameters of in-hospital outcomes & inflammatory markers pre- and post-administration as compared to those who didn't receive drug. Study includes all adult individuals diagnosed as moderate & severe COVID-19 Pneumonia Categorized according to ICMR guidelines for COVID 19[12]. Cytokine release syndrome was identified by laboratory reports showing rise in inflammatory markers such as CRP, Ferritin and IL-6 levels. The baseline data regarding patients' demographics, comorbidities, treatment, laboratory parameters (CRP, IL6, S. Ferritin, NLR, D-DIMER, HBA1c, LFT & KFT), and outcomes were retrieved from medical records. We excluded the patients who had present or past TB, were reactive for Hepatitis B, Hepatitis C & HIV viral markers. Serum Procalcitonin levels were done to rule

Variables		Tocilizumab Not Received (N=45)		Tocilizumab Received (N=45)		Chi sq	p-value
		No.	%	No.	%		
Age	< 40 years	0	0.0%	3	6.7%	3.42	0.490
	40 - 49 years	4	8.9%	5	11.1%		
	50 - 59 years	11	24.4%	11	24.4%		
	60 - 69 years	19	42.2%	17	37.8%		
	>= 70 years	11	24.4%	9	20.0%		
Sex	Male	32	71.1%	39	86.7%	3.27	0.071
	Female	13	28.9%	6	13.3%		
Comorbidities	T2DM	27	60.0%	27	60.0%	0.00	1.000
	HTN	24	53.3%	25	55.6%	0.05	0.832
	Bronchial asthma	4	8.9%	4	8.9%	0.00	1.000
	CAD	4	8.9%	4	8.9%	0.00	1.000

Table-1: Baseline characteristics

Variable	Reading time	Tocilizumab Not Received		Tocilizumab Received		Mann Whitney Test	
		Mean	SD	Mean	SD	z-value	p-value
Ordinal scale	1st	4.1	0.4	4.04	0.706	-0.19	0.847
	repeat	4.7	2.1	5.82	2.081	-2.86	0.004
	Significance	z=-0.91, p=0.365		z=-4.39, p<0.001			
TLC counts	1st	10428.9	5349.2	10153.33	4450.158	-0.14	0.891
	repeat	13393.5	6837.3	14048.87	7617.120	-0.21	0.834
	Significance	z=-2.37, p=0.018		z=-3.11, p=0.002			
NLR ratio	1st	13.9	10.7	13.92	10.713	-0.05	0.958
	repeat	18.4	13.0	18.35	12.996	0.00	1.000
	Significance	z=-1.14, p=0.255		z=-2.00, p=0.045			
Platelets counts	1st	187222	70498	188444	69869	-0.15	0.880
	repeat	193853	99959	205200	114514	-0.38	0.701
	Significance	z=-0.08, p=0.937		z=-1.55, p=0.122			
IL6 levels	1st	60.2	82.0	202.54	301.873	-3.54	<.001
	repeat	45.8	42.9	53.53	35.845	-1.62	0.106
	Significance	z=-0.38, p=0.705		z=-4.28, p<0.001			
CRP	1st	44.2	32.5	77.68	21.940	-4.75	<.001
	repeat	44.5	50.6	14.03	13.431	-3.16	0.002
	Significance	z=-0.36, p=0.718		z=-5.84, p<0.001			
S. ferritin	1st	368.4	227.9	549.48	302.033	-2.98	0.003
	repeat	525.6	368.7	404.66	265.103	-1.26	0.206
	Significance	z=-2.44, p=0.015		z=-3.83, p<0.001			
S PCT	1st	2.0	3.1	0.33	0.367	-2.85	0.004
	repeat	2.3	3.0	2.55	1.779	-4.09	0.129
	Significance	z=-0.67, p=0.506		z=-1.50, p=0.013			

Table–2: Intergroup and Pre to Post Test Comparison of Study Parameters

out Sepsis, other contraindications like thrombocytopenia and leukopenia were also ruled out. Written and informed consent was taken from next to kin before administration of Tocilizumab. Patient were receiving broad spectrum antibiotics, Corticosteroids, Anticoagulants & rest supportive management according to protocol. The inflammatory markers were evaluated twice; first on baseline (7±2 days) of symptoms onset & Second 14±2 days of symptom onset or At least 48 hours after tocilizumab administration whichever is later in either group. We also analysed outcomes on the basis of comorbidities. The clinical outcomes were assessed based on WHO Ordinal Scale which included functional disability, need & mode of oxygen support and survival or death.

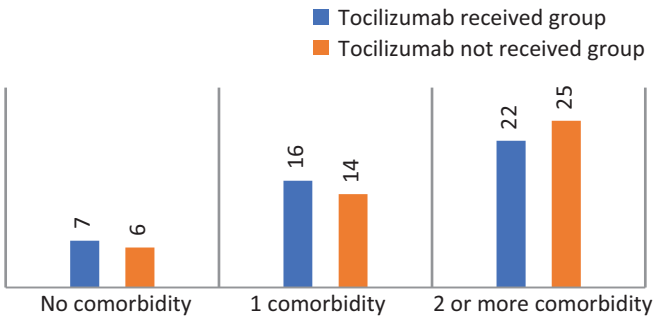

Figure-1 : Distribution of comorbidites in both groups

RESULTS

Out of 90 patients from both groups 13 patients (14.4%) had no comorbidity, 30 patients (33.3%) had either T2DM or HTN as comorbidity & 47 patient (52.2%) had 2 or more comorbidity (T2DM, HTN, CAD & Bronchial Asthma)

FIGURE 2. Shows comparison of both groups with kidney Function assessment at 7th and 14th day showed that more Kidney dysfunction was found in TOCILIZUMAB receiving group than not receiving group.

In figure 3&4 shows that Facemask and NRM were the most common modes of oxygen delivery with 37.8% and 35.6% proportion respectively. The final mode of oxygen delivery was mechanical ventilator in maximum in Tocilizumab group. However in tocilizumab not receiving group maximum patients were in Room air group followed by mechanical ventilator group.

Figure no. 5 shows the comparison of outcomes between both the group. Maximum Patient survived belonged to TOCILIZUMAB Not received group compared to TOCILIZUMAB received group. However maximum mortality was more in TOCILIZUMAB Receiving group

Out of all the study parameters, In TOCILIZUMAB Not

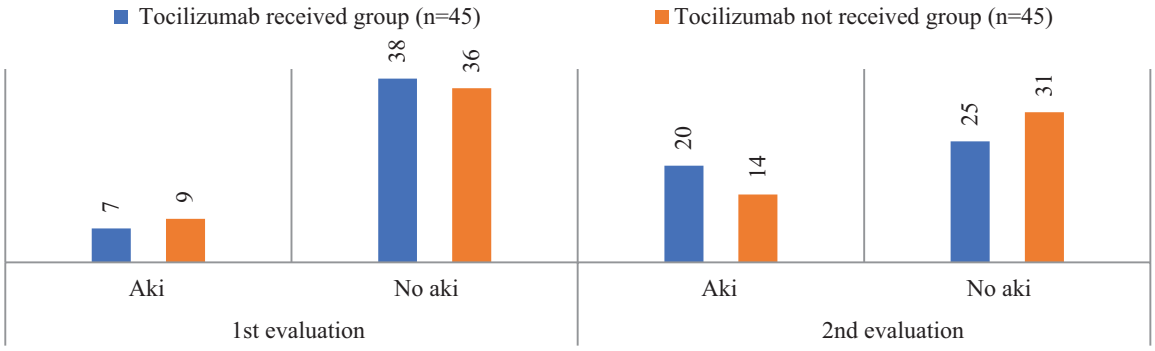

Figure-2 : Comparision of both group with AKI on two instances of evaluation

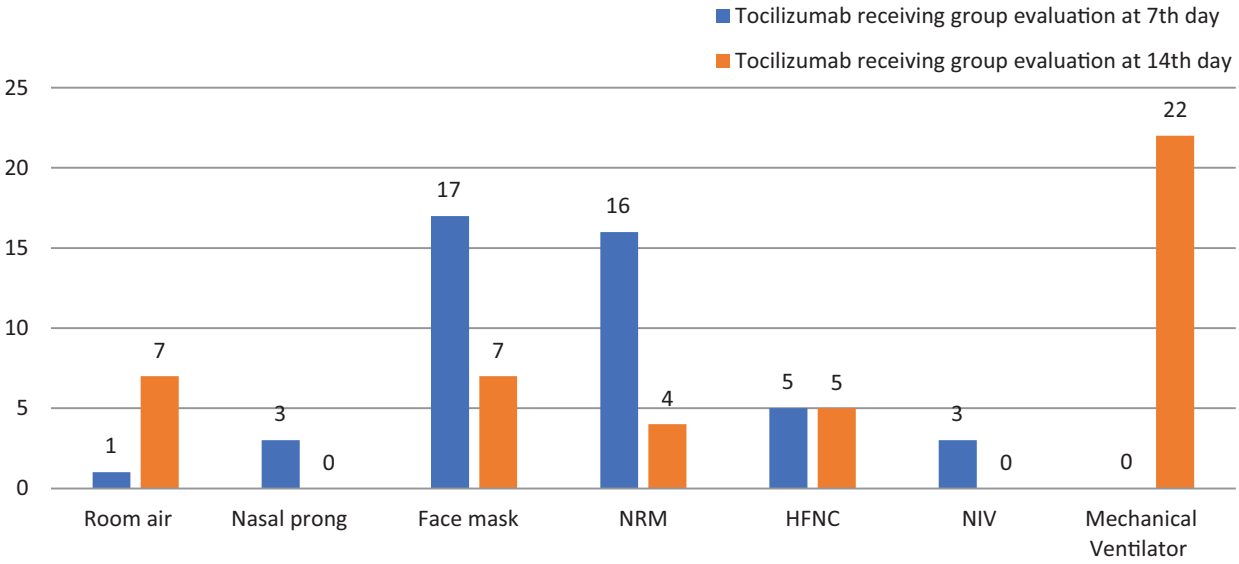

Figure-3: Evaluation of O2 mode of delivery in patients recieving tocilizumab at 7th and 14th day

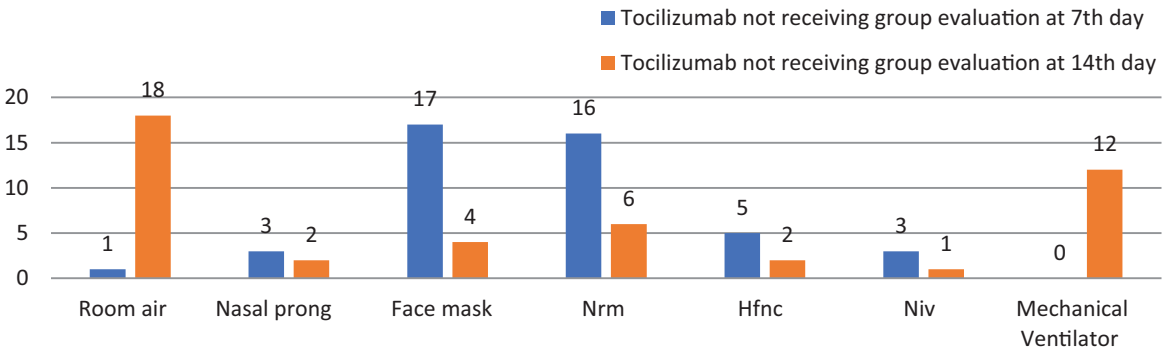

Figure-4: Evaluation of O2 mode of delivery in patients not recieving tocilizumab at 7th and 14th day

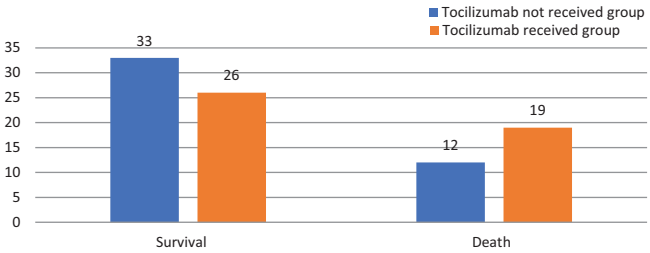

Figure-5: Comparision of outcomes in both group

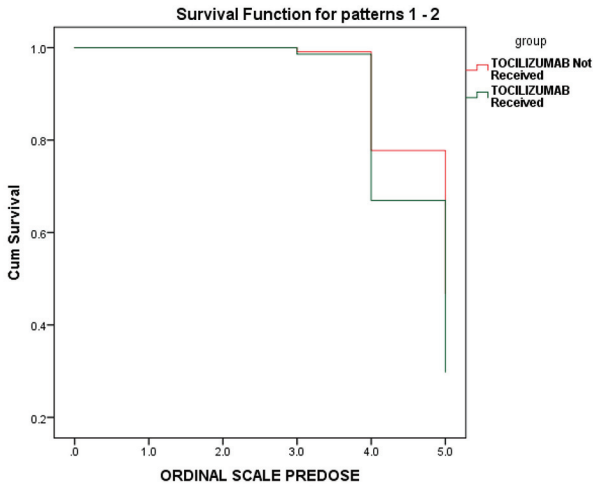

Figure-6:

Received group, significant changes from pre to post dose were observed in TLC count (p=0.018) and S.Ferritin (p=0.015) only. While in TOCILIZUMAB Received group significant changes from pre to post dose were observed in Ordinal score (p<0.001), FiO2 (p=0.035), TLC count (p=0.002), NLR ratio (p=0.045), IL6 level (p<0.001), CRP (p<0.001) and S. Ferritin (p<0.001).

Further at post dose, significant differences between the groups were observed for the parameters Ordinal scale (p<0.001), FiO2 (p=0.004), PaO2:FiO2 RATIO (p=0.037), CRP (p=0.002) and S PCT (p<0.001). Though in S Ferritin case significant difference is not observed at post dose, however it was increased in TOCILIZUMAB not Received group while decrease in TOCILIZUMAB Received group.

The regression equation to predict death is given by,

D = 2.740 + 0.744(T.received) – 0.595(Ordinal scale)

Death will be predicted if D > 0.

According to survival analysis though overall survival of TOCILIZUMAB Not Received was slightly more than the TOCILIZUMAB Received. However, no significant effect either positive or negative was found over final outcome

DISCUSSION

Tocilizumab is a recombinant humanized monoclonal antibody against human interleukin 6 (IL-6) receptor of immunoglobulin IgG1 subtype. Tocilizumab specifically binds soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits sIL-6R and mIL-6R-mediated signal transduction.

In our study which was retrospective analytical case control study, we have included 45 cases and 45 controls respectively. We have classified cases as those having a moderate and severe COVID infection at our institute which was level 3 COVID Care hospital having facilities of ICU and dialysis center. We selected subjects having age of ≥ 18 years either with or without comorbidities. After initial assessments of subjects, they underwent various biochemical investigations including CBC, CRP, S. ferritin, S. PCT, S.IL6 Levels & D-Dimer and were categorized in two groups. Those who received Tocilizumab and those who didn't receive.

Majority of the cases were belonging to the age group 60-69 years (42.2% & 37.8% in not received and received groups). Males were more in proportion than females (71.1% vs 86.7% in not received and received groups). No significant difference in proportion of age and sex was found between TOCILIZUMAB Not Received and Received groups (p>0.05). Muhammad zain Mushtaq et.al. have similar age group of 62.4 years and 33 males and 7 females [24]. The mortality was insignificantly higher among male patients (48.6%) than females (33.3%) in Received group. The mean duration of hospital stay was insignificantly higher (p=0.063) amongst Received group (13.44±7.712 days) than not received (12.75±7.78 days). Giovanni guaraldi et.al. showed statistically significant association of hypertension and diabetes, but no association with bronchial asthma, with outcome[25]. But in our study, there was no significant (p>0.05) association of outcomes with comorbidities. Among the two groups TOCILIZUMAB Not Received and TOCILIZUMAB Received included almost same proportion of comorbidities T2DM (60% in each group), Hypertension (53.3% & 55.6%), Bronchial Asthma (8.9% each) and CAD (8.9% each).

Doses of Tocilizumab used by majority of case reports and

series is 8mg/kg [25]. Luo et. al. in their case series had kept the dose in the range from 400 to 600mg[27]. In our study, majority of patients (n= 36, 81.6%) received one dose of tocilizumab & a lesser number (n=9,18.4%) received two doses of tocilizumab.

We have distributed oxygen delivery system as pre-dose (7th day) and post-dose (14th day) in Tocilizumab received and not received group and noted its association with outcomes. Facemask and NRM were the most common modes of oxygen delivery with 37.8% and 35.6% proportion respectively. The final mode of oxygen delivery was mechanical ventilator in maximum 37.8% cases followed by the room air (27.8%). The significant difference was found in TOCILIZUMAB Not Received and received group in final mode of oxygen delivery. While one patient from both groups was on room air at Day 7, there were around 15 patients from TOCILIZUMAB not received group and 7 patients from TOCILIZUMAB received group at 14 days. Most of the patients had improved oxygenation after receiving single dose of tocilizumab. The mean flow rate was insignificantly higher ($p>0.05$) among Tocilizumab group patients than not received group patients at 7th day & 14th day. Muhammad zain Mushtaq et.al found significant difference ($P<0.001$) in patient's oxygenation before and after tocilizumab[24]. In our study, the comparison of oxygen requirement with outcome was done which showed mean oxygen requirement was insignificant ($p>0.05$) higher among expired patients than alive at pre-dose. However, the mean oxygen requirement was significantly higher ($p=0.0001$) higher among expired patients than alive at post-dose. We found that the mean oxygen requirement was significantly ($p=0.0035$) higher amongst the received group at 14th day than at 7th day. We also found that the mean oxygen requirement was significantly ($p=0.004$) higher amongst the received group at 14th day with the not received group. Corrado campochiaro et.al. found clinical improvement on Pao_2:FIO_2 after administration of tocilizumab[28]. In our study, on a similar analysis the mean Pao_2: FIO_2 at 14th day analysis this ratio improved much in those who received tocilizumab as compared to those who didn't receive and the difference between the Pao_2:FIO_2 ratio of the two group became statistically significant $p=0.037$. While Pao_2:FIO_2 ratio at 7th day was statistically insignificant ($p>0.05$) in both groups.

We have distributed patients according to mode of oxygen delivery system (Facemask, Non-Rebreathable mask [NRM], High Flow Nasal Cannula [HFNC], Non-Invasive ventilator [NIV] & Mechanical ventilators on the basis of their O2 requirement at 7th day & 14th day of tocilizumab administration and not receiving it. Initially in both group Facemask and NRM were the most common modes of oxygen delivery with 17 patients (37.8%) and 16 patients (35.6%) at 7th day respectively in both groups. In the tocilizumab receiving group out of 17 Patients who were on Facemask at 7th day, 7 patients were still on facemask as oxygen mode of delivery comparing to no patients in TOCILIZUMAB not received group at 14th day. 16 Patients who were on NRM at 7th day showed higher rate of better outcome in terms of only 4 patients (8.9%) of not receiving group than 6 patients (13.3%) patients in tocilizumab group required NRM as mode of ventilation at 14th day. 5 patients who were on HFNC, there was high rate of mortality of 80% and around 1 patient of HFNC was alive. 3 Patients who were on NIV of which 2 patients died and a1 patient remained alive. Therefore, the mortality was higher among patients whom mode of oxygen delivery was HFNC (80%) than other modes at 14th day in both groups. There was no significant ($p>0.05$) association of outcome with mode of oxygen delivery at 7th day in both groups. Mechanical ventilation mode of delivery was in 22 patients (48.9%) in tocilizumab received group than only 12 patients (26.7%) who didn't received it at 14th day. We had about 22 patients on mechanical ventilation out of which 20 patients (90%) died to other complications related to ventilators and we have successfully extubated and discharged 2 patients in tocilizumab group. However in the TOCILIZUMAB not receiving group we had about 12 patients on mechanical ventilation out of which all died to other complications related to ventilators. About 7 patients were discharged on room air after 14th day who received tocilizumab & 18 patients who didn't received tocilizumab group. About 16 patients in tocilizumab group and 15 patients in didn't receive tocilizumab group were referred to Non-COVID facility for further management were on facemask, nasal prongs, HFNC & NRM respectively.

In our study, there was statistically significant ($p>0.05$) difference in TLC count between received and didn't receive tocilizumab patients at both 7th day and 14th day. Similar results were not found regarding difference in TLC count between expired and alive patients by case series by Giovanni Guaraldi et. al. [ref]. In a case series by Muhammad zain Mushtaq et.al. there was significant decrease in NLR ratio in patients who improved after administration of Tocilizumab [ref]. But in our study, we find that NLR ratio was increased at 14th day (18.35±12.996) compared to 7th day (13.92±10.713) in patients who received tocilizumab. This indicates that due to increase in NLR ratio at 14th day it signifies statistical significance mortality as outcome in patient who received tocilizumab. The mean NLR ratio was also insignificantly ($p>0.05$) higher among the patient who didn't received tocilizumab at 7th day (13.9±10.7) than at 14th day (18.4±13). However, the mean NLR ratio was insignificantly higher ($p>0.05$) amongst comparison of both group with each other. Giovanni Guaraldi et. al. in their case series also didn't find any significance of platelets after administration of tocilizumab & on its outcome [25]. Likewise, we also dint find any statistical significance platelet count between Tocilizumab received and didn't receive group at both at 7th and 14th day.

In our study, we found an interesting finding that the patients who died showed an significant decrease in CRP, IL-6 & S. Ferritin after Tocilizumab administration. This effect of can correlate that Tocilizumab have profound effect on inflammatory markers. Comparable results were obtained by Muhammad zain Mushtaq et.al. on CRP Levels on patient who expired following administration of Tocilizumab [24].

The CRP Levels were significantly reduced (p= <0.001) in tocilizumab received group at 7th day (77.68±21.94) than levels at 14th day (14.03±13.431) and were statistically insignificant amongst the patients who tocilizumab not received group. While the CRP levels were statistically significant (p= <0.001) amongst the patients who didn't receive tocilizumab & did received at 7th day and 14th day.

The mean IL-6 Levels were significantly reduced (p= <0.001) in tocilizumab received group at 7th day than levels at 14th day and were statistically insignificant amongst the patients who didn't receive tocilizumab compared at 7th and 14th day. While the mean IL-6 levels were statistically significant (p= <0.001) amongst the patients who didn't receive tocilizumab & did receive at 7th day & were statistically insignificant (p= 0.106) amongst the patients who didn't receive tocilizumab & received at 14th day.

The S. Ferritin Levels were significantly reduced in tocilizumab received group & not received group at 7th day than levels at 14th day . While the CRP levels were statistically significant (p=0.003) amongst the patients who didn't receive tocilizumab & did received at 7th day & were statistically insignificant (p= 0.206) amongst the patient's 14th day.

Among the study cases, the mean D- Dimer level of tocilizumab didn't received group was 1.47±1.34 while tocilizumab Received group it was 1.83±1.49 & it was statistically significant between the groups (p=0.039). While the S. PCT levels were statistically significant (p=0.004) amongst the patients who didn't receive tocilizumab & did received at 7th day & were statistically significant (p= <0.001) amongst the patients of both the groups at 14th day.

Adverse events were carefully monitored during the study period. We paid careful attention to the development of new episodes of infection following administration of tocilizumab, which include sepsis (7 patients) and Fungal sepsis (4 patients) in both groups. Interestingly we found 6 out them developed *Klebsiella pneumonia* and *Acinebacter baumanni* from tracheal cultures from both groups. So, its administration should be done very carefully and post administration we should check about any secondary infection which can occur.

CONCLUSION

Tocilizumab, a recombinant monoclonal antibody has been used as a rescue therapying patients of COVID-19 having hyperinflammation. In the above study tocilizumab has demonstrated significant reduction of inflammatory markers post administration as compared to the group which has not received the drug, however there is no significant difference in either group. The reason behind this may be severe immune paralysis done by tocilizumab which had led to increased incidence of opportunistic infections and sepsis related complications. It can be concluded that if we may provide ideal ICU settings and asepsis for the prevention of secondary infection in these patients then there can be some benefit derived in individual patients. Moreover, the timing of administration is also important because tocilizumab acts best when the patients in the early phase of cytokine storm or where the cytokine release syndrome can be anticipated or predicted by rising IL-6 levels. There is a transient improvement in clinical parameters in patients receiving tocilizumab on 7th & 14th day in clinical improvement ultimately did not translate into any mortality benefit.

REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; published online Feb 24.
2. BMJ 2020; 371 doi: https://doi.org/10.1136/bmj.m4857
3. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. (2020) 130:2620–9.
4. Cron R, Behrens EM. Cytokine Storm Syndrome. 1 ed. Cham: Springer Nature Switzerland AG; Springer International Publishing (2019).
5. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39:529–39.
6. Swerdlow DI, Holmes MV, Kuchenbaecker KB, et al. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. Lancet 2012; 379: 1214–24.
7. Norelli M, Camisa B, Barbiera G, et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. Nat Med 2018; 24: 739–48.
8. Kotch C, Barrett D, Teachey DT. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. Expert Rev Clin Immunol 2019; 15: 813–22.
9. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med 2017; 377: 317–28.
10. Ciascia S, Aprà F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatology 2020; 38: 529–32.
11. Klopfenstein T, Zayet S, Lohse A, et al. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. Med Mal Infect 2020; published online May 6. .
12. https://www.mohfw.gov.in/pdf/Updated Clinical Management Protocol for COVID19 dated 03072020.
13. Lau SK, Lau CC, Chan K-H, Li CP, Chen H, Jin D-Y, et al. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. J General Virol. 2013;94:2679– 90.
14. Yen Y-T, Liao F, Hsiao C-H, Kao C-L, Chen Y-C, Wu-Hsieh BA. Modeling the early events of severe acute respiratory syndrome coronavirus infection in vitro. J Virol. 2006; 80:2684–93.
15. Tynell J, Westenius V, Rönkkö E, Munster VJ, Melén

K, Österlund P, et al. Middle East respiratory syndrome coronavirus shows poor replication but significant induction of antiviral responses in human monocyte-derived macrophages and dendritic cells. J General Virol. 2016;97(Pt 2):344. Zhou J, Chu H, Li C, Wong BH-Y, Cheng Z-S, Poon VK-M, et al.

16. Active replication of Middle East respiratory syndrome coronavirus and aberrant induction of inflammatory cytokines and chemokines in human macrophages: implications for pathogenesis. J Infect Dis. 2014;209:1331– 42.
17. Smolen JS, Landewe RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79:685–99.
18. Firestein GS, Budd R, Gabriel SE, McInnes IB, O'Dell JR. Kelley's Textbook of Rheumatology E-Book. Amsterdam: Elsevier Health Sciences (2012).
19. Nishimoto Norihiro, Kanakura Yuzuru, Aozasa Katsuyuki, et al. Humanized an ti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood 2005: 106:2627-32, 143.
20. Ito Hiroaki, Takazoe Masakazu, Fukuda Yoshihiro, et al. A pilot randomized human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. Gastroenterology 2004; 126:989 -947.
21. Grupp Stephan A, Kalos Michael, Barrett David, et al. Chimeric antigen receptrial of tor-modified T cells for acute lymphoid leukemia The New England journal of medicine 2013:368:1509-18.
22. Winkler U, M, Manzke O, et al. Cytokine-release syndrome in patients V. Jensen with B-cell Chronic lymphocytic leukemia and high lymphocyte count after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2BS). Blood 1999:94:2217-24.
23. Instruction of Tocilizumab https://www.gene.com/download/pdflactemra. prescribing.pdf (accessed March 11, 2020).
24. Muhammad Zain Mushtaq, Saad Bin Zafar Mahmood, Bushra Jamil. Outcome of COVID-19 patients with use of Tocilizumab: A single center experience. International Immunopharmacology 2020;88:106926.
25. Giovanni Guaraldi, Marianna Meschiari, Alessandro Cozzi-Lepr et.al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol 2020; 2: e474–84.
26. Pan Luo et.al. Tocilizumab treatment in COVID-19: A single center experience. J Med Virol. 2020 Jul;92(7):814-818.doi: 10.1002/jmv.25801. Epub 2020 Apr 15.
27. Corrado Campochiaro , Emanuel Della-Torrea , Giulio Cavallia et.al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single centre retrospective cohort study. https://doi.org/10.1016/j.ejim.2020.05.021.

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 02-06-2022; **Accepted:** 15-06-2022; **Published:** 30-06-2022