Research Article

Effect of Tocilizumab on Clinical Outcome in Patients with Severe COVID-19 Pneumonia

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ABSTRACT

In severe Covid-19 pneumonia, acute respiratory distress syndrome (ARDS) associated with cytokine storm is the leading cause of death. Tocilizumab was approved for chimeric antigen receptor T-cell therapy induced cytokine release syndrome and it may provide clinical benefit in these severe covid-19 pneumonia. In this retrospective cohort study, we evaluated patients with severe COVID-19 pneumonia admitted between May 2021 and June, 2021. Patients who were received tocilizumab during treatment, were enrolled for the study. Systemic steroids, hydroxychloroquine, and azithromycin were concomitantly used for the patients. The outcome was measured as an improvement in peripheral oxygen saturation by change in mode of oxygen therapy and improvement in laboratory parameters after tocilizumab administration. Out of 23 treated patients (18 Male, 5 Females), 19 patients received a single dose of tocilizumab and another four patients received two doses of it. Of these 23 patients, 3/3 with NRBM (non-rebreather mask) showed improvement and shifted to nasal cannula for oxygenation. 11/12 patients with NIV(non-invasive) showed improvement. 5/8 patients with invasive ventilation showed gradual improvement and shifted to NIV. A total of 4/23 (17%) patients didn't show any improvement and died. Inflammatory markers like CRP, percentage of lymphocytes, and ferritin also showed significant improvement after administration of tocilizumab. Our study showed that in patients with severe COVID-19, tocilizumab was associated with significant improvement in clinical and laboratory parameters. These findings require further validation from ongoing clinical trials of Tocilizumab in COVID-19 patients.

Keywords: Tocilizumab, TCZ, Covid-19, IL-6 receptor antagonist.

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INTRODUCTION

The coronavirus disease 2019 (covid-19) pandemic has led to massive demand for oxygen, invasive and non-invasive ventilation in a short period of time, causing significant worldwide health, economic, and social losses. Epidemiological data from various research have revealed the route of person-to-person transmission in COVID-19, responsible for its rapid spread.[1] This is the reason it has become a worldwide public health issue.

Asymptomatic infection to acute respiratory distress syndrome (ARDS), circulatory shock, multi-organ failure, and even death are all possible outcomes of this infectious disease.[2]

Common clinical features at onset include fever, cough, sore throat, and myalgia. It causes acute respiratory distress syndrome in extreme situations. Epidemiological data regarding the severity of disease varies from study to study. The majority of the study found that complications, primarily ARDS, are evident in 25-28% of hospitalized patients, and more than 30% require intensive care upon admission, with a mortality rate of up to 15%. Another study found that 17% of patients with covid-19 pneumonia developed ARDS with mortality up to 11%.[3]

ARDS is the leading cause of mortality in COVID-19 patients. The pathogenesis of ARDS in these patients is yet unknown; nevertheless, these patients have laboratory evidence of systemic inflammation similar to cytokine release syndrome (CRS), which leads to poor prognosis. CRS is marked by a surge in the production of a significant number of proinflammatory cytokines. CRS is marked by a surge in the production of a significant number of proinflammatory cytokines.[4] The activation of macrophages by infection, first in the lungs and later throughout the body, is an important source of pro-inflammatory cytokines and chemokines. IL-6 is one of these proinflammatory cytokines that has a key function in the development of ARDS.[5]

Symptomatic and supportive care are the mainstays of treatment for patients with Covid-19 pneumonia. Dexamethasone is the only therapy that has been shown to reduce mortality so far. Effective treatment is still lacking.[6] Immunomodulation has emerged as the most potential therapeutic strategy to COVID-19 in the absence of effective antiviral medications.[5]

Interleukin-6 (IL-6)–related cytokine storm has been proposed as a major target for the treatment of COVID-19. Thus, blocking interleukin 6 activity might play a role in reducing the inflammatory response and improve clinical outcomes in patients with covid-19.[7]

Tocilizumab, an anti–interleukin-6 receptor monoclonal antibody, has previously been approved by the FDA for the treatment of a variety of inflammatory diseases, including rheumatoid arthritis, and has been shown to improve outcomes in Covid-19 patients with high inflammatory biomarkers in observational studies conducted in the United States and around the world.[8] Tocilizumab therapy has been associated to lower hospital mortality in patients with COVID-19, according to several observational studies. We hereby report our experience with tocilizumab in hospitalized patients of severe COVID-19 pneumonia.

METHODS

In this observational study, we evaluated patients who were admitted to the Indira Gandhi Institute of Medical Sciences- Patna (India), diagnosed with COVID-19 by reverse-transcriptase-polymerase-chain reaction assay (RT-PCR) between 10 May 2021 and 15 June 2021, retrospectively. This State government declared this hospital a dedicated covid-19 tertiary centre during this period. Ethical approval for this observational study was obtained from ethics committee.

For this study, inclusion criteria were patients aged more than 18 years and diagnosed with severe covid-19 pneumonitis according to Covid-19 guidelines issued by the Ministry of Health & Family Welfare (MoHFW), Government of India. Severe covid-19 was defined as patients having a respiratory rate of > 30/min with breathlessness or having an oxygen saturation of less than 90% on room air. Patients with negative or unknown RT-PCR (Covid-19) reports were excluded from the study.

A total of 23 patients were included in the study who received tocilizumab in addition to standard treatment for Covid-19, as recommended by the National Clinical Management Protocol for Covid-19; MoHFW (INDIA). Tocilizumab was given to these severe covid-19 patients in view of clinical deterioration on standard treatment protocol, after ruling out the following contraindications; confirmed or suspected bacterial, fungal or tubercular infections, neutrophil count < 2000/mm3, and raised (more than three times the upper limit of normal range) alanine aminotransferase (ALT) or aspartate aminotransferase (AST), and intestinal perforation. The dose of tocilizumab was 4-6 mg/kg (400 mg in a 60kg adult), and it was given as a 60-minutes single intravenous infusion diluted in 100 ml normal saline.

Various clinical data of patients, including gender, age, coexisting disease, clinical symptoms, mode of oxygen therapy, use of invasive and non-invasive ventilation, laboratory parameters like total leucocytes count, lymphocytes percentage, CRP, IL-6, ferritin, and d-dimer, treatment given, adverse effects, and outcomes were collected. This study was mainly focused on the changes in clinical features and laboratory parameters after treatment with tocilizumab.

For statistical analysis, we use frequencies for categorical variables, and mean, median, and interquartile ranges for the description of continuous variables.

RESULTS

A total of 23 patients, who received tocilizumab were identified for the study. The average age of the patients enrolled was 55.4 ± 13.8 years and varied from 29 to 85 years. Out of 23 patients, 18 were males (78.26%), and 5 were females (21.73%). Out of 23 patients, 19 patients received a single dose of tocilizumab, and another 4 received two doses. All patients had complaints of fever, while cough was present in 86.95% (20/23), breathing difficulty was present in all patients (23/23) and chest pain or tightness in 8.69% (2/23). There was a mean time of 6.8 ± 2.2 days (range, 5 days to 9 days) from the onset of first symptoms to symptoms of breathing difficulty. All patients were on oxygen therapy. Before administration of tocilizumab, 13% (3/23) patients were on non-rebreather mask (NRBM) oxygenation, 52% (12/23) on non-invasive ventilation (NIV), and 35% (8/23) patients were on invasive mechanical ventilation. (Baseline characteristics are summarized in table.1.)

Table 1: Baseline Clinical Characteristics of Patients

Age (mean±SD)	**55.4±13.8**
Male: female ratio	18:5
Co-morbidities	
Hypertension	71%
Type 2 diabetes mellitus	37%
Asthma /COPD	18%
Chronic kidney disease	16%
Coronary artery disease	18%
Symptoms at presentations	
Fever	100% (23/23)
Breathing difficulties	100% (23/23)
Cough	86.95% (20/23)
Nausea/vomiting	21.73% (5/23)
Chest pain/chest tightness	8.63% (2/23)

White blood cell count was abnormal in 16 patients (mean 6.30 ± 2.77x10^9/L) and the remaining 7 had near normal values. Lymphopenia was present in all patients (mean, 15.52 ± 8.89%). The mean of D-Dimer was 0.80 ± 0.92mcg/ml. C-reactive protein (CRP) levels increased in all 23 patients at the time of presentation (mean, 75.06 ± 66.80mg/L). Before administration of tocilizumab, IL-6 level were estimated in all patients, and it was increased in all (mean, 153.44 ± 296.63pg/mL). HRCT chest revealed bilateral ground glass opacities mainly distributed in

peripheral areas, especially the sub-pleural region in all 23 patients.

Body temperature of all patients returned to normal on the very first day after receiving tocilizumab. The peripheral oxygen saturation showed marked improvement. All three patients with NRBM support showed improvement in the form of decreasing oxygen demand and a shift to nasal cannula oxygenation. Eleven out of twelve patients with NIV showed improvement in oxygen demand in the form of decreasing FiO2. The remaining one patient was given a second dose of tocilizumab as their condition deteriorated further. Five out of eight patients with invasive ventilation showed gradual improvement and shifted to NIV. And the remaining three patients didn't show any improvement. And the treating doctor didn't consider a second dose of tocilizumab for these patients on invasive ventilation. (Table 2.)

Table 2: Change in mode of oxygen therapy after tocilizumab administration.

Mode of oxygen therapy	Numbers of patient		
	Day 0	7-14 days	>14 days
On room air	0	0	6
Nasal Canula	0	2	8
NRBM	3	8	3
NIV	12	7	2
Invasive Ventilation	8	6	4

A significant change in the percentage of lymphocytes, CRP, and other inflammatory marker levels was observed after tocilizumab treatment, as shown in the table. On the 5th day after treatment, only four patients had abnormal values in white blood cell count, lymphocyte count, and CRP. The value of IL-6 was increased just after treatment with tocilizumab. (Summarized in Table 3.)

Table 3: Change in laboratory parameters with Tocilizumab administration.

	Day 0	Day 3	Day 7	Day 14
White cell count	6.30±2.77	8.05±4.39	6.02±3.05	5.25±2.11
Lymphocytes (%)	15±8.89	11.78±8.36	16.93±13.59	22.62±13.48
CRP	75±66.80	38.13±54.21	10.61±13.79	2.72±3.60
Ferritin	1689±122.56	1352±98.32	906±388.46	480±248.48
IL-6	153.44±296.33	129±131.79	300±341.90	274.9±414.08

Nineteen patients have been discharged, while four patients died during treatment. The mean hospital stay days after the treatment with tocilizumab were 17.6±6.8 days.

Adverse drug reactions, including elevated transaminase, neutropenia, infections, etc. are not recorded after tocilizumab administration.

DISCUSSION

Starting in February, 2020, when the first case of Covid-19 was identified in China, the pandemic quickly spread throughout the country, with increasing morbidity and mortality, causing an emergency-like situation around the world. As a result of the emergency, several off-label drugs are being used for its management like antiretroviral drugs, hydroxychloroquine, remdesivir, tocilizumab, and others.

Researchers have recommended repurposing IL-6 receptor antagonists to control the cytokine storm based on our current understanding of COVID-19's pathogenesis. Tocilizumab has gained traction as a potentially effective option for reducing IL-6-related fevers and preventing clinical deterioration in COVID-19.[9]

The effect of tocilizumab in the treatment of 23 patients with severe COVID-19 pneumonitis was evaluated retrospectively in this study. Data showed that symptoms, laboratory markers, and outcomes improved quickly in the majority of patients after therapy with tocilizumab. This is consistent with other observational studies that have found tocilizumab treatment to be beneficial.

In our study, clinical symptoms like fever, chest tightness, and dyspnoea showed improvement in 69% (11/23) of patients after 24–72 hrs of receiving tocilizumab. P. Taniatia et al. also reported rapid improvement in clinical and respiratory conditions in 58% (58/100) of enrolled patients after tocilizumab administration in their observational study.[8] In a retrospective study, T. Kewan et al. also reported improvement in body temperature, chest tightness, the respiratory functions to some extent in most of the patient after treatment with tocilizumab.[9] A recently published single-centre study also found that tocilizumab therapy improved the alveolar- arterial oxygen and the pulmonary vascular radiologic score.[10]

The peripheral oxygen saturation showed marked improvement in our study. 100% (3/3) of patients on NRBM support, 91% (11/12) on NIV support, and 62% (5/8) with invasive ventilation showed improvement during the course of treatment. 17% (4/23) of patients (one on NIV and three on ventilator) didn't show any improvement with treatment and died. The mean hospital stay days were 17.6±6.8 days. In a single-center observational study, P. Taniatia et al. also found improvement in respiratory functions in 83% (40/57) of patients, while 17% (10/57) of

patients died during treatment in non-ICU settings. And in ICU settings, improvement was seen in 76% of patients.[8] X. Xua et al. reported improvement in oxygen saturation in 75% of patients within five days of tocilizumab administration in their observation study. The mean hospitalization time was 15.1±5.8 days after treatment with tocilizumab.[11] In a study from Italy, authors reported improvements in oxygenation in 65% (37/57) of patients on invasive ventilation and in 74% (32/43) of patients on non-invasive ventilation.[8] All of these studies found that once a patient shifts to invasive ventilation, improvement is on the lower side, which is similar to our findings. Several large observational studies have also found significant reductions in the need for invasive mechanical ventilation (IMV) or all-cause mortality in COVID-19 patients treated with tocilizumab compared to standard of care alone.[12]

In an observational study, X. Xua et al. found that all patients had increased CRP, IL-6, and D-Dimer levels at baseline. And, 64% of patients had leukopenia, while 85 % of patients had lymphopenia. After five days of treatment with tocilizumab, only 10% of patients had an abnormal white blood cell count, and in 62% of patients, lymphocytes returned to normal. In 84% of patients, CRP dropped dramatically and recovered to normal. However, the value of IL-6 did not decrease considerably after tocilizumab administration. This is similar to the results of our research.[11] In a study by Italian researchers, all patients exhibited high levels of inflammatory markers such as CRP, fibrinogen, ferritin, and IL-6 at the time of tocilizumab administration. Ten days after treatment with tocilizumab, the lymphocyte count increased especially in better patients. CRP, fibrinogen, and ferritin levels fell into the normal range, while IL-6 levels rose in both improved and worsened individuals.[8] In the above mentioned research, elevated CRP levels were consistently found in COVID-19 patients. The decrease of the percentage of lymphocytes has been considered an important diagnostic and severity indicator. The level of IL-6 increased in all patients before treatment. Because tocilizumab has inhibition on the receptors for IL-6, as a compensatory effect its levels briefly rise in the days following treatment. Some case series also showed results such as fever resolution, decrease in inflammatory biomarkers, and improvement in oxygenation after tocilizumab for COVID-19 patients who required mostly non-invasive ventilation.[11] Another Italian study found that 62 COV-ID-19 patients treated with tocilizumab had a considerably higher chance of surviving than patients treated with a combination of hydroxychloroquine, lopinavir, and ritonavir.[13]

Contrary to observational studies, most of randomized trials the of tocilizumab, did not find a benefit with tocilizumab treatment. Salvarani et al. enrolled hospitalized patients in Italy with severe COVID-19 who needed oxygen by nasal cannula but did not yet require ICU-level care. Their objective was to see how early tocilizumab dosing (8 hours after randomization) affected the outcome. The trial was declared futile by the data and safety board after preliminary analysis revealed no indication of improvement in the primary endpoint.[14]

In the Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients with Severe COVID-19 Pneumonia (COVACTA), which enrolled 452 hypoxemic patients, tocilizumab showed no effect on clinical outcomes at 28 days.[15] The CORIMUNO trial included 131 hypoxemic patients and did not show an effect of tocilizumab on clinical outcomes at 28 days.[16]

However, Recent published randomized controlled trials have dampened enthusiasm for IL-6 antagonizing agents. But results of several ongoing clinical trials will provide more evidence on the role of TCZ in treating COVID-19 prior to routine clinical application.

Nevertheless, there are several shortcomings in this study. The number of patients was limited. It was a single observation study, and a significant bias could have possibly existed.

CONCLUSION

Despite the limitations, our findings have important clinical implications. Treatment with tocilizumab in patients with severe COVID-19 was associated with a reduction in improvement in clinical symptoms, and laboratory parameters and represses the deterioration of severe COVID-19 patients. Due to the observational nature of our study, these observations require further evaluation in clinical trials to determine the effectiveness of this treatment.

Ethics statement: Ethical clearance was obtained from the Institutional Ethical Committee (IEC), IGIMS to conduct this study.

The authors have equal contributions in the study.

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