Original Article

DOI: https://doi.org/10.47648/jswmc2022v1201-10

Assessment of The Effect of Tocilizumab in Adult Hospitalized COVID-19 Pneumonia Patients: A Clinical Trial

*Ahmad S[1], Salam MU[2], Patwary MI[3], Alam N[4], Taher MA[5], Ahmed MR[6], Goswami A[7], Jumma MA[8], Razzaque MF[9].

Abstract:

Background: Coronavirus disease 2019 (COVID-19) is a life-threatening infectious disease causing potentially severe acute respiratory infection which may lead to multi-organ dysfunction or failure due to severe acute respiratory syndrome coronavirus (SARS-CoV-2) also known as novel coronavirus (nCoV). Tocilizumab is anti-interleukin-6 receptor antibody may have potential role in minimizing mortality and mechanical ventilation requirements among hospitalized COVID-19 patients.

Objective: To analyze the effect of tocilizumab in adult hospitalized COVID-19 pneumonia patients.

Methods: This non-randomized, controlled, open-label trial was carried out at a tertiary care hospital, Sylhet, Bangladesh. Hospitalized COVID-19 pneumonia patients with hypoxia (oxygen saturation < 92% on air or required oxygen) and proof of systemic inflammation(C-reactive protein ≥50mg/L) were assigned (in 1:1 ratio) to receive a standard care plus single dose of tocilizumab (8mg/kg up to a maximum of 800mg) or only standard care, who were not provided mechanical ventilation. Primary outcomes were 28-day mortality and necessity of mechanical ventilation.

Results: The mean age was 59.08±12.39 years in tocilizumab group and mean age was 55.41±12.82 years in control group. Maximum patients were >60 years. The most common symptoms were fever (44.4%) then cough (38.9%), and others including diarrhoea, fatigue (33.3%). Majority risk factors were DM (47.7%) followed by HTN (30.5%). Mortality was more in control group than tocilizumab group which was 83.3% and 44.4% respectively. It is also observed that tocilizumab group patients needed mechanical ventilation significantly lower than the control group which was 19.4% and 44.4% respectively. The difference was statistically remarkable between the two groups (P<0.05).

Conclusion: This study shows that hospitalized COVID-19 patients who were not receiving mechanical ventilation,tocilizumab increased survival rate and reduced the need of mechanical ventilation.

Keywords: Effect of Tocilizumab, COVID-19 pneumonia, mechanical ventilation, anti-IL-6

JSWMC 2022[12(01)] P: 68-73

Introduction

COVID-19 disease is a potentially severe respiratory tract illness with variable multi organ dysfunction or failure resulting from SARS COV-2, first detected at Wuhan, China (December 2019).[1-2]

1. Shahed Ahmad, Assistant professor, Dept. of Medicine, SWMCH.
2. Mahjuba Umme Salam, Professor and head, Dept. of Medicine, SWMCH.
3. Md. Ismail Patwary, Professor, Dept. of Medicine, SWMCH.
4. Nazmul Alam, Consultant, Shahid Shamsuddin Ahmed Hospital, Sylhet.
5. Md Abu Taher, Registrar, Department of Medicine, AHHPL.
6. Md. Rajbir Ahmed, Registrar, Dept. of Medicine, SWMCH.
7. Ashis Goswami, Medical Officer, Dept. of Medicine, SWMCH.
8. Mashuq Ahmad Jumma, Assistant Registrar, Dept. of Medicine, SWMCH.
9. Moona Farzana Razzaque, Medical Officer, Dept. of Medicine, SWMCH.

Corresponding author: Shahed Ahmad,
Assistant professor, Dept. of Medicine,
SWMCH Sylhet, Bangladesh.
Email: doc.s.s.ahmad@gmail.com

Most COVID-19 patients have only mild symptoms, but approximately 10% to 15% have moderate to severe disease that requires hospitalization and oxygen support, and 3% to 5% require admission to intensive care unit (ICU) support.[2] Its severe cases complicated by acute respiratory distress syndrome (ARDS).[3]

COVID-19 patients with hypoxic respiratory failure is associated with systemic inflammation that releases pro-inflammatory cytokines, mainly interleukins (IL-1, IL-6) and tumour necrosis factor α, and found with elevated C-reactive protein (CRP), D-dimer and ferritin level.[4] The host's immunity is thought to play a vital role in

driving an acute inflammatory pneumonic process with diffuse alveolar injury.[5]

It is revealed that certain corticosteroids in COVID-19 patients with respiratory failure show some beneficial effects suggest that immunomodulatory agents might provide additional improvements in clinical outcomes.[6]

Tocilizumab, acts as recombinant humanized anti-IL-6 receptor monoclonal antibody that constrains binding of IL-6 to both membrane and soluble IL-6 receptors, blocks IL-6 signaling and help reducing inflammation. It is also used to treat a variety of diseases such as Rheumatoid arthritis (RA), Giant cell arteritis and cytokine release syndrome.[7] Besides, these patients with critical and severe COVID-19 have positive correlation with higher level of interleukin-6, whereas mild disease correlated with lower level of IL-6.[8-9] Randomized trials of tocilizumab in COVID-19 have so far demonstrated varied results for 28-day mortality.[10–12] Several studies documented the possible potency of tocilizumab for moderate, severe, or critical COVID-19.[13-15] The aim of this study was to determine the efficacy of tocilizumab in hospitalized adult COVID-19 patients.

Materials and methods

This was a single center non-randomized, controlled, open-label trial carried out in COVID unit of department of Medicine, Sylhet Women's Medical College Hospital, Sylhet from January 2021 to April 2021. Ethical approval certificate was taken from institutional research board (IRB). Sampling method was purposive. Hospitalized COVID-19 patients, aged ≥ 18 years confirmed by a positive SARS COV-2 nasopharyngeal swab via polymerase chain reaction (PCR) who had blood oxygen saturation (SPO_2) ≤ 92% on air and CRP ≥ 50 mg/L were eligible for enrollment. The patients were excluded from the study if they were receiving mechanical ventilation, tocilizumab is contraindicated or who expired within 48 hours of admission. Informed written consent was obtained from all patients or their legal representative in case of mental incapability. Total 72 patients were included, 36 in tocilizumab group and 36 in control group. The tocilizumab treatment group received a single intravenous dose of tocilizumab (8 mg/kg upto 800mg).

The control group only received standard care treatment. The standard care treatment included antivirals (remdesivir), anticoagulants, systemic glucocorticoids and supplemental oxygen. Outcome was assessed up to 28 days after being included in tocilizumab group versus control group. All the enrolled patients underwent thorough clinical history with particular emphasis on age, sex, duration of disease, clinical symptoms and laboratory investigations. Data was collected on predesigned data collection sheet. On the day number 4, 7 and 14, WHO Clinical Progression Score was collected. CRP, D-dimer and serum ferritin readings were documented at the time of admission and discharge. All the parameter including oxygen requirement and hospital staying period was documented.

The primary outcome was COVID-19 related mortality and requirement of invasive mechanical ventilation, while secondary outcome was hospital length of stay. Data analysis was performed on SPSS 25 (SPSS inc. Chicago, IL, USA). Means and standard deviation values were presented for all continuous variables, descriptive analysis was performed, for categorical variables numbers and percentages were used. Chi-square and student T-test were also used. Significance level was set at < 0.05

WHO clinical progression scale (www.who.int [16])

Patient state	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymtomatic; viral RNA detected Symptomatic; independent Symptomatic; assistance needed	1 2 3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy Hospitalised; oxygen by mask or nasal prongs	4 5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow Intubation and mechanical ventilation, pO2/FIO2, ≥150 or $SpO_2$2/FIO2, ≥200 Mechanical ventilation SpO_2/FIO2, <150 (SpO2/FIO2, <200) or vasopressors Mechanical ventilation SpO_2/FIO2, <150 and vasopressors, dialysis, or ECMO	6 7 8 9
Dead	Dead	10

Results:

After eligibility assessment 36 patients treated with tocilizumab and 36 control patients were incorporated in the study analysis. The demographic characteristics are discussed in Table I and II. This study showed, the mean age was 59.08±12.39 years in tocilizumab group and 55.41±12.82 years in control group (Table I). Male participants were 33.3% and females were 66.7%. Majority of patients were >60 years (Table II). The common symptoms were fever (44.4%) then cough (38.9%), and others (33.3%) (Table III). Commonest risk factors were DM (47.7%) followed by Hypertension (30.5%) (Table IV). Mortality was more in control group than in tocilizumab group which was 83.3% and 44.4% respectively. It was also observed that tocilizumab group patients needed mechanical ventilation less frequently than the control group which was 19.4% and 44.4% respectively. The control group had a longer hospital stay than tocilizumab group (19.55 ±9.38 vs 16.50±6.48) (Table VI)

Table I: Demographic characteristics of the study subject (n=72)

Characteristics	Tocilizumab group (n=36)		Control (n=36)		P value
	No	%	No	%	
Age in years					
21-30	0	00	2	5.6	0.461
31-40	5	13.9	6	16.7	
41-50	3	8.3	4	11.1	
51-60	10	27.8	12	33.3	
>60	18	50.0	12	33.3	
Mean±SD	59.08±±12.39		55.41±12.82		

Table II: Demographic characteristics of the study subject (n=72)

	Tocilizumab group (n=36)		Control (n=36)		P value
	No	%	No	%	
Sex					
Male	14	38.9	12	33.3	0.624
Female	22	61.1	24	66.7	

Data were analyzed using chi-square test

Table III: Clinical features of the study subject (n=72)

Clinical features	Tocilizumab group (n=36)		Control (n=36)		P value
	No	%	No	%	
Fever	16	44.4	17	47.2	0.813
Cough	14	38.9	15	41.7	0.810
Diarrhoea	0	00	1	2.8	0.314
Fatigue	6	16.7	1	2.8	0.047
Others	12	33.3	8	22.2	0.293

Data were analyzed using chi-square test

Table IV: Comorbidity of the study subject (n=72)

Comorbidity	Tocilizumab group (n=36)		Control (n=36)	
	No	%	No	%
DM	17	47.7	16	44.1
HTN	11	30.5	15	41.6
BA	3	8.3	2	5.6
Old MI	1	2.8	2	5.6
ALVF	3	8.3	1	2.8
MI	1	2.8	0	00
IHD	2	5.6	2	5.6
Hypothyroidism	2	5.6	0	0
CKD	0	00	1	2.8

Table V: Laboratory investigation of the study subject (n=72)

	Tocilizumab group (n=36)	Control (n=36)	P value
D-Dimmer	1.16±2.11	1.19±1.51	0.938
Ferritin	839.98±944.44	800.74±748.57	0.875
CRP	71.68±60.38	98.16±89.66	0.412

Data were analyzed using student T-test

Table VI: Outcome of the study subject (n=72)

Outcome	Tocilizumab group (n=36)		Control (n=36)		P value
	No	%	No	%	
Outcome					
Survived	20	55.6	6	16.7	0.001
Died	16	44.4	30	83.3	
Need ventilation					
Need	7	19.4	16	44.4	0.023
Not needed	29	80.6	20	55.6	
Hospital stay	16.50±6.48		19.55±9.38		0.116

Data were analyzed using chi-square test and student 't' test

ISSN: 2708-2857 (P), 2710-0405 (O)
2022 January; Volume 12; Issue 01

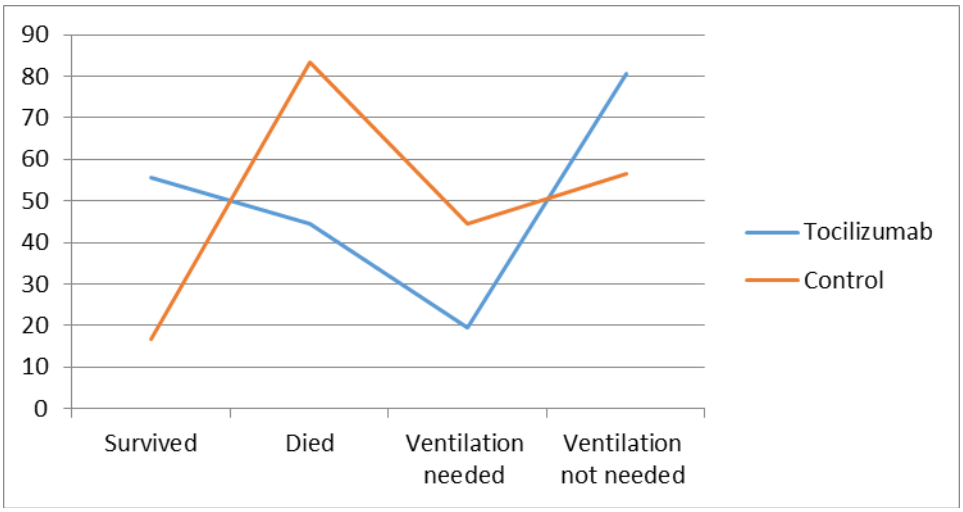

Figure 1: Effects of Tocilizumab on 28-day mortality and need of mechanical ventilation.

Discussion

This study shows that the mean age was 59.08±12.39 years in COVID 19 patients (Tocilizumab group) and mean age was 55.41±12.82 years in control group. Maximum patients were >60 years. This finding related to age was similar to other studies.[5] In Saliaj et al. study the average age was 62.5 years.[17] In COVID 19 disease older age group were the main contributors in most countries.[18] In current study it is found that the commonest of symptoms were fever (44.4%) then cough (38.9%), and others (33.3%). Cough and fever were globally regarded as main symptoms in previous studies.[5, 17] In consideration of symptom factors; cough was the main symptom of severe COVID-19[6, 10, 11]. In this study, majority risk factor were DM (47.7%) followed by HTN (30.5%).

Several studies reported that the diabetes and hypertension were significantly associated with the severity and mortality of COVID-19.[18] Another study in the United States observed that 58% of severely ill patients admitted in Intensive Care Units (ICUs) were with Diabetes mellitus, which exhibited an association between severe COVID-19 and diabetes mellitus.[16,17] Mortality from COVID-19 was apparently high among the patients with hypertension published in a Chinese study .[3] In this study, mortality was more in control group than tocilizumab group which was 83.3% and 44.4% respectively. It is also observed that requirement of mechanical ventilation was significantly lower in the tocilizumab group than control group which was 19.4% and 44.4% respectively. The difference was statistically noticeable between the two groups ($P < 0.05$). Here COVID – 19 deaths was defined as patients who died after being SARS-CoV2 rtPCR positive and consequence of the COVID-19. Primary cause of deaths was hypoxic respiratory failure due to severe COVID-19 pneumonia and or ARDS with or without multi-organ dysfunction.[19]

The tocilizumab group had a comparatively briefer median time to hospital discharge than the control group which was 16.50±6.48 and 19.55±9.38 respectively. Therefore, the findings of the research are in well agreement with the findings of other studies.[20] They reported patients who had undergone mechanical ventilation or expired by day 28, were remarkably fewer in number in the tocilizumab group (12.0%) than in the placebo (19.3%). Moreover, the median period to discharge from hospital or preparedness for discharge was about 6.0 days in the placebo class. As estimated with the seven-category ordinal scale in 28-day time period, the median period of improving clinical status was 6.0 days in tocilizumab group and 7.0 days with placebo. From previous clinical trials it is found that tocilizumab might have declined the discharge timespan or reduce the necessity of invasive mechanical ventilation or death.[21]

Eight RCTs of tocilizumab have been published since mid-2020 on COVID-19 that comprises seven small trials (< 100 deaths) and a larger REMAP-CAP trial, with critically ill patients. Out of which more than 99% patients required respiratory support either non-invasive or invasive.[22,23] An observational study demonstrated out of 10,021 hospitalized Covid-19 patients, 17% received mechanical ventilation. Consequently, mortality during hospital stay was higher in invasively ventilated group than the patient who did not require invasive ventilation (53% and 16% respectively).[24] In this study, tocilizumab group patients needed mechanical ventilation significantly lower than the control group which was 19.4% and 44.4% respectively. In recovery trial, it has also been observed that patient treated with tolicilizumab required less mechanical ventilator support.[18] Therefore; available data so far including our study findings could suggest the effect of tocilizumab in reducing necessity of mechanical ventilation is significant.

Conclusion

This study revealed benefits of tocilizumab in terms of reducing mortality and low requirement for ventilatory support, in comparison to the standard treatment. However, Physicians should be cautious regarding proper timing of administration of this medication and its potential side effects. Further studies should be conducted to determine the benefit of tocilizumab alone or combined with corticosteroids or other antiviral agents in COVID-19 patients.

Study Limitations:

1. Small population size was a limitation of the study, but this was due to scarcity and high cost of tocilizumab.
2. Single participant had been included in control group with early CKD, that was an exclusion criteria

Declarations

Funding: It was a self-funded study.

Conflicts of Interest: Authors declared no conflict of interest.

References

1. WHO.Naming the coronavirus disease (COVID-19) and the virus that causes it. Retrieved from WHO: https;//www.who.int/emergencies/diseases/novel-coronavirus2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus that-causes-it. 2020a:75-80.
2. Team TNCPERE: The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19). China CDC Weekly. 2020;2(8):113-122.
3. Hermine O, Mariette X, Tharaux PL,Rigon MR, Porcher R, Ravaud P, Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia A Randomized Clinical Trial. JAMA Intern Med. 2021; 181(1):32-40.
4. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8:475-481.
5. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med 2021; 384:1503-1516.
6. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 2020;27(6):992.e3-1000.e3.
7. Rubbert-Roth A, Furst DE, Nebesky JM, Jin A, Berber E. A review of recent advances using tocilizumab in the treatment of rheumatic diseases. Rheumatol Ther 2018;5:21-42.
8. Zhu J, Pang J, Ji P, et al. Elevated interleukin-6 is associated with severity of

COVID-19: a meta-analysis. J Med Virol 2020 May 29 (Epub ahead of print).
9. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: a meta-analysis. J Med Virol 2020; 92:2283-2285.
10. Pons S, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. Crit Care 2020; 24:353-353.
11. Cellina M, Orsi M, Bombaci F, Sala M, Marino P, Oliva G. Favorable changes of CT findings in a patient with COVID-19 pneumonia after treatment with tocilizumab. Diagn Interv Imaging 2020;101:323-324.
12. Michot J-M, Albiges L, Chaput N, et al. Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: a case report. Ann Oncol 2020;31:961-964.
13. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad SciUSA. 2020;117(20):10970-10975.
14. Roumier M, Paule R, Groh M, Vallee A, Ackermann F. Interleukin-6 blockade for severe COVID-19. medRxiv. Published online April 22, 2020.
15. Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol. 2020;2(8):e474-e484.
16. Marshall, J. C. et al. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect. Dis. 20, e192–e197 (2020).
17. Saliaj M, Li M, PharmD, Rizzo V, Nassar M, Nso N. Tocilizumab Treatment Reduces Mortality in Hospitalized Patients with COVID-19. Research Square 2021;1-27.
18. Horby PW, Landray MJ. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021; 397: 1637–45.
19. Bhaskaran K, Bacon S, Evans SJW et al; Factors associated with deaths due to COVID-19 versus other causes: population-based cohort analysis of UK primary care and linked national death registrations within the OpenSAFELY, volume 6, 100109, July 1, 2001; www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00086-7/fulltext#seccesectitle0001 (accessed 30 January 2022)
20. Salama C, Han J, Yau L, Reiss WG, Pharm.D., Kramer B, et al,Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2021; 384:20-30.
21. Veiga VC, Prats JAGG, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ 2021; 372: n84.
22. Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with covid-19 and moderate or severe pneumonia: a randomized clinical trial. JAMA Intern Med 2021; 181: 32–40.
23. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with covid-19 pneumonia: a randomized clinical trial. JAMA Intern Med 2021; 181: 24–31.
24. Karagiannidis C, Mostert C, Hentschker C, et al. Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 German hospitals: an observational study. Lancet Respir Med 2020;8:853-862.