ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 03 | March - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A RETROSPECTIVE COHORT STUDY ASSESSING THE EFFECTIVENESS OF TOCILIZUMAB IN IMPROVING OXYGENATION IN MODERATE TO SEVERELY ILL COVID-19 PATIENTS ADMITTED IN A TERTIARY CARE CRITICAL CARE UNIT

Anesthesiology

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ABSTRACT

Introduction: The clinical presentation of COVID-19 is highly heterogeneous-ranging from asymptomatic to severe pneumonia with respiratory failure that could lead to invasive mechanical ventilation or death. It is characterised by an initial phase of viral replication followed by a second phase of host inflammatory response(hyperimmune response)-Cytokine storm- assossiated with increased production of many cytokines producing longterm damage and lung fibrosis.Tocilizumab, a recombinant humanised monoclonal antibody of the IgG1 class is directed against both the soluble and membrane-bound forms of the IL-6 receptor and may be considered as a promising treatment modality in fighting with cytokine storm of COVID 19 infection.Considering the scarcity of knowledge about this new pandemic situation and the course of the disease, we conducted this study with a purposes of assessing the efficacy of Tocilizumab in COVID patients.

Methods: This retrospective, observational, cohort study was conducted in Critical care units(CCU) in Medical College and Hospital, Kolkata with a primary purpose to treat the patients. All patients were treated with the standard of care according to hospital protocol and a non-randomly selected subset of patients(20) also received Tocilizumab. Tocilizumab was given intravenously at 8 mg/kg bodyweight (up to a maximum of 800 mg) in two infusions, 12 h apart and level of oxygen support during hospitalization (nasal cannula, high flow nasal oxygen cannula[HFNOC], non-invasive ventilation[NIV], invasive mechanical ventilation [IMV]) was recorded . The PaO2/FiO2 before and after giving the drug recorded and analyzed .

Results: Among all the patients who received inj Tocilizumab(65% male,35% female) 70% of patients were on BiPAP,15% on HFNC and rest 15% on invasive mechanical ventilation. Statistical analysis comparing PaO2/FiO2 before and after receiving Tocilizumab shows non-significant changes(p value- 0.30).

Discussion: Tocilizumab is not effective in improving PaO2/FiO2 ratio and thus oxygenation.Though serial monitoring of IL-6 and other biomarkers were not possible and we had a small sample size due to limited time period,this study can give us a small reflection of larger picture.

Conclusion-Tocilizumab is not an effective treatment modality in improving oxygenation status of moderate to severe COVID infected patients.

KEYWORDS

INTRODUCTION-

Since December, 2019, COVID-19 spread rapidly in Wuhan and throughout the Hubei province of China, and more recently in Europe and worldwide[1,2,3]. World Health Organization (WHO) declared novel coronavirus outbreak a "pandemic" on March 11th, 2020[5]. In India, the first case of COVID-19 was reported on January 30th, 2020. Since then, the case load is in a rising trend leading to 9,351,224 confirmed cases and 136,238 deaths [4]. India has already reached Stage 2 (local transmission) and the Indian Government, in collaboration with the Indian Council of Medical Research (ICMR), is taking all necessary steps to halt the community transmission(Stage 3).

The clinical presentation of COVID-19 is highly heterogeneous, ranging from asymptomatic to severe pneumonia with respiratory failure that could lead to invasive mechanical ventilation or death. The disease is characterised by an initial phase of viral replication that can be followed by a second phase driven by the host inflammatory response[6]. Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) infection might cause a hyperimmune response that is associated with acute respiratory distress syndrome, as suggested by typical radiological findings[7].

The most critical patients can develop a so-called cytokine storm, characterised by increased production of many cytokines that produce long-term damage and lung tissue fibrosis[8]. Similar to the infammatory cytokines in SARS and MERS, patients with COVID-19 also have increased plasma concentrations of inflammatory cytokines, such as tumour necrosis factor α (TNFα),interleukins (IL) 2, 7, and 10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1, macrophage infammatory protein 1 alpha, and interferon-γ-inducible protein 10, especially in ICU patients, which implied a cytokine storm occurred [7].

No therapy has been approved for COVID-19 pneumonia,but current clinical approaches consider the combination of antiviral drugs and immunomodulatory drugs.

Tocilizumab is a recombinant humanised monoclonal antibody of the IgG1 class, which is directed against both the soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor. Tocilizumab is the first marketed IL-6 blocking antibody through targeting IL-6 receptors and has proved its safety and effectiveness in therapy for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis. The proinflammatory cytokine IL-6 exerts its effect through IL-6 receptors.It plays an important role in the host defence ,and its dysregulation has been implicated in the pathophysiology of various inflammatory conditions.By interacting with IL-6 receptors ,Tocilizumab inhibits the binding of IL-6 to its receptors[9,10,11,12].

In this cohort, we collected data on baseline signs,symptoms, comorbidities, blood count, and biochemical markers[1].

Medical College and Hospital, Kolkata, a tertiary care hospital, was announced as an exclusive COVID-19 setup from May 7th, 2020. On the May 10th, 2020, CCU received its first critically ill COVID-19 positive patient who required intensive care.

Considering the scarcity of knowledge about this new pandemic situation and the course of the disease, we conducted this study. The purposes of this study is to determine if the treatment with TOCILIZUMAB is able to significantly improve oxygenation status in patients suffering from moderate to severe COVID-19 infection or not, admitting in critical care unit , from an academic health care system in India. Various studies conducted all over the world found a strong association between the use of tocilizumab and reduced risk of death .But there are very few studies conducted with tocilizumab in our country and the effectiveness of Tocilizumab in improving oxygenation and reducing mortality in COVID pneumonia is still questionable. So the aim of our study is to assess the effectiveness of Tocilizumab in improving oxygenation status and reducing serum levels of prognostic markers ,thus improving patient outcome.

METHODOLOGY-

STUDY DESIGN AND PARTICIPANTS-

This retrospective, observational, cohort study was conducted in Critical care units(CCU) in Medical College and Hospital, Kolkata with a primary purpose to treat the patient. As per the WHO guidelines [10], laboratory confirmation for SARS-CoV-2 was defined as a positive result of realtime reverse transcriptase-polymerase chain reaction (RTPCR) assay of nasal and pharyngeal swabs. Only laboratory confirmed critically ill patients who were admitted in SSB-CCU(Super speciality Block- Critical care unit) between 20 nd July, 2020 and August 22nd, 2020. Among these patients, deaths were recorded on and death record was followed up to August 22nd, 2020. Subsequently, patients who were stepped down and discharged were included for data record. For patients with a readmission during the study period, data from the first admission are presented.

We obtained demographic data, baseline comorbidities, information on clinical symptoms or signs at presentation during CCU admission. Patient underwent blood gas, routine blood examinations i.e. complete blood count, coagulation profile, serum biochemical tests (including renal and liver function, creatine kinase, lactate dehydrogenase, and electrolytes), interleukin-6 (IL-6), serum ferritin,CRP and procalcitonin. Chest radiographs were also done for all inpatients. Frequency of examinations was determined by the treating intensivists. Inpatient medications, treatments, and outcomes (including length of stay, discharge, readmission, and mortality) were also evaluated. Level of oxygen support during hospitalization (nasal cannula, high flow nasal oxygen canula[HFNOC], noninvasive ventilation[NIV], invasive mechanical ventilation [IMV]), was recorded.

The study population was adults (≥18 years) with COVID-19, confirmed by PCR on nasopharyngeal swab, who were admitted to SSB-CCU of Medical College Kolkata during the stipulated time period. Eligible patients had severe pneumonia, defined as at least one of the following: presence of a respiratory rate of 30 or more breaths per minute, peripheral blood oxygen saturation (SaO2) of less than 93% in room air, a ratio of arterial oxygen partial pressure (PaO2) to fractional inspired oxygen (FiO2) ofless than 300 mm Hg in room air, and lung infiltrates of more than 50% within 24–48 h and the patients or whose authorized family member agreed to use Tocilizumab treatment and signed the informed consent.

Exclusion criteria for the use of tocilizumab were patients below 18 years of age, patients who left against medical advices, patients who were participating in clinical trials of other drugs , pregnant or lactating women ,patients having Rheumatoid immune-related diseases ;patients having active pulmonary tuberculosis with bacterial and fungal infections ; organ transplant patients ; patients with mental disorders; coexistent infection other than COVID-19; a PaO2/FiO2 ratio greater than 300 mm Hg; chronic or current glucocorticoid use; history of severe allergic reactions to monoclonal antibodies; less than 500 per μL neutrophils or less than 50×10^9 platelets; active diverticulitis, inflammatory bowel disease, or another symptomatic gastrointestinal tract condition that might predispose patients to bowel perforation; severe haematological, renal, or liver function impairment.

Sample size has been calculated with help of Epi Info (TM) 3.5.3. EPI INFO which is a trademark of the Centers for Disease Control and Prevention (CDC). For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 24.0. and Graph Pad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables.

The study was approved by the Ethical Committee of Medical College Kolkata.

PROCEDURE-

We obtained demographic data, baseline comorbidities, information on clinical symptoms or signs at presentation during CCU admission. Patient underwent blood gas, routine blood examinations i.e. complete blood count, coagulation profile, serum biochemical tests (including renal and liver function, creatine kinase, lactate dehydrogenase, and electrolytes), interleukin-6 (IL-6), serum ferritin CRP and procalcitonin. Chest radiographs were also done for all inpatients. Frequency of examinations was determined by the treating intensivists. Inpatient medications, treatments, and outcomes (including length of stay, discharge, readmission, and mortality) were also evaluated. Level of oxygen support during hospitalization (nasal cannula, high flow nasal oxygen canula[HFNOC], noninvasive ventilation[NIV], invasive mechanical ventilation [IMV]), was recorded. All patients received standard of care treatment at the time of hospital admission according to the hospital protocol. Standard of care treatment included oxygen supply to target SaO2 reaching at least 90%, hydroxychloroquine (400 mg twice on day 1, followed by 200 mg twice per day on days 2–5,eventually adjusted for creatinine clearance estimated by a chronic kidney disease algorithm), antibiotics at the physician's discretion when suspecting a bacterial respiratory superinfection,Multivitamines and low molecular weight heparin for prophylaxis of deep vein thrombosis according to bodyweight and renal function.

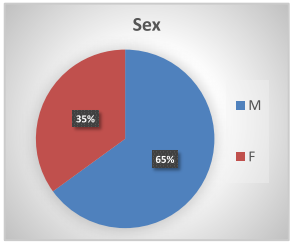
In addition to receiving the standard of care treatment, a non-randomly selected subset of patients also received tocilizumab treatment. Intravenous tocilizumab was administered at 8 mg/kg bodyweight (upto a maximum of 800 mg) administered twice, 12 h apart.The second dose was given because pharmacokinetic data suggested that adequate plasma levels of the drug could be obtained only after two doses, based on the results of pharmacokinetic models for severe or life-threatening chimeric antigen receptor T cell-induced cytokine storm in adult and paediatric patients.

Other treatments were recorded, including glucocorticoids for acute respiratory distress syndrome. The risk of multiorgan failure and mortality was assessed with a standardised Subsequent Organ Failure Assessment (SOFA) score.30Clinical data, including symptoms, complete blood count,coagulation, inflammatory, and biochemical markers were routinely registered in the electronic patient charts for the cohort only.

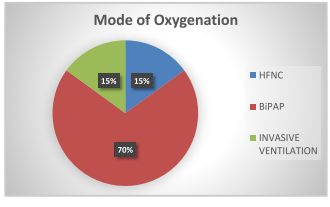
OUTCOME-

STATISTICAL ANALYSIS-

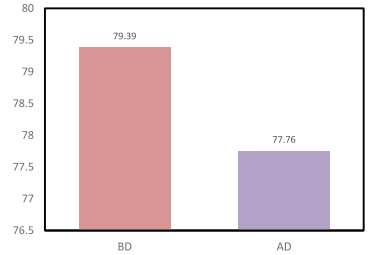
All recorded data were analyzed using standard statistical methods, diagrams and graphs Among all the patients who received injection Tocilizumab 65% were male and 35% were female.Among all the patients,70% of patients were on BiPAP,15% on HFNC and rest 15% on invasive mechanical ventilation. Statistical analysis comparing PaO2/FiO2 before and after receiving Tocilizumab shows non-significant changes(p value- 0.30).



Ratio of male and female in patient population



Modes of oxygenation



PaO2/FiO2 Ratio Before and after administering Tocilizumab

DISCUSSION-

This retrospective, observational, cohort study which was conducted in the Critical Care Unit of Medical College Kolkata demonstrates that Tocilizumab is not efficient enough to increase PaO2/Fi02 ratio in patients suffering from moderate to severe COVID pneumonia.There is no significant improvement in the PaO2/FiO2 ratio in the blood gas analysis of the patients receiving injection Tocilizumab(as evidenced by p-value =0.30). As well as there is neither any clinical improvement nor any decrease in oxygen requirement of these patients.

But this study has its limitations also. Serial monitoring of IL-6 and other biomarkers were not possible and we had a small sample size due to limited time period, But in spite of these limitations,this study can give us a small reflection of larger picture.

Recently Roche trial (COVACTA study)also showed that Tocilizumab did not meet its primary endpoint of improved clinical status in hospitalized adult patients with severe COVID-19 pneumonia.

CONCLUSION-

Tocilizumab is not an effective treatment modality in improving oxygenation status of patients suffering from moderate to severe COVID-19 assossiated pneumonia.

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