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Effect of Tocilizumab on Clinical Outcome in Patients with Severe and Critical COVID-19 Infection in Kashmir Valley (North India): A Retrospective Observational Study

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Abstract

Aim and Objective: The aim and objective of this study was to determine whether Tocilizumab (IL-6 Inhibitor) improves the clinical outcome in patients with severe and critical COVID-19 infection.

Design: A retrospective observational single centre study in a COVID designated 170 bedded tertiary care hospitals in Srinagar, Kashmir (North India).

Method: Adults above 18 years of age with confirmed COVID-19 infection (RTPR positive nasopharyngeal swab) who were receiving supplemental oxygen and/or mechanical ventilation having abnormal levels of inflammatory Bio-Markers (CR, LDH, Ferritin and IL-6) were given 8 mg/kg body weight Tocilizumab + standard care.

Results: Out of 521 COVID-19 patients admitted 430 were moderate to severe in severity and 91 were critical COVID in severity. Out of 91 only 13 patients received tocilizumab due to off-label use, non availability of drug in pandemic, financial constrictions, contraindication to medicines and non-availability of consent. The mortality in Tocilizumab group was 10/13 (76.92%) while mortality in non Tocilizumab group was 61/78 (78.2%). IL-6 Levels had no correlation with severity and mortality in COVID-19. IL-6 Levels had no correlation with progression and outcome in COVID-19. Role of Tocilizumab in COVID-19 remains controversial.

Conclusion: Adding Tocilizumab to the standard care in severe and critically ill COVID-19 patients doesn't change the outcome.

Keywords: Interleukien; Tocilizumab; COVID-19; Monoclonal antibody

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Introduction

Infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2) causes Coronavirus Disease 2019 (COVID-19). COVID-19 has infected 32.8 crore people in the world. It has caused 3.74 crore infections in India till date. It has caused 55.4 lakhs deaths worldwide and about 4.86 lakhs deaths in India till date and still counting on. It is a worldwide disease [1,2]. It manifests as influenza like mild illness in 95% cases but only 3% to 5% cases proceed to severe infection and only 1% to 2% cases proceed to critical illness death [3]. Evidences suggest that the pathophysiological bases for the severe illness is severe inflammatory response characterized by marked release of inflammatory markers like CRP, LDH, Ferritin and IL-6. High Concentration of IL-6 [4,5] is associated with severe mortality and morbidity in COVID-19 infection [6-10].

This pathophysiology compelled the scientists across the globe to focus on IL-6 receptor blockade to prevent the progression of moderate and severe COVID to critical illness and death due to it [11-13].

Tocilizumab is a humanized monoclonal antibody that binds IL-6 receptors and halts the IL-6 mediated Cytokine storm [14,15]. This drug is routinely used in many inflammatory disorders like Inflammatory Arthritis, Cytokine storm related to chimeric antigen receptor t-cell therapy and Giant Cell Arteritis. Many therapies were introduced in treatment of COVID-19 infection in the form of hydroxychloroquin, azithromycin, anti virals [Remdesivir [16], steroids [17] (Dexamethasone and Methyl Prednisolone)]. With limited success from the above therapies and early observations from China showing high risk of death from COVID-19 infection in patients with elevated levels of IL-6 suggesting beneficial effects from tocilizumab [14,15].

With this level of evidence off label use of tocilizumab became standard care for patients of COVID-19 infection with high IL-6 and other markers of inflammation. Based on these pathophysiological features, Chinese observations and few Randomised Control Trials (RCTs), both off label and on label use of tocilizumab became a routine practice worldwide including India. However, the results from COVACTA and EMPACTA multicentric trials and many observational studies on tocilizumab on COVID-19 till date compelled us to step back and reconsider the proper placement of tocilizumab in COVID-19 protocol algorithm [13].

Material and Methods

This observational, Retrospective single centre study was conducted in SKIMS Medical College Hospital Bemina Srinagar, Kashmir (a tertiary care COVID designated 170 bedded hospital). 521 patients admitted in this hospital in year 2021 were all those patients who were full filling the criteria of moderate to severe COVID i.e.: Respiratory rate >30/min with SPO2 less than 92% on room air, fever >38 degree Celsius, Respiratory infection or need for oxygen with at least one of the following lab criteria:

a. CRP >50 mg/litre

b. Ferritin >500 ng/ml

c. LDH > 250 u/l

d. IL-6 >30 pg/ml

e. SPO2 <92 on oxygen

f. Patient on high flow oxygen

g. Patients who need high flow oxygen/HFNC/Ventilation within 24 h of admissions

With consent for treatment and availability of medicine (tocilizumab).

Following exclusion criteria was used:

- Hypersensitivity to drug
- Uncontrolled severe infection other than COVID
- Diverticulitis
- ANC <500
- Platelets <50,000
- ALT >5x normal
- Increased risk of gut perforation (Severe Diverticulitis)

Outcomes used were primary and secondary outcomes.

Primary outcomes included:

- Intubation after death of Tocilizumab use
- Death before/after intubation after intake of Tocilizumab

Secondary outcomes were clinical worsening defined on ordinal clinical improvement scale with scores of:

1. Discharge from hospital
2. Shift to Non ICU ward without oxygen
3. Shift to Non ICU ward with oxygen
4. ICU/Non ICU NIV/HFNC
5. ICU with mechanical ventilation
6. ICU with ventilation + Organ Support
7. Death

Results

Total patients admitted in the year 2021=521

Severity

1. Moderate to severe = 430
2. Critical = 91

Patients (Critical COVID) who received tocilizumab =13

Patients (Critical COVID) who did not receive tocilizumab =78

Mortality in Tocilizumab group =10/13 (76.92%)

Mortality in Non-Tocilizumab group =61/78 (78.2%)

Tocilizumab group

Median BMI = 26

Hypertension = 8/13

CAD = 0/13

MI = 0/13

COPD = 1/13

CKD = 0/13

Obese = 0/13

Stress hyperglycemia = 6/13

Median Hb = 13.2 Median TLC = 16.2

Median ALC = 1700 Median Blood Glucose Random = 185

Median LDH = 1026 Median Ferritin = 1200

Median CRP = 124 Median IL-6 = 200

Age greater than 60 = 8/13 (61.53%)

Male:Female = 8:5

Discussion

Our findings do not provide support for early IL-6 Blockade concept in the treatment strategy of moderate to severe COVID-19 patients admitted in hospital. Logic behind our study was that adding IL-6 Inhibitors in severe COVID patients that had not been yet intubated will stop or decrease the cytokine storm associated with disease and would prevent Intubation, Morbidity and Mortality associated with severe COVID but the results from this retrospective observational study indicated that this intervention with IL-6 inhibitor (Tocilizumab) had to significant effect on the risk of intubation, death or disease worsening and on time to discontinue supplemental oxygen. The results of this study correspond to many worldwide studies showing IL-6 inhibitor is not beneficial in 30 day mortality [11,12,18,19]. Our study results stand in contrast to many trials some of which suggested that IL-6 blockade had good results on outcome of patients with severe COVID-19 infections [20].

Our observations are in tandom with results of many clinical trials [21,22] that IL-6 inhibitors are not beneficial in severe and critical COVID-19 infection. Our results also confirm the relationship

between high blood sugars and poor outcome in COVID-19. Our study also confirmed that there is no correlation between severity of COVID-19 and IL-6 levels. IL-6 levels also do not reflect the progression and outcome of COVID-19. Role of IL-6 inhibitors is hence controversial as proved by our study.

This study has certain weaknesses like the small sample size but in view of financial constrictions, poor socio-economy, non-availability of medicine (Tocilizumab), absence of health insurance, limited supply of medication during pandemic and refusal of consent for treatment and discouraging results of many studies were the various reasons for this small sample size. Hence we conclude our observations in this study that blockade of IL-6 receptors in severe and critical COVID have discouraging results.

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