Original Article

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

Abdul Ahad Wani, Manzoor Teli, Nath Mohd Yousuf , Tariq Bhat , Muzafar Naik , Mubarik Naqash , Jawhar ul Islam , Malik Latief ,Aamir Shafi.

Abstract

Aim and Objective

The aim and objective of this study was to determine whether Tocilizumab (IL-6 Inhibitor) improves the 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 hospital in Srinagar, Kashmir (North India).

Method

Adults whose age was above 18 years with confirmed COVID-19 infection (RTPR positive nasopharyngeal swab) who were on supplemental oxygen and/or invasive mechanical ventilation having significantly elevated levels of inflammatory Bio-Markers(CR, LDH, Ferritin and IL-6) were given 8mg/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 questionable.

Conclusion

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

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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[1]. It has caused 3.74 crore infections in India till date. It has caused 55.4 lakh deaths worldwide and about 4.86 lakh deaths in India till date and still counting on. It is a worldwide disease[2]. It manifests as influenza like mild illness in 95% cases but only 3-5% cases proceed to severe infection and only 1-2% cases proceed to critical illness[3]. Evidences suggest that the patho-physiological bases for the severe illness is severe inflammatory response characterised by marked release of inflammatory markers like CRP,

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Keywords

Interleukein 6, Tocilizumab,Covid-19, Monoclonal antibody..

LDH, Ferritin and IL-6. High Concentration of IL-6 [4,5] is associated with severe mortality and morbidity in COVID- 19 infection [6,7,8,9,10].

This patho-physiology 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[11,12,13].

Table 1: Comparison of mortality Tocilizumab v/s non-Tocilizumab group

Number of patients in Tocilizumab group	Mortality in Tocilizumab group	%age	Number of patients in non Tocilizumab group	Mortality in non Tocilizumab group	%age
N=13	N=10	76.9	N=78	N=61	78.2

Tocilizumab is a humanised monoclonal antibody that binds IL-6 receptors and halts the IL-6 mediated Cytokine storm[14,15,16]. 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[17], steroids[18],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[15,16].

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 patho- physiological 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.

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 atleast one of the following lab criteria:

a. CRP > 50mg/litre
b. Ferritin > 500ng/ml
c. LDH > 250 u/l
d. IL-6 > 30 pg/ml
e. SPO2 < 92 on oxygen
f. Patients on high flow oxygen
g. Patients who needed high flow oxygen/ HFNC/ Ventilation within 24 hrs 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 outcome included :
- Death before/after intubation after administration 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:-

I. Moderate to severe = 430
II. 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 hyperglycaemia = 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 finding do not provide support for early IL-6 Blockade concept in the treatment strategy of severe and critical 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[11,12,19,20]. 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[21].

Our observations are in tandom with results of many clinical trials[22,23,24] 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 has discouraging results.

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