Original Article

Effectiveness Of Tocilizumab In Reducing Inflammatory Response Associated With COVID-19 Pneumonia At Islamabad Medical Complex, Islamabad

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Abstract

Objective: To determine the effectiveness of Tocilizumab in covid-19 related severe pneumonia.

Introduction: COVID-19 is a global health problem causing respiratory infection. This is triggered by IL-6 characterized by raised inflammatory markers that are called cytokine release storms. Severe disease leads to hospitalization, oxygen requirement, and poor outcome.

Methods: This interventional study (descriptive-analytic) was conducted in July-December 2021 at Intensive Care Unit, after ethical approval. Seventy cases of COVID-19 pneumonia with cytokine storm were included. Twenty cases have dropped either refusal to tocilizumab, pregnancy, or having contraindications to tocilizumab, leaving 50 study participants. The patient's demography, clinical, laboratory, and radiological findings, timing, and response variables of tocilizumab were recorded. The temporal readings of inflammatory markers, oxygen requirement, and clinical status were compared at admission and after tocilizumab. SPSS version 25 was used for data analysis. The chi-square test was applied with a significant p-value < 0.05.

Results: There was a male predominance of 66% with a mean age of 58.6±14.8 years. The mean day of illness and hospital stay was the 8th day and 17.56 days respectively. C-reactive protein levels improved in all cases 50(100%) (p <0.0001), ferritin in 31(62%) (0.019), D dimers in 28 (56%) (p0.014), LDH in 30(60%) (p 0.02) and interleukin-6 in 32(64%) (0.017. Survival benefit with tocilizumab was significant in patients that received it within the 10th day of illness (p 0.021). At discharge, 66.6% were off oxygen and 33.3% required domiciliary oxygen.

Conclusion: COVID-19 Pneumonia with cytokine release storm bears high mortality. Significant improvement in inflammatory markers like CRP, ferritin, D-dimers and LDH shows the effectiveness of tocilizumab. Early administration within 10 days of illness has survival benefits.

Keywords: COVID-19 infection, Cytokine storm, Tocilizumab

Introduction

COVID-19 disease has rapidly evolved into a global health threat since its emergence in China in late 2019. The clinical presentations of COVID-19 are quite heterogeneous, ranging from asymptomatic to severe pneumonia with respiratory failure that could lead to acute respiratory distress or death.

The disease is characterized by an initial phase of viral replication that may be followed by a second phase driven by the host's inflammatory response.[1] Approximately 15% of patients infected with the COVID-19 virus develop the severe acute respiratory syndrome, associated with high mortality and immense burden on intensive care units for mechanical ventilation and supportive care.[2]

The exact mechanism of COVID-19-related injury is not well understood but possibly CD4+ associated T-lymphocytes are rapidly activated and differentiated into helper T cells, and these generate granulocyte-macrophage colony-stimulating factor (GM-CSF). The cytokine environment provides inflammatory monocytes with high production of inflammatory cytokines such as IL-6, IL-1, and tumor necrosis factor.[3]

IL-6 is of great importance in the pathogenesis of various inflammatory diseases including COVID-19 infection that leads to tissue damage ending in fast-paced fibrosis.[4] For this reason, tocilizumab, an IL-6 receptor antagonist, has been used to control this inflammation before tissue damage.[5-6] Tocilizumab is an immunosuppressive humanized monoclonal antibody that selectively competes and binds to the soluble expression on the IL-6 receptor and blocks the signaling pathways leading to inhibition of inflammation.[7,8,9]

Objective: The study was designed to assess the effectiveness of tocilizumab, an IL-6 receptors blocker, in reducing the cytokines-mediated inflammatory response leading to reduced oxygen requirement, and survival benefits in patients with severe COVID-19 pneumonia.

Materials and Methods

This interventional study (descriptive-analytic) was conducted at the Department of Intensive Care, after the ethical committee approval. The study duration was six months (July 01, 2021, to December 31, 2021).

COVID-19-associated cytokine release storm.

Its COVID-19 virus-related severe infection with raised IL-6 levels causing increased requirement of oxygen i.e., more than 5L/min; respiratory rate >30/min, fever ≥38°C, hypotension (systolic blood pressure <90 mmHg) and SPO2 less than 90% on room air. The raised inflammatory markers include CRP more than 10 times normal; D Dimers more than 1000ng/ml or 1mg/l, high ferritin levels of more than 600ng/ml, and serum LDH of more than 1000U/L.

Inclusion criteria

70 patients (age more than 18 years) of both genders were included by consecutive non-probability purposive sampling. Adults with confirmed COVID-19 pneumonia by positive COVID-19 PCR/antigen or radiology proven, having cytokine storm were included. Informed consent was taken from patients/families as per protocol.

Exclusion criteria

Patients below 18 years of age, pregnant women, and patients who didn't comply with consent and refused to receive the tocilizumab therapy, outdoor cases, left against medical advice, insufficient data, and those having absolute or relative contraindications to tocilizumab were excluded. Contraindications to Tocilizumab therapy are ALT or AST >5 times the upper limit of normal, hemoglobin <8.0 mg/L, leukocytes <2.0 g/L with absolute neutrophil count <1.0 g/dl, platelets <50 g/dl and raised creatinine levels more than 1.5mg/dl.

Data Collection & Analysis

50 indoor COVID-19-associated cytokine storm pneumonia cases meeting the inclusion criteria were enrolled. Study participants received oxygen therapy, BiPAP and ventilatory support where needed, appropriate antibiotics, chest physiotherapy, deep venous thrombosis, and stress ulcer prevention. All the cases received Tocilizumab was administered at a dose of 8mg/kg IV infusions in 100ml NS over one hour after confirmation of the cytokine storm. Daily clinical assessment, laboratory, and radiology investigations were carried out. The patient demography, clinical parameters, laboratory results, radiological findings, tocilizumab dosage, timing, and response to tocilizumab was recorded. Note: temporal readings of inflammatory markers, oxygen requirement, patient subjective feelings, and clinical parameters at admission and after tocilizumab were noted. All the data was entered into the specified proforma. The statistical package for social sciences (SPSS version 25) was used to record and analyze the

collected information. Descriptive and inferential statistical techniques were used to examine the significant impact. Moreover, a sufficient comparison between variables was carried out by using the Chi-square test. A p-value of < 0.05 was considered as a level of significance.

Results

The study included 50 cases of COVID-19-related severe pneumonia. There were 33(66%) males and 17(34%) females. The mean age was 58.6±14.8 years, with a range of 34-92 years. There were 26(52%) cases above 60 years age and 24(48%) cases below 60 years age.

12(24%) cases were COVID-19 PCR positive, 36(72%) were COVID-19 antigen positive and 2(4%) were diagnosed radiologically. The mean HRCT score was 23.38±8.02 (total score of 40). (*Figure 01)*

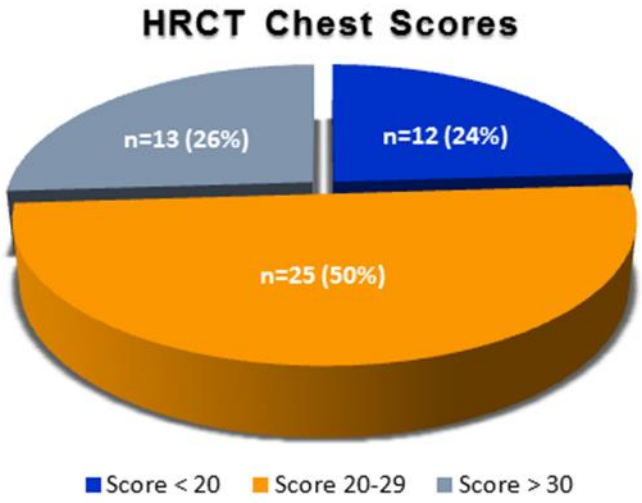

Figure 1: *HRCT Severity scores of COVID-19 Pneumonia cases that received Tocilizumab.*

The mean day of illness at admission was the 8th day (range 03-16 days). The mean hospital stay was 17.56 days (03-51 days). 13(26%) cases presented within 10 days of their illness, 19(38%) between day 11-20 and 18(36%) presented after 20th day of illness. Day of illness at admission and hospital stay were not associated with survival outcomes with a p-value of 0.601 and 0.734 respectively. Similarly, clinical conditions (patient's subjective feeling of wellness and chest tightness) improved with tocilizumab. (p <0.001) The overall survival rate was 42% (n=21) with a mortality of 58% (n=29). The response of tocilizumab on inflammatory markers is shown in Table 1 and variation in survival and non-survival is in Figure 2.

Table 1: *Tocilizumab response on inflammatory markers*

Parameters	*Mean (Admission)*	*Range*	*Improved*	*Worsened*	*P-value*
CRP (mg/dl)	11.44	8->2000	50(100%)	0(0%)	0.00
Ferritin (ng/ml)	1031	301->2000	31(62%)	19(38%)	0.019
D-Dimers (ng/ml)	1172	222 – 10736	28(56%)	22(44%)	0.014
LDH (µ/L)	558.15	272-1410	30(60%)	20(40%)	0.002
IL-6 (pg/ml)	91.96	7.8-556	32(64%)	18(36%)	0.017
O2 demand (litres)	12.46	0-16	20(40%)	30(60%)	<0.0001

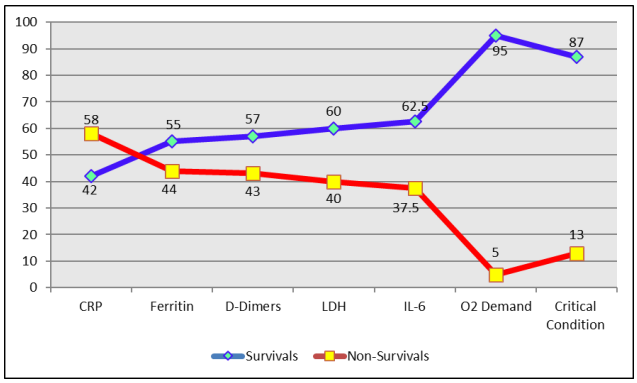

***Figure 2**: Percentage improvement trends with tocilizumab administration among survivals and non-survivals*

All patients at admission were on oxygen. The mean oxygen requirement at admission was 12.6±4.36 liters (0-16 liters) and 10.30±5.29 liters after tocilizumab administration (p=0.023). 40(80%) patients required BiPAP during their hospital stay. 66.6% of survivors were off oxygen at discharge while 33.3% required domiciliary oxygen (1-5 litre/min). overall reduction in oxygen demand was significant with tocilizumab administration p<0.0001.

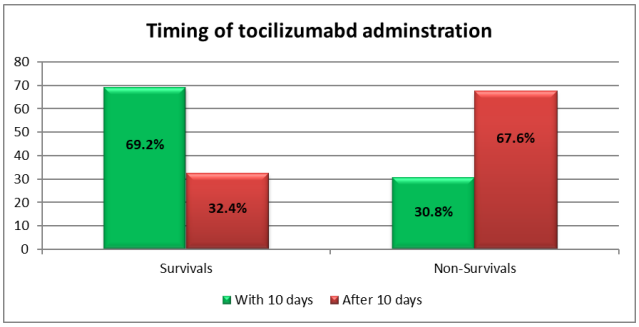

***Figure 3:** Survival benefit of tocilizumab administration, early (with 10 days) versus late (after 10 days) of illness (P=0.02)*

Discussion

The use of tocilizumab in COVID-related cytokine storms has been studied in the local population. The youngest case received tocilizumab was age 34 years while the eldest was 74 years. COVID-19 rapid antigen positivity rate was 72% in our study. Most patients presented after 10 days of illness in a critical phase, requiring oxygen therapy with an HRCT severity score between 20-30. Disease severity was accessed with biomarkers like CRP, ferritin, IL-6, D-dimers, and LDH. These indicators were significantly reduced with tocilizumab use. COIVD-related respiratory complications like tachypnea, chest tightness, oxygen demand, and critical status were also improved. The best response was seen in patients that received tocilizumab within 10 days of the start of the disease.

COVID-19 pneumonia bears high mortality[10] and patients with COVID-19 pneumonia fall into the moderately severe to the critical category of illness. In this study, a comparatively higher mortality of 58% even with tocilizumab was observed than in a multi-center study by Carbonell et al with 29-32% mortality.[11] The affecting factors that affect are public and healthcare workforce-associated demurrals, organizational and regulatory voids, and travel trends in the country.[12] Also the limited resources, lack of access to a health care facility, myths, and beliefs, socioeconomic factors, particular training, and the ratio of health care providers are additional factors.[13] There hasn't been consensus on a single test that can be considered as a specific marker to predict and monitor the response in COVID patients despite comprehensive studies with recent knowledge. The most reliable biochemical markers for disease severity and organ dysfunction are consolidated as c-reactive proteins, ferritin, d-dimers, and lactate dehydrogenase.[14] Therefore these biochemical markers are used for grading of disease[15] and monitoring of therapeutic response in COVID-19 patients.[16]

***Table-2** Response of tocilizumab on the inflammatory marker in COVID-19 infection*

Inflammatory markers	***Before Tocilizumab***	***After Tocilizumab***	***P-value***
C-reactive protein(mg/dl)	11.44 ± 7.09	2.49±2.91	p<0.0001
Serum ferritin (ng/ml)	1031 ± 651.6	951.7 ± 628.9	p=0.244
D-dimers (ng/ml)	1172 ± 2132	1766 ± 3134	p=0.077
LDH(µ/L)	558.5±211	648.5 ± 435	p=0.118
IL-6 (pg/ml)	91.96±93.09	120.97+215.76	p=0.346

Rising levels of inflammatory markers in relation to the severity of COVID-19 pneumonia have been

shown by Islamabad based study by Aziz-un-Nisa et al.[17] Response of tocilizumab was also analyzed in the same study that resulted in a significant reduction of c-reactive proteins, ferritin, d-dimers, and lactate dehydrogenase. IL-6 levels monitoring has been found markedly improved with tocilizumab in survivals by Quartuccio et al therefore IL-6 levels can be helpful to differentiate survivors from non-survivors.[18] In our study, mean IL-6 levels rose from 91.90pg/ml to 120.97pg/ml with tocilizumab and were not associated with a survival benefit (0.346). This could be due to the counter-inflammatory response of the studied population that needs to be investigated and validated with the randomized controlled trail.

Limitations: Exact duration of symptoms and severity prior to hospital presentation was subjective. Single-center study with a relatively small sample size without a control group during the delta variant phase of COVID-19 cannot predict the tocilizumab response for other variants. The study targeted the acute phase of COVID-19 infection and lacks long-term consequences. Multicenter, randomized studies including pregnant and pediatric population needs to be chalked out for a better understanding of COVID-19 infection.

Conclusion

COVID-19 Pneumonia with cytokine release storm bears high mortality. Early administration of Tocilizumab is found to have survival benefits. Survival indicators post tocilizumab are improved inflammatory markers, reduction in oxygen demand and step down from critical care unit.

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