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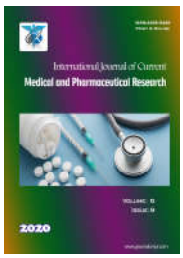

Research Article

STUDY ON EFFICACY OF TOCILIZUMAB IN MODERATE TO SEVERE COVID 19 INFECTION

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ABSTRACT

Background: Cytokine Storm Release (CRS) is considered as major culprit for high mortality in Covid 19. Tocilizumab has shown promising results in initial trials by controlling CRS. We present our observations on Tocilizumab use.
Methods: A retrospective case control study of total 39 adult patients of moderate to severe covid 19 infection admitted to dhiraj hospital was enrolled in this study.Out of total patients, 9 were given tocilizumab along with standard care of treatment assigned as group A and 30 patients were given standard care of treatment only assigned as group B. Data including clinical and laboratory parameter was collected and recorded on 1st and 7th day of admission in CRF.
Results: out of 39 moderate to severe RT PCR positive Covid 19 patients, only 9 patients received tocilizumab due to scarcity of drug and non affordability.Mean age was 54.22 ± 11.50 years and 7 were male in tocilizumab group. Statistically significant improvement was noted with ESR and Sr.LDH only. Other laboratory parameters (TLC,NLR,CRP, D-Dimer, Sr.Ferrtin) showed minor improvement only(p value =>0.05).High mortality was observed with tocilizumab group (4 out of 9 patients, 44.4%) compared to standard group (8 out of 30 patients;27%).
Conclusion: Toclizumab therapy is showing conflicting results as first line therapy for Cytokine Release Storm in Covid 19. Cautious use of tocilizumab is warranted till large scale RCT shows promising results.

INTRODUCTION

COVID-19 is caused by a novel coronavirus, named severe acute respiratory syndrome coronavirus 2. Beginning in December 2019, several patients with pneumonia emerged in Wuhan City, Hubei Province, Central China.This infection was declared as a pandemic by the WHO on March 11th 2020.[1] As of 10th Aug 2020, there have been 26 million confirmed cases of Covid-19, including 8,70,286 deaths, with a mortality rate of 3.2%, as reported by the WHO. The highest number of cases have been reported from USA, followed by Brazil.[2]In India first case was reported in January 2020 and as of now India has a reported 40.02 lakh cases with a total of 69,561 deaths with mortality of 1.7%.[2]

SARS CoV 2 and other viruses in the corona family (SARS CoV 1 and Middle East respiratory syndrome) infection induce a hyperinflammatory response resembling Cytokine Release Storm (CRS), with markedly elevated pro-inflammatory markers such as interleukins (IL1β and IL 6) , lactate dehydrogenase (LDH), D-dimer, ferritin, and procalcitonin (PCT) have been associated with lung damage and death which is independent of the actual viral burden and is usually seen following the acute phase of the disease[3,4]. At this time while there are a number of medicines being investigated for treatment and prevention of COVID 19 ,none have yet to demonstrate efficacy and safety in humans diagnosed with or exposed to COVID 19.

In the absence of specific effective treatment to prevent progression of respiratory symptoms in patients with SARS CoV 2 pneumonia, researchers have tried different monoclonal antibodies to block IL 1 and IL 6 receptor for the management of CRS with some success. Tocilizumab is a humanized monoclonal antibody which selectively targets the interleukin-6 (IL-6) receptor. Recently, tocilizumab has become one of the popular therapeutic options for the management of Cytokine Release Storm (CRS), a life-threatening complication of chimeric antigen receptor (CAR)- T cell therapy [5]. Since a proportion of hospitalized patients with respiratory failure due

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to COVID-19 develop clinical and laboratory features reminiscent of CRS (including high fever, intense fatigue and myalgia, and elevated serum inflammatory markers C-reactive protein, ferritin, and IL-6) [6,7], it was hypothesized that timely inhibition of inflammation by blocking IL 1& IL-6 receptors with monoclonal antibodies could be clinically effective for this population [8] .

We report efficacy of tocilizumab in patients of moderate to severe Covid 19 infection in addition to standard treatment.

METHODOLOGY

A retrospective case control study was carried out at Department Of Medicine in tertiary care centre, Dhiraj Hospital, Pipariya , Sumandeep Vidyapeeth from June to August 2020 after the approval from Ethics Committee.

Total consecutive 39 adult patients with RT-PCR confirmed Covid 19 infection having moderate to severe infection were enrolled in this study. During the study duration, all patients were eligible to receive tocilizumab. Out of 39 patients, 9 patients were given tocilizumab and remaining patients were not given tocilizumab due non availability and financial constrains. The decision to administer TCZ was based on the presence of any or all three of the following: SPO2 of ≤94%, PaO2/FiO2 less than 300 on room air laboratory indication of CRS as indicated by markedly elevated inflammatory markers (CRP, Sr ferritin, D dimer, ESR) and worsening respiratory status or persistent high grade fever.

Patients who had co-infection other than COVID-19; a PaO2/FiO2 ratio greater than 300 mm Hg; chronic or current glucocorticoid use; history of severe allergic reactions to monoclonal antibodies; less than 500 per µL neutrophils or less than 50,000 platelets; active diverticulitis, inflammatory bowel disease, or another symptomatic gastrointestinal tract condition that might predispose patients to bowel perforation; severe haematological, renal, or liver function impairment[9] were excluded. Patients who were given tocilizumab assigned as Group A and patient who were not given tocilizumab assigned as Group B.

After the admission, data regarding the presenting history, comorbidity status, contact history and vital signs were collected. Laboratory investigations like Complete blood count, coagulation profile, LFT, RFT, LDH, PCT ,CRP, ESR and D dimers along with radiological investigation like Chest Xray and if needed CT thorax were obtained. All patients received same treatment as per institutional protocol for standard of care.Along with the standard care of treatment, patients of Group A were given Tocilizumab intravenously at a dose of 400 mg . A second dose of 400 mg of tocilizumab was given after minimum of 12 hours duration based on treating physician opinion after evaluating the patient .Group received only standard care of treatment. Data including clinical and laboratory parameter was collected and recorded on 1st and 7th day of admission in CRF.

Statistical Analysis

Descriptive statistics (mean and standard deviation) have been assessed before and after the intervention. Paired t test was used to analyse the difference between the values before and after the intervention. The statistical significance is calculated at 95% confidence level with significance at less than 5%.

RESULTS

Total 39 patients admitted in our hospital with moderate to severe covid 19 infection having indication for tocilizumab as describe in methodology were included in this study . Out of these patients , 9 patients were given tocilizumab (Group A) and 30 patients who were not given tocilizumab (Group B). Mean age of group A was 54.22 ± 11.50 and that of group B was 56.81 ± 10.96. 7 were male and 2 were females in group A while 19 were male and 08 were females in group B. Majority of patients in both the group belongs to urban area. Most of the patients were of moderate category of illness in both the groups(Group A Vs Group B ; 55.5% vs 77%) at presentation. The mean duration of symptoms onset to hospitalisation was 4 days(2-8) in group A and 6 days(3-9) in group B. Mean PaO2 /Fio2 ratio of group A was 190±105.69 while that of group B was 154 ± 45.52(Table 1). Most common presenting symptoms were shortness of breath (67%%Vs 82%), Fever(55.5%Vs 57%) and Cough (55.5% Vs 48%) followed by Sore throat, Bodyache and Diarrhoea in both the groups in decreasing frequency. Comorbidities were present in 6(66.6%) patients and 18(60%) patients in group A and group B respectively. Hypertension was the most common comorbidity found in both the group followed by Diabetes, Ischemic Heart Disease and Hypothyroidism. (Fig.1, Fig.2)

Table 1 Demographic data and disease profile

Characteristics	*n*/ Percentage(%) / Mean/Range	*n*/ Percentage(%) / Mean/Range
Age (Years)	9 (54.22 + 11.50)	30(56.81 + 10.96)
Sex (M:F)		
Male	7(78%)	19(63.3%)
Female	2(22.2%)	11(37%)
Locality		
Urban	6(67%)	22(73.3%)
Rural	3(33.3%)	08(27%)
Category of illness		
1.Moderate	5(55.5%)	23(77%)
2.Severe	4(44.4%)	07(23.2%)
Duration Of Symptoms To Admission(DAYS)	4.3 (2-8)	5.8(3-9)
P/F Ratio	190.55 ± 105.69	154.93 ± 45.52

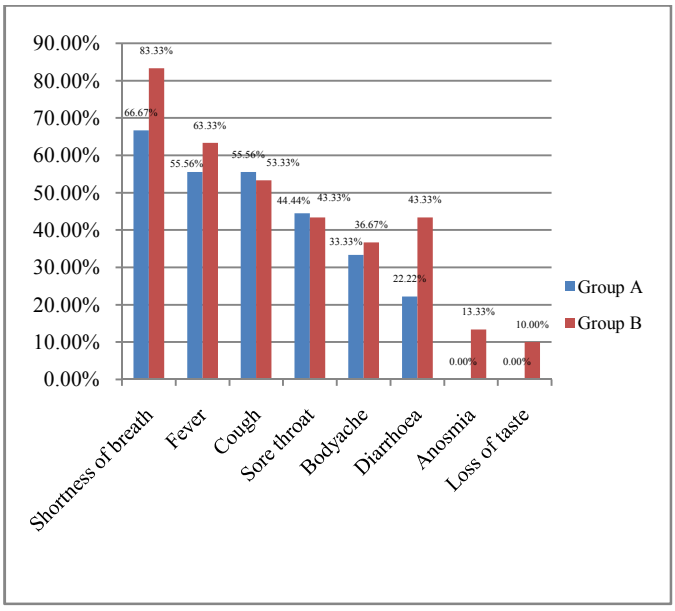

Figure 1 Frequency distribution of presenting symptoms in both the groups

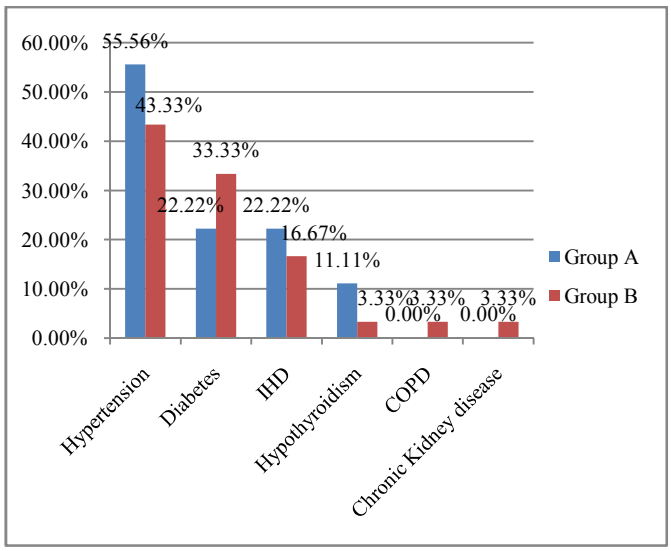

Figure 2 Frequency distribution of comorbidities in both the groups

We have assessed inflammatory markers, total duration of hospital stay and mortality between two groups to evaluate efficacy of tocilizumab in moderate to severe Covid 19 patients.

Difference of Mean was calculated for all inflammatory parameters (Total leucocyte count, Neutrophils to lymphocyte ratio, ESR, CRP, Ferritin, Ddimer, LDH) between values on admission and 7th day of admission for both the groups and analysed for significance using appropriate statistical tests (Table 2). No significant statistical difference noted in most of the specific inflammatory markers as shown in the table. Only ESR and Sr.LDH has shown statistically significant reduction in patients receiving tocilizumab as compared to those who receive standard care of treatment only.(Table 3)

Mean values of total leucocyte count and neutrophil to lymphocyte ratio were increased after tocilizumab administration, but the difference is not statistically significant. While in group B, the increase in total leucocyte count was more in comparison to group A and this difference is statistically significant **(p=0.009).** Mean values of other inflammatory markers i.e CRP and Ferritin were reduced after giving tocilizumab but the difference is not statistically significant as P value >0.05 for both. More reduction in mean CRP values noted in group B as compared to group A while mean ferritin was rather increased in group B. Though we could not show statistical significant for this finding.(Table 3) Surprisingly, Mean D-Dimer values were increased in both the groups, though the rise in value is less in patients who were given tocilizumab. Increase in P/F ratio which is considered as one of the important marker of clinical improvement was noted with tocilizumab group (p value = 0.722), while mild deterioration in P/F ratio is noted in patients of standard care of treatment. Positive effect of tocilizumab was observed for almost all markers of inflammation, but this difference is not statistically significant for most of them. Number of patients of were very less to extrapolate the beneficial effect of tocilizumab on inflammatory markers.(Table 3)

Table 2 Mean values of Inflammatory markers and other parameters

	Investigations		
Group A (n=09)	**On admission (Mean±SD)**	**7th day (Mean±SD)**	**Difference of mean(GroupA-Group B)**
TLC	7500 ± 4522.99	9588.88 ± 4446.47	-2088.88889
N/L Ratio	16.34 ± 16.51	20.32 ± 16.32	-3.98444
ESR	69.44 ± 26.40	24.66 ± 13.02	44.77778
CRP	56.41 ± 43.82	45.23 ± 58.93	11.18556
Ferritin	558.22 ± 378.56	511.88 ± 379.50	46.33333
Ddimer	2277.66 ± 3011.32	2912 ± 2099	-635.22222
LDH	874.88 ± 535.39	481.22 ± 279.64	393.66667
P/F Ratio	190.55 ± 105.69	201.77 ± 154.28	-11.22222
Group B(n=30)	**On admission (Mean±SD)**	**7th day (n=30)**	
TLC	9236 ± 5086.79	12776.66± 6340	-3540.00000
N/L Ratio	20.06 ±16.12	18.04 ± 15.90	2.02800
ESR	66.96 ±24.53	54.63 ± 24.02	12.33333
CRP	89.20 ± 67.49	65.52 ± 63.55	23.67500
Ferritin	523.33 ± 344.32	583.30 ± 379.2	-60.06667
Ddimer	1137 ± 876.77	2681.56 ± 2178.45	-1544.56667
LDH	694.30± 313.58	705.13 ± 359.30	-10.83333
P/F Ratio	156.10 ± 44.60	151.16 ± 86.97	4.93333

Table 3 Comparison of difference of mean in group A and Group B

Parameters	Group A (Mean Difference from Admission to 48 hours after tocilizumab)	P Value	Group B (Mean Difference from Admission to 7th day of admission)	P Value
TLC	-2088.88889	.378	-3540.00000	**.009**
NLR	-3.98444	.570	2.02800	.669
ESR	44.77778	**.008**	12.33333	.062
CRP	11.18556	.682	23.67500	.145
Ferritin	46.33333	.637	-60.06667	.465
D Dimer	-635.22222	.631	-1544.56667	**.001**
Sr.LDH	393.66667	**.035**	-10.83333	.877
P/F ratio	-11.22222	.722	4.93333	.744

4 out of 9 patients who received tocilizumab died (Mortality 44.44%) while 8 out of 30 patients who received standard care of treatment died (Mortality 26.66%).we could not able to calculate mean duration of hospital stay for tocilizumab group because of high mortality in the group can affect the result and can lead to wrong interpretation. No side effects were observed in tocilizumab group.

DISCUSSION

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus become global emergency. Despite emerging cluster of cases at this time, there are no proven therapies for the management of the disease Acute respiratory distress syndrome (ARDS) is the most devastating complication of SARS-CoV-2. It was indicated that cytokine-release syndrome and dominantly interleukin (IL)-6 play a central role in the pathophysiology of ARDS related to the novel 2019 coronavirus disease (COVID-19). Tocilizumab is a humanized monoclonal antibody which selectively targets the interleukin-6 (IL-6) receptor thereby reducing hyperinflammatory response had introduced as an effective off-label treatment option for moderate to severe covid 19 infection.

Earlier studies on effect of tocilizumab on moderate to severe covid 19 infection had shown promising results [10,11,12,13,14]. One of the retrospective observational cohort study on 1351 patients on effect of tocilizumab on severe covid 19 infection states that treatment with tocilizumab, whether administered intravenously or subcutaneously, might reduce the risk of

invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia[11]. Other study on appropriate use of tocilizumab states that earlier use of TCZ in COVID-19 infection is beneficial for survival, length of hospitalization, and duration of oxygen support[14] .

As the use of tocilizumab as off label treatment was increased , several researchers have shown conflicting results for the use tocilizumab [15,16] . Hence this study was conducted to evaluate the safety and efficacy of tocilizumab in moderate to severe covid 19 infection.

Some numerical reduction in mean values of most of the inflammatory parameters was observed in our study, but when compared with values of non tocilizumab group, no significant difference was noted. This marginal to moderate reduction in markers was not founf to be correlating with good clinical outcome.While most of the studies regarding effect of tocilizumab showed marked reduction in laboratory parameters especially inflammatory markers along with the clinical improvement[11,12]. Though the sample size for tocilizumab group is very less, mortality is quite high (4 out of 9 patients:44.4%) in tocilizumab group as compared to standar treatment group. In one of the retrospective cohort study published on 03 aug 2020 by J.Eimer *et al*, the administration of tocilizumab did not reduce all-cause mortality but was associated with a shorter time on mechanical ventilation and a shorter length of stay in hospital and in ICU in critically ill patients with ARDS due to COVID-19.[17]

Small sample size is a major limitation of our study. Because of very high cost of the drug, non affordability of patients and severe scarcity of drug in our region,we could not give drugs to many patients having indications as per standard regional treatment protocol. Another limitation is non-inclusion of IL-6 level comparison. IL-6 levels was not included as inflammatory parameter for indication or follow-up in tocilizumab treatment as per local government protocol.

CONCLUSION

Conflicting results were noted by various researchers for efficacy of tocilizumab in treatment of Cytokine Release Storm(CRS) in Covid 19 till now. A larger randomized controlled trial or large sample size studies are required to confirm the efficacy of tocilizumab. Till then cautious use of tocilizumab is advisable.

References

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KS, Lau EH, Wong JY, Xing X. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *New England Journal of Medicine*. 2020 Jan 29.
2. WHO | Coronavirus disease (COVID-2019) https://covid19.who.int/
3. Xu Z, Shi L, Wang Y, *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8:420-422.
4. Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223): 497-506.
5. Le RQ, Li L, Yuan W, *et al*. FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. Oncologist 2018;23(8):943–7.https://doi.org/10.1634/theoncologist.2018-0028.
6. Kaur S, Bansal Y, Kumar R, Bansal G. A panoramic review of IL-6: Structure, pathophysiological roles and inhibitors. Bioorganic Med Chem 2020;28(5). https://doi.org/10.1016/j.bmc.2020.115327
7. CDC COVID-19 Response Team. Geographic Differences in COVID-19 Cases, Deaths, and Incidence — United States, February 12–April 7, 2020. MMWR Morb Mortal Wkly Rep 2020.
8. Lee DW, Gardner R, Porter DL, *et al*. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124 (2):188–95. https://doi.org/10.1182/blood-2014-05-552729
9. Actemra (tocilizumab) [package insert], South San Francisco, CA: Genentech, Inc.; 2013.
10. Biran N, Ip A, Ahn J, Go RC, Wang S, Mathura S, Sinclaire BA, Bednarz U, Marafelias M, Hansen E, Siegel DS. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. The Lancet Rheumatology. 2020 Aug 14.
11. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, Franceschini E, Cuomo G, Orlando G, Borghi V, Santoro A. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. The Lancet Rheumatology. 2020 Aug 1;2(8):e474-84.
12. Patel A, Shah K, Dharsandiya M, Patel K, Patel T, Patel M, Reljic T, Kumar A. Safety and efficacy of tocilizumab in the treatment of severe acute respiratory syndrome coronavirus-2 pneumonia: A retrospective cohort study. Indian journal of medical microbiology. 2020 Jan 1;38(1):117.
13. Wang L, Peng X, Wang ZH, Cai J, Zhou FC. Tocilizumab in the treatment of a critical COVID-19 patient: a case report. European Review for Medical and Pharmacological Sciences. 2020 May 1;24(10):5783-7.
14. Keske Ş, Tekin S, Sait B, İrkören P, Kapmaz M, Çimen C, Uğur S, Çelebi İ, Bakır VO, Palaoğlu E, Şentürk E. Appropriate use of Tocilizumab in COVID-19 Infection. *International Journal of Infectious Diseases*. 2020 Jul 26.
15. Cortegiani A, Ippolito M, Greco M, Granone V, Protti A, Gregoretti C, Giarratano A, Einav S, Cecconi M. Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review. Pulmonology. 2020 Jul 20.
16. Klopfenstein T, Zayet S, Lohse A, Selles P, Zahra H, Toko L, Royer PY, Balblanc JC, Gendrin V, Conrozier T. Impact of Tocilizumab on mortality and/or invasive mechanical ventilation requirement in a cohort of 206 COVID-19 patients. International Journal of Infectious Diseases. 2020 Aug 13.
17. Eimer J, Vesterbacka J, Svensson AK, Stojanovic B, Wagrell C, Sönnerborg A, Nowak P. Tocilizumab shortens time on mechanical ventilation and length of hospital stay in patients with severe COVID-19: a retrospective cohort study. *Journal of internal medicine*. 2020 Jan 1.