RESEARCH ARTICLE

Clinical outcome in coronavirus disease patients treated with tocilizumab at a dedicated COVID hospital: A retrospective observational study

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ABSTRACT

Background: The severe acute respiratory syndrome coronavirus 2 (coronavirus disease [COVID-19]) is a global pandemic since December 2019. Cytokine release syndrome (CRS) is a promising etiology for the severe manifestations of COVID-19. Along with viral invasion of cellular immunity, cytokine storm plays an important role in disease progression. For tackling the immune response, immunomodulators play an important role. Various studies have reported that there has been a decrease in IL-6 level, C-reactive protein (CRP) level, and lower risk of death with the use of tocilizumab in patients with severe COVID-19 disease. Aims and Objectives: Our study aimed to investigate the association between tocilizumab exposure and outcome among COVID-19 patients in a dedicated COVID hospital. The objectives of the study were to assess the clinical outcome in COVID-19 in terms of death and discharge as well as to compare the total leukocyte count, CRP, lactate dehydrogenase, creatine kinase MB, and D-Dimer before and after the administration of tocilizumab. Materials and Methods: After obtaining ethics committee approval, we included 41 patients who received injection tocilizumab. After going through all the records, we entered the data in the Microsoft Excel sheet and assessed the data with the use of statistical analysis of Microsoft Excel. Results: Out of 41 patients, 19 patients were discharged and 22 patients did not survive. The laboratory investigations showed significant improvement after the administration of tocilizumab. Conclusion: Tocilizumab use has shown improvement in the laboratory investigations, but the clinical outcome did not show significant results.

KEY WORDS: Immunomodulators; Tocilizumab; Coronavirus disease

INTRODUCTION

The world is facing the global pandemic of novel coronavirus disease (COVID-19) since December 2019. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease is highly infectious which can spread by infected droplets or by touching surfaces that have settled droplets on it. The COVID-19 infection may present as asymptomatic or have mild symptoms. Furthermore, few patients may present with acute respiratory distress syndrome and respiratory failure with multiorgan dysfunction,[1] Cytokine release syndrome (CRS) is a promising etiology for the severe manifestations of COVID-19.[2] CRS is a state of systemic hyper inflammation which can be a lethal complication of various infections, malignancies, and autoimmune diseases such as juvenile idiopathic arthritis.[3]

The exact mechanism which explains the damage to the respiratory system with COVID-19 is not known. It is described in one study that, after rapid activation by the viral invasion, CD4+ T lymphocytes are differentiated into T helper cells and form granulocyte-macrophage colony-stimulating factors which can induce acute respiratory distress syndrome (ARDS) in patients with severe COVID-19 disease.

The objectives of the study were to assess the clinical outcome in COVID-19 in terms of death and discharge as well as to compare the total leukocyte count, CRP, lactate dehydrogenase, creatine kinase MB, and D-Dimer before and after the administration of tocilizumab.
factor. This leads to the production of inflammatory cytokines such as IL-6. Furthermore, it is observed that in the lungs of COVID-19 patients, a large number of inflammatory cells get infiltrated. This may be the cause of immune damage as well as lung functional injuries which can lead to increased mortality.\(^5\) Few studies in ICU patients with COVID-19 have shown the raised levels of inflammatory cytokines leading to a cytokine storm which is related to the severity of the disease.\(^5\) Therefore, cytokine storm has an important role in disease progression with the viral invasion of the cellular immunity. Thus, immunomodulatory agents may play an important role in handling the immune response. Studies have reported there has been a decrease in IL-6 level, C-reactive protein (CRP) level, and lower risk of death with the use of tocilizumab in patients with severe COVID-19 disease.\(^6,7\)

Tocilizumab (Actemra\(^8\)) is a recombinant IL-6 receptor monoclonal antibody which can specifically bind to the membrane-bound IL-6 receptor and soluble IL-6 receptor. Thus, it inhibits signal transduction and prevents further damage due to immune response. Tocilizumab is currently FDA approved for the management of rheumatoid arthritis, giant cell arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis. It is also approved for the management of CRS, which makes it a possible therapeutic option for CRS of severe COVID-19 patients who have high IL-6 levels and extensive lung functional injuries.\(^8\)

As mentioned in a study by Samaee et al., few case reports, retrospective studies have been published about the efficacy of tocilizumab in severe COVID-19 in many affected countries. However, still, no study confirms the efficacy of treatment with tocilizumab.\(^9\) Despite so many studies, it is not claimed that tocilizumab has a positive therapeutic effect on COVID-19.

Therefore, this study aims to assess the effect of tocilizumab on clinical outcomes in terms of death and discharge in patients who received tocilizumab at our institution. The objectives are to assess the effect of tocilizumab on laboratory investigations such as total leukocyte count (TLC), CRP, lactate dehydrogenase, creatine kinase-MB, and D-Dimer.

**MATERIALS AND METHODS**

This retrospective study was done after obtaining the ethics committee approval. We collected the data of demographics, comorbidities, laboratory investigations, and clinical outcomes from the record section of the medicine department with the permission of the COVID-19 in charge. We included 41 patients who received injection tocilizumab. After going through all the records, we entered the data in the Microsoft Excel sheet. We assessed the data with the use of statistical analysis of Microsoft Excel. For demographic characteristics and clinical outcomes, we used descriptive statistics. For comparing the laboratory investigations before and after receiving inj. tocilizumab, we used the Z test. \(P < 0.05\) was considered statistically significant.

**RESULTS**

The present study was a retrospective observational study. In our study, 41 patients received inj. tocilizumab, 400 mg in 100 ml normal saline over 60 min. The mean age was 51.67 ± 12.64 years. Table 1 shows, out of a total of 41 patients, 21 (52.5%) were male and 20 (48.78%) were female. Furthermore, the urban population was 56.09% and the rural population was 43.90%. Breathlessness was the most common symptom observed, which was found in 38 patients (92.6%) [Figure 1]. The most common comorbidity was hypertension (HTN) found in 22 (53.65%) patients followed by diabetes in 21 (51.21%) patients [Figure 2]. The laboratory investigations including inflammatory markers such as total leukocyte count, CRP, lactate dehydrogenase, creatine kinase-MB, and D-Dimer showed improvement after the administration of tocilizumab. The highest values before administration of tocilizumab and lowest values after administration of tocilizumab were considered and the z test was applied in Microsoft Excel. \(P < 0.05\) was considered statistically significant [Table 2]. The clinical outcome was considered by the deaths and discharge among the patients treated with tocilizumab [Figure 3]. Out of 41 patients, 19 patients were discharged and 22 patients did not survive. Out of 22 patients, 13 were female patients and

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>(n=41)</th>
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<tbody>
<tr>
<td>Age (in years)</td>
<td>51.67 ± 12.64</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (51.21)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (48.78)</td>
</tr>
<tr>
<td>Population (%)</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>23 (56.09)</td>
</tr>
<tr>
<td>Rural</td>
<td>18 (43.90)</td>
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</tbody>
</table>

**Table 1: Demographic data**

**Figure 1: Bar diagram showing symptoms**
nine were male patients. The mean duration of hospitalization was 14.4 ± 14.14 days.

DISCUSSION

The SARS-CoV-2 causes alveolar mucus infiltration because of the inflammatory cells due to host immune response. It is found that, in critical patients, the severity, as well as increased mortality, is associated with the higher levels of cytokines. The present study was a retrospective study, which included 41 patients who received tocilizumab. The most common symptom was found to be breathlessness at the time of admission while hypertension was found in 53.65% of patients among 41 patients. The laboratory investigations including total leukocyte count, CRP, lactate dehydrogenase, creatine kinase-MB, and D-dimer showed improvement after the administration of tocilizumab as p value was found to be significant. Out of 41 patients, 19 patients were discharged and 22 patients did not survive.

Hypertension was the most common comorbidity in our study which is also shown in the studies which were done by Richardson et al., and Nasa et al.[10,11] Similarly, a systematic review shows the same comorbidity as the most common one.[7] Our results show the improvement in the inflammatory markers after administration of tocilizumab. These results are consistent with the study conducted by Luo et al. which showed the marked decrease in CRP values.[12] Furthermore, another study by Mushtaq and Nasa et al. shows similar results when compared the CRP and lactate dehydrogenase (LDH) values except for the D-dimer values which do not show significance.[1,11] The results regarding total leukocyte count and CRP are also consistent with the study published by Xu et al.[13]

The present study shows 54% deaths out of a total of 41 patients who received tocilizumab despite the significant improvement in inflammatory markers. A study showing
the outcome in terms of death shows nine deaths out of 40 patients who received tocilizumab.\(^{[1]}\)

The result regarding mortality is consistent with the study which concludes that there was no reduction in mortality in severe COVID-19 patients with the use of tocilizumab.\(^{[14]}\) The mean age of non-survivors in our study is more as compared to survivors. These results are consistent with the studies concluding the patients who were older and had more comorbidities did not survive.\(^{[10,15]}\) The other observational studies, in contrast, show that the patients with severe COVID-19 had reduced mortality with the use of tocilizumab.\(^{[16,17]}\)

Our study is not free of limitations. The major limitation is that we lack the control arm of patients who received the standard treatment. Studies with a larger sample size are required. We could not include IL-6 values as this test is not available at our institute. Furthermore, the adverse effect could not be monitored because of the retrospective study design.

CONCLUSION

Tocilizumab use has shown improvement in the laboratory investigations such as TLC, CRP, LDH, CK-MB, and D-Dimer. The percentage of death was 54% and 46% of patients were discharged, out of 41 patients who received tocilizumab. There should be judicious use of tocilizumab. The adverse effects should also be monitored. Furthermore, studies with a larger sample size are required to claim the efficacy of tocilizumab in severe COVID-19 patients.

REFERENCES


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