JMSR
Journal of Medical and Scientific Research

ORIGINAL RESEARCH

Tocilizumab treatment and outcomes in severe COVID-19 patients: Retrospective study from a tertiary care institute in western India

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is a pandemic caused by a novel beta coronavirus severe acute respiratory syndrome coronavirus (SARS-CoV-2). The symptoms range from mild to severe in nature. The severity of respiratory symptoms is due to the cytokine storm. The tocilizumab, interleukin-6 inhibitor, can prevent the cytokine release and decrease the mortality.

Patients and methods: This is a retrospective observational study of 20 COVID-19 positive cases who received tocilizumab.

Results and conclusion: There were 75% males with a mean age of 47.20±9.68 years in our study. 50% had diabetes mellitus, 35% had hypertension, 5% had Chronic kidney disease, 5% had obesity and 5% had hypothyroidism. Mortality was reduced to 65% with tocilizumab administration. There was statistically significant reduction of C- reactive protein ($p<0.00052$) and IL-6 (interleukin) ($p<0.023$) after administration of tocilizumab.

Keywords: tocilizumab; interleukin-6; COVID-19; C-reactive protein

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Received 24 September 2020; *Revised* 9 November 2020; *Accepted* 17 November 2020; *Published* 25 November 2020

Citation: Peta RK, Panchal HP, Patel A, Parikh S, Khanikar D, Himthani N. Tocilizumab treatment and outcomes in severe COVID-19 patients: Retrospective study from a tertiary care institute in western India. J Med Sci Res. 2020; 8(S1):6-10. DOI: http://dx.doi.org/10.17727/JMSR.2020/8S1-1

Introduction

In the past century, there were four major global pandemics [1] (1918 pandemic by H1N1 Virus, 1957-58 pandemic by H2N2 virus, 1968 pandemic by H3N2 virus and 2009 pandemic by H1N1pdm09 virus), before the present coronavirus disease 2019 (COVID-19) pandemic. Severe acute respiratory syndrome coronavirus (SARS-CoV-2), a novel beta coronavirus, which caused coronavirus disease 2019(COVID-19) was first identified in China in December 2019 [2-4]. This was followed by global spread causing SARS-CoV-2 pandemic, that was declared by World Health Organization (WHO) on 11, March 2020 [5].

The SARS-CoV-2 causes mild to moderate illness in

majority of the patients. Presentation may vary from being asymptomatic to having clinical symptoms like fever and dyspnea, with or without pneumonia [6]. However, some of the patients may develop severe pneumonia with or without Acute respiratory distress syndrome (ARDS) and multiorgan failure requiring urgent admission to intensive care unit (ICU) for critical support and management [6, 7].

Currently, 215 nations are affected by COVID-19 pandemic [8]. In India, there are about 28 lakh cases with 54,000 deaths till 20th August 2020 [8]. There are no therapeutic options approved for COVID-19 and many antivirals, IL-6 inhibitors are being clinically evaluated for the therapeutic efficacy [9].

The pathogenesis of COVID-19 is unclear, but in severe cases there is laboratory evidence of systemic inflammation similar to cytokine release syndrome (CRS) with increase of proinflammatory cytokines like ferritin, IL-6, D dimer, etc. [10-12]. Hence, blocking of IL-6 can reduce the cytokine storm [10]. Tocilizumab (TCZ), a humanized monoclonal antibody is an IL-6 inhibitor is being used to treat rheumatoid arthritis, CRS induced by chimeric antigen receptor T-cell (CAR-T) therapy and other autoinflammatory conditions [13, 14]. In an initial single arm Chinese trial, administration of TCZ showed radiological improvement, reduction of body temperature and oxygen supplementation in 21 COVID-19 positive patients [15].

The aim of our study was to evaluate data and report the first experience with TCZ in 20 patients with severe SARS-CoV-2 infection in a Tertiary care Hospital in Western India.

Patients and methods

This was a retrospective observational study with inclusion of all SARS-CoV-2 RTPCR positive patients who received tocilizumab. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS), version 25.0. Descriptive analysis was presented as Mean ± standard deviation for continuous variables and percentage for categorical variables. Statistical tests of significance (paired t-test) was performed for analysis of survived patients excluding the expired patients. P-value of <0.05 was considered statistically significant.

Results

The 20 patients who were in ICU at the time of receipt of TCZ were evaluated for baseline characteristics and outcomes (table 1). The majority were males (75%, 15) and the mean age was 47.20±9.68 years. Comorbid conditions included diabetes mellitus (50%,10), hypertension (35%, 7), chronic kidney disease (5%, 1), Obesity (5%, 1) and hypothyroidism (5%,1). Of total patients, 6 (30%) were having single co-morbid conditions and 7 (35%) were having two comorbid conditions. Respiratory symptoms (80%, 16), myalgia (45%, 9), fever (35%, 7), cough (20%, 4) and others like headache, diarrhea were the major complaints. All patients have bilateral pulmonary infiltrates on chest radiographic images pre TCZ and improvement was seen post TCZ (Figure 1).

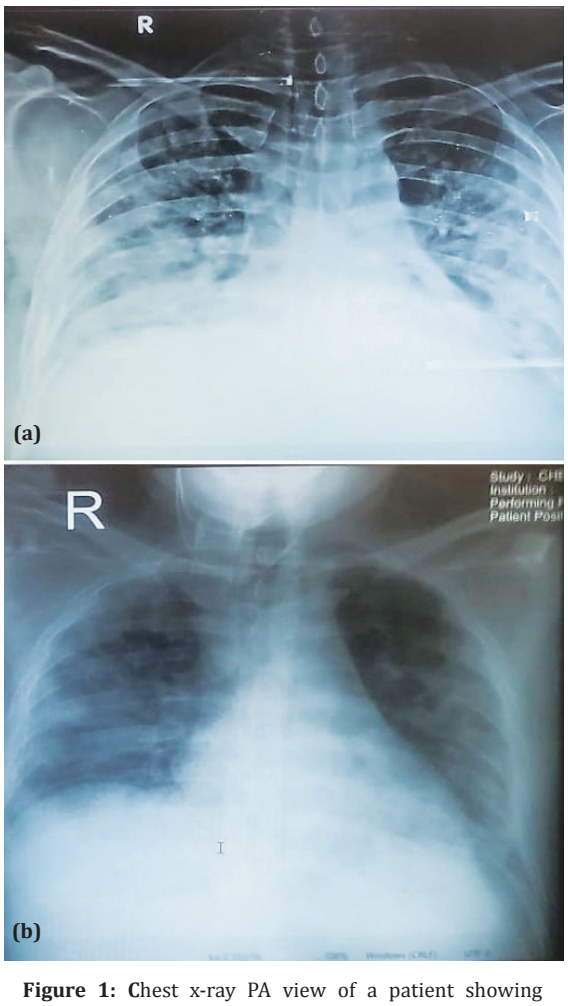

Figure 1: Chest x-ray PA view of a patient showing improvement after tocilizumab administration.

The procalcitonin was raised in one patient but the culture sensitivity was negative. There were

5 patients (25%) on NRBM (Non Re-Breather Mask), 12(60%) on BIPAP and 3(15%) on IPPV pre TCZ. Mortality reduced by 65%(13) after TCZ administration. The Mean duration of hospital stay for all patients was 13.90±8.44 days.

All patients were initially treated with azithromycin, hydroxychloroquine and methyl prednisolone. The patients who were progressing in symptoms and in radiographic images were then administered TCZ at a dose of 6-8mg/kg.

The mean IL-6 pre TCZ was 981.70±650.98. All patients were initially treated with azithromycin, hydroxychloroquine and methyl prednisolone, and were progressing in symptoms and in radiographic images. Patients were then administered TCZ at a dose of 6-8mg/kg. All patients who survived were evaluated for laboratory parameters pre and post TCZ (n=13). There was statistically significant decrease of C- reactive protein ($p<0.00052$) and ferritin ($p<0.023$) post TCZ administration (Table 2).

Table 1: Patient baseline characteristics (pre TCZ).

Patient characteristics (total number of patients N = 20)		
Age (Mean±SD)		Mean 47.20±9.68 years
Gender (%, frequency)	Female	25% (5)
	Male	75% (15)
Comorbid conditions (%, frequency)	Diabetes mellitus	50% (10)
	Hypertension	35% (7)
	Chronic kidney disease	5% (1)
	Obese (BMI >30)	5% (1)
	Hypothyroid	5% (1)
	1 comorbid condition	30% (6)
	2 comorbid conditions	35% (7)
	No comorbid conditions	35% (7)
Clinical symptoms (%, frequency)	Fever	35% (7)
	Myalgia	45% (9)
	Respiratory symptoms	80% (16)
	Cough	20% (4)
	Others (headache, diarrhea)	15% (3)
Complete blood count (Mean±SD)	Hemoglobin (gm/dl)	12.34±2.00
	Total leukocyte count ($x10^9$ /L)	9.626±4.176
	Platelet count ($x10^9$ /L)	256±107
Renal function test (Mean±SD)	Serum creatinine(mg/dl)	1.06±1.14
Liver function test (%, frequency)	Elevated liver enzymes	50% (10)
IL-6 (pg/ml) (Mean±SD)		981.70±650.98
Procalcitonin (%, frequency)	Negative	95% (19)
	Positive	5% (1)
Oxygen therapy (%, frequency)	Non Re -Breather Mask	25% (5)
	BIPAP	60% (12)
	IPPV	15% (3)
Treatment outcomes (%, frequency)	Survived	65% (13)
	Expired	35% (7)
Duration of hospital stay (Mean±SD)	For all patients	13.90±8.44 days
	For survived patients	17.69±7.55 days
	For expired patients	6.86±4.74 days

Table 2: Various parameters before and after tocilizumab in survived patients (n = 13).

Laboratory parameters	*Pre- TCZ Mean±SD*	*Post-TCZ Mean±SD*	*P-Value*
Hemoglobin (gm/dl)	12.13±2.01	12.60±1.86	0.308
Total leukocyte count (x10^9/L)	9.588±4.292	10.103±4.867	0.801
Absolute neutrophil count (x10^9/L)	8.171±4.251	9.433±5.688	0.571
Absolute lymphocyte count (x10^9/L)	1.008±0.625	0.981±0.695	0.893
Neutrophil lymphocyte ratio (NLR)	10.31±6.24	16.71±16.24	0.190
Platelet count (x10^9/L)	269±107	370±113	0.016
C- Reactive protein (mg/L)	79.69±55.57	7.93±8.11	0.000502
LDH (U/L)	549.83±229.23	433.08±137.25	0.147
D-dimer (ng/ml)	1862±4242.65	1219.54±1734.34	0.633
Ferritin (ng/ml)	660±564.43	387.70±318.52	0.023

Discussion

In our study we analyzed the patient baseline characteristics and outcomes in 20 patients. We also analyzed the laboratory parameters pre and post TCZ in the survived patients (n=13). The mortality decreased to 65% (13) after TCZ in our study with a Mean duration of hospital stay 13.90±8.44 days.

Several studies have reported the benefit of tocilizumab in severe COVID-19 patients [15-17]. Xu et al., in their study described 21 patients with severe to critical COVID-19 disease. Their study included 2 patients on mechanical ventilation and seven on oxygen supplementation. All patients were discharged alive after tocilizumab administration with no significant adverse effects [15].

Klopfenstein et al., in their case control study of 20 patients showed lower composite endpoint of mortality and ICU admission in the tocilizumab group. The difference in mortality in the standard therapy and tocilizumab group was not statistically significant [18].

In another study, Toniati et al., described 100 consecutive patients treated with multiple doses of tocilizumab for severe to critical COVID-19 disease. There was 18% mortality in patients receiving non invasive ventilation and 24% mortality in intubated patients. Only 15% patients are discharged [19]. Most of the studies had some pitfalls with small study sample and lack of control group.

Few studies have reported that tocilizumab is ineffective in treatment of severe COVID-19 pneumonia. Interim analysis of phase 3 randomized controls COVACTA trial of tocilizumab vs placebo, did not show improvement in mortality but decreased hospital stay by a week [20]. A randomized clinical trial done by Rosas et al., on 452 severe COVID-19 pneumonia patients showed that tocilizumab did not improve the clinical status or mortality [21].

Conclusion

Our study showed that there was 65% (13) reduction in mortality in patients with severe COVID-19 disease treated with TCZ. The mean duration of hospital stay in our study for all patients was 13.90±8.44 days. Many randomized trials are required for confirming the efficacy, effect on various laboratory parameters and also to know the adverse effects.

Limitations

The limitations of our study are that it is a retrospective observational single arm study. The size of the sample in the present study was small which is a limitation and the results cannot be generalized. The study excluded expired patients to compare the various parameters and inflammatory cytokines pre and post TCZ. This could lead to selection bias.

Conflicts of interest

Authors declare no conflicts of interest.

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