Role of Tocilizumab in Combating Cytokine Storm in Moderate & Severe Covid 19 Patients: Retrospective Observational Study

Nithish Sattoju a++,#,*, Santosh Gattu a†, Sai Sashank Merugu a‡, Vydhika Anneboina b++, Sai Ram Ganapaka b++ and Anvesh Maram b++

a Medisys Hospitals, LB Nagar, Hyderabad, Telangana, India. b Chilkur Balaji College of Pharmacy, Telangana, India.

Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2022/v34i53B7231

Received: 08/09/2022
Accepted: 15/11/2022
Published: 21/11/2022

ABSTRACT

Background: The wide spread of COVID-19 disease and mortality associated with it as never seen before urged the medical research field to formulate and investigate the efficacy of various new drugs alongside with the existing drugs.

Objective: To evaluate the potential benefits of Tocilizumab (TCZ) in addition to the Standard of Care (SoC) in reducing mortality in moderate & severely ill COVID 19.
Methodology: Study population is sorted by 1:1 matching depending on the High-Resolution Computed Tomography (HRCT) Chest CT Severity Score. Outcome is measured as deaths, discharge with or without Long Term Oxygen Therapy (LTOT) along with clinical improvement of the patient measured using 9 points ordinal scale score of WHO and length of stay in Intensive Care Unit (ICU) post administration & levels of inflammatory markers (CRP, IL 6) on day of administration- baseline (D0), 1- & 3-days post administration (D+1 & D+3). The group received TCZ+SoC is considered as Test Group and the group received only SoC as Control Group.

Results: Deaths and discharge with LTOT were slightly higher in test group with OR 1.68 & 1.63 respectively. Clinical improvement in terms of 9-point ordinary scale score & difference in the levels of CRP & IL 6 was insignificant in both the groups. No difference in post administration ICU stay is observed between the groups.

Conclusions: Our study concludes no marked benefits with the addition of TCZ to the SoC in treating moderate and severe COVID 19 patients.

Keywords: COVID 19; tocilizumab; standard of care; inflammatory markers; 9-point ordinary scale developed by W.H.O.

ABBREVIATIONS

HRCT Chest : High Resolution Computed Tomography of Chest
CT Chest : Computed Tomography of Chest
LTOT : Long Term Oxygen Therapy
ICU : Intensive Care Unit
WHO : World Health Organization
CTSS : CT Severity Score

1. INTRODUCTION

COVID-19 disease is caused by SARS CoV 2, a novel corona virus strain, first detected in Wuhan, Hubei province, CHINA and was reported to WHO on December 31 2019 [1,2]. Soon after the first case was reported in China on December 31st, it rapidly got spread to other countries with the reproduction rate (R0) as 2.2 [3] and 2.8 [4] and declared as pandemic on March 11th 2020 by WHO [1]. Since then, the spread of COVID 19 to other countries took place at faster rate reporting mortality as never seen before due to any other illnesses. The elderly patients with age >65 years and with comorbidities are at higher risk of mortality [5].

The disease is characterized by hyperinflammatory syndrome along with cytokine storm [6]. The disease progresses as early infection followed by moderate pulmonary involvement with or without hypoxia and finally to a severe systemic hyperinflammatory phase [7]. The severe form of disease is characterized with higher levels of proinflammatory cytokines like IL 6, IL2, IL10, INF γ, C reactive protein (CRP), Ferritin & D- dimer [8,9]. To combat this cytokine storm several new molecular entities are being discovered. The role of these new entities in COVID 19 treatment is under study. Alongside with the development of new entities, the use of immune modulators, anti-viral’s, steroids are also under investigation.

Following infection by SARS- CoV- 2, CD4+ T cells gets activated into T helper cells-1 that generates Granulocyte- Macrophage Colony Stimulating Factor (GM-CSF). This cytokine environment produces inflammatory monocytes CD14+ & CD16+ with a higher expression of IL-6 that are responsible for inflammation seen in COVID 19 disease [10]. Inflammatory cell infiltrates found in the lungs of severe COVID 19 patients made this pathology more evident [11]. Based on these evidences, it was thought that blocking the pathways of inflammatory cytokines production may be useful in protecting the lungs from getting damaged. There comes the role of monoclonal antibodies targeting GM-CSF or IL-6 in treating severe COVID 19 illness [10,12].

Tocilizumab is an immunosuppressive humanised monoclonal IL 6 antibody drug approved for treating Rheumatoid Arthritis (RA), being only one drug used as biological agent in treating RA [13], and in polyarticular-course juvenile idiopathic arthritis, systemic-onset juvenile idiopathic arthritis and Castleman’s disease [14]. Tocilizumab is available in the brand names Actemra or RoActemra [15]. It works by inhibiting the IL6/sIL6 complex binding to IL6 receptors and blocking the IL6 signalling pathway. Evidences suggest that, blocking the key inflammatory mediator IL 6 in severe COVID 19 reduces the disease severity [16].

The current study is to demonstrate the effect of TCZ in addition to SoC to improve patient outcome in terms of final outcome (Death or...
Discharge or Discharge with Long Term Oxygenation Therapy (LTOT)), improvement according to 9-point ordinary scale developed by W.H.O. reduction in the levels of inflammatory markers (CRP, IL 6) on 1 day after administration (D +1) & 3 days after administration (D +3) on comparison with baseline values (D0) along with the length of ICU stay following administration.

According to the scale 9-point ordinary scale of W.H.O., 0 point is given for the patients who are uninfected, 1 for ambulatory patients with no limitations in activities, 2 for ambulatory patients with limitations in activities, 3 for hospitalized mild diseases patients with no oxygen requirements, 4 for hospitalized and requiring oxygen by mask or nasal prongs, 5 for hospitalized severe diseased patients requiring non-invasive ventilation or high flow oxygen, 6 for patients with intubation or mechanical ventilation, 7 for patients requiring ventilation & additional oxygen support- pressors/ RRT/ECMO & 8 for death patients [17].

2. AIM

To study the role of tocilizumab in combating cytokine storm in moderate & severe COVID 19 patients.

3. OBJECTIVES

Primary: To evaluate the potential benefit of TCZ in addition to the SoC in reducing mortality in moderate to severely ill COVID-19 patients.

Secondary: To demonstrate the clinical improvement of moderate to severely ill COVID-19 patients receiving TCZ in addition to SoC using 9-point ordinary scale developed by W.H.O., reduction in the levels of inflammatory markers, length of ICU-stay following administration.

4. METHODS

4.1 Methodology

A retrospective observational study is carried out to compare the efficacy of TCZ + SoC with SoC alone in terms of final outcome (Death/ Discharge/ Discharge with LTOT), reducing the levels of inflammatory markers (CRP, IL 6), improving the clinical outcome of the patient according to the 9-point ordinary scale developed by WHO & duration of ICU stay post administration.

Selection of subjects is done in 1:1 criterion matching by COVID-19 HRCT Chest CT Severity; moderate or severe, comorbidities, 9-point ordinary scale score while adjusting for age and sex. The study population is divided into 2 groups viz, Group 1/ Test group (receiving TCZ + SoC) and Group 2/ Control group (SoC alone). SoC is as detailed in procedure.

Inclusive criteria:

- RTPCR proven Covid 19 patients & moderate to severe on HRCT Chest (CTSS ≥ 9).
- Patients in ICU at the time of TCZ administration.
- Patients in ICU matched with TCZ group.
- Patients whose SpO₂ is ≤ 93% on room air and requiring oxygen support.
- Patients with 9-point ordinary scale score of ≥ 4.

Exclusive criteria:

- Immune compromised patients.
- Pregnant women.
- Patients who have history of taking TCZ due to other illness.
- Patients with severe renal or hepatic impairment.
- Patients with auto immune diseases or other co-existing illness like Mucormycosis, HIV, HBV, etc.

4.2 Procedure

Medical records of all the patients admitted to the hospital between 19-05-2020 to 18-05-2021 due to COVID 19 illness were screened for selection of patients. The patients found to have taken TCZ along with SOC are grouped together into test group. Test group patients are matched as 1:1 by COVID-19 CT Severity; moderate or severe, comorbidities, 9-point ordinary scale score while adjusting for age and sex for inclusion under control group.

All the patients, both in test & control groups, were given with SoC that includes Oxygen support to maintain SpO₂ ≥ 93%, Glucocorticoid; Dexamethasone (0.1 mg/kg/day given in a single dose), Anti-viral; Remdesivir (200mg stat dose followed by 100mg once daily for 4 days to a cumulative dose of 600mg given in 5 days), Antibiotic; Doxycycline (100mg twice daily for 7 days) or Azithromycin (500mg for 5 days) at physician discretion when a bacterial infection is
suspected, low molecular weight heparin as prophylactic treatment for deep venous thrombosis, dose adjusted according to the body weight and renal function of the individual patient, along with symptomatic treatment that includes antitussives, antihistamines, antipyretics, etc.

The test group patients, in addition to this SoC, were given with TCZ as single dose of intravenous TCZ at 8 mg/kg body weight upto maximum of 400 mg.

On the day of administration (D0) and 1 day after administration (D+1), and 3 days after administration (D+3) the test group patients along with the matched patient in control group were given with a score value according to the 9-point ordinary scale of W.H.O. and the levels of inflammatory markers (CRP, IL-6) were screened, length of ICU stay is calculated and noted along with final outcome.

Note: The CRP & IL 6 levels are reported as mg/lit & pg/ml respectively.

4.3 Statistical Analysis

The above-mentioned endpoints are measured in both the test group and control group & using appropriate statistical tests p-value is determined to test the statistically significant difference among the values as described herein.

Our study compared the numerical variables like, baseline values of W.H.O. ordinary scale score, CRP & IL 6 with those on D+1 and D+3. The values on these 3 time points in each group were tested for statistically significant difference using Annova one way method. The group with significant difference in the values across the 3 time points is considered as the group with better outcome. P value calculated using the above-mentioned statistical test is used to test the hypothesis as p≤0.05 indicating the existence of statistically significant difference between the values of 3 time points and vice-versa.

Another numerical variable of the study, post administration ICU stay, the difference in the length of ICU stay in both the groups is tested for statistical significance using unpaired t test. The mean± SD is calculated for both the groups and reported.

Odds ratio was calculated to determine the odds (final outcome viz, Death, Discharge with or without LTOT) occurring in the test group in comparison to the control group.

Categorical variables are presented as % population and are compared directly between groups.

5. RESULTS

The test group included 17 patients with mean age of 51.5 ± 9.4 with 15 males (88.2%) & 2 females (11.7%), and the control group included 17 patients with mean age of 49.1 ± 10.1 with 12 males (70.5%) & 5 females (29.4%).

In the test group 41.18% population died, 11.76% population were discharged without LTOT & 47.06% population discharged with LTOT (OR 1.68, 0.2, 1.63; 95% CI= 0.79, 13.54; 0.03, 1.16; 1.29, 6.46 respectively). In control group 29.41%, 35.3 % & 35.3% population died, discharged without and with LTOT respectively.

Death & discharge with LTOT were seen in both groups in almost equal percentages but the discharges without LTOT were more in control group on comparison to the test group.

Study values are graphically presented using 100% stacked column graph, Fig. 1.

According to the W.H.O. 9-point ordinary scale score value, in the test group, on D0 82.5% population were with score 4, 5 & 6 respectively. On D +3 5.88%, 70.59%, 5.88% & 5.88% were with scores of 4, 5, 6 & 8 respectively. On D +3 5.88%, 70.59%, 5.88%, 11.76% population were with score value of 3, 4, 5, 6, & 8 respectively, Fig. 2a. Annova single factor assay was conducted that gave a p value of 0.92 implicating there exists no statistically significant difference between the values on 3 time points. The scores of individual patients on 3 time points presented pictographically in the Fig. 2b.

In the control group, on D0 94.5% & 5.88% population were with score value 5 & 6 respectively. On D+1 11.76%, 82.35% & 5.88% population were with score value of 4, 5 & 6 respectively. On D+3 29.41%, 64.70% & 5.88% population were with score 4, 5, 6 & 8 respectively, Fig. 2c. Annova single factor assay was conducted that gave a p value of 0.73 implicating there exists no statistically significant difference between the values on 3 time points. Fig. 2d represents the individual patient’s WHO scale score on different time points.

The length of ICU stay following administration in test group was 9.06±6.18 days & in control group was 7.32± 1.84 days with p-value 0.07 indicating
no statistically significant difference between the two groups. The individual patient’s ICU stay is represented using 100% stacked graph, Fig. 1b.

In test group the average values of CRP on D0 were 28.56±16.4 which dropped down to 22.48±13.29 by D+1 & to 19.72±14.12 by D+3. Anova single factor test gave p value of 0.21 reporting no significant differences in the values across 3 time points. The levels of CRP on D+1 & D+3 in comparison with the baseline values in test group is pictographically presented in the Fig. 3a.

In control group the average value of CRP on D0 was 45.45±20.4 that dropped to 36.75±15.17 by D+1 & to 33.43±17.75 by D+3. Anova single factor test reported p value of 0.14 reporting no significant difference in the values across 3 time points. The levels of CRP on D+1 & D+3 in comparison with the baseline values in control group is pictographically presented in the Fig. 3b.

Another inflammatory marker studied was IL 6. The average value of IL6 in test group on D0 was 146±28.96, on D+1 was 136.53±24.67 and on D+3 was 132.06±29.85. Anova single factor test was conducted that reported p value of 0.34 reporting no significant difference in the values across 3 time points. The levels of IL 6 on D+1 & D+3 in comparison with the baseline values in test group is pictographically presented in the Fig. 3c.

The average value of IL 6 in control group on D0 was 141.41±20.66, on D+1 was 134.76±22.52 & on D+3 was 133.35±25.96. Anova single factor test conducted & reported p value of 0.56 reporting no significant difference in the values across 3 time points. The levels of IL 6 on D+1 & D+3 in comparison with the baseline values in control group is pictographically presented in the Fig. 3d.

The trend of inflammatory markers, CRP & IL 6, was in same fashion in both the groups with no significant difference over 3 time points reporting p value of 0.21 & 0.14 in test and control group respectively in case of CRP & p value 0.34 & 0.56 in case of IL 6 respectively.

Clinical improvement of the patient measured in terms of W.H.O. ordinary scale score showed no significant reduction in both the groups with p values 0.92 & 0.73 in test group and control group respectively. Correlating the clinical improvement with length of the ICU stay following administration showed neutral results with a p value of 0.07 stating no significant statistical difference between the groups.

Table 1 provides the values of both the groups and all the parameters considered in our study.

6. DISCUSSION

Initial studies conducted by Xiaoling Xu et al. [18], showed benefits of using TCZ in treating severe COVID 19 patients with improvements as seen in oxygen requirement, CT imaging, CRP levels, blood lymphocyte counts.

However, a single centre experience on TCZ in treating the COVID-19 as conducted by Pam Luo, et al, reported the failure of single dose TCZ in reducing the levels of CRP & IL6. But it could be beneficial in treating the severely ill patients with IL 6 levels 10 times greater than the normal and to the moderately ill patient with 90 times greater than the normal. Initially the IL6 levels following the TCZ administration increases and later decreases in the following days [19]. This is due to accumulation of IL6 in the serum upon inhibition of IL6 receptors by TCZ which gets cleared later resulting in a decreased level. The decreased levels are responsible for clinical improvement of the patient [20].

Reduced mortality rate with non-statistically significant difference in comparison to the control group is reported in a case control study conducted by G Rojas- Marte [21]. The similar results are reported in a prospective study conducted by Marta Colaneri, et al as non-statistically significant reduction in mortality and ICU admission in patients treated with TCZ on comparison with patients treated with SoC [22].

Retrospective cohort study conducted on non-ICU admitted patients by Corrado Campochiaro, et al. reported similar results of non-statistically significant decrease in mortality in TCZ treated patients over a 28 day follow up [23].

Rapid beneficial effect of TCZ on fever and inflammatory markers are seen with no effect on clinical outcome is reported in a study conducted by Valentina Morena et al. The study also reported the side effects of TCZ of which most frequently seen are increase in hepatic enzymes, thrombocytopenia and serious bacterial and fungal infections [24]. Depending on these study results, TCZ administration could be of higher risk for critically ill patients and careful supervision is required while administration.
**Fig. 1.**

a: Final outcome of the study groups in 100% stacked column graph, b: Post administration ICU stay of individual patients of both the groups in 100% stacked column graph

**Fig. 2.**

a: % population of test group with each score value on different time points. 
b: W.H.O. score of individual patient of test group on different time points.  
c: % population of control group with each score value on different time points.  
d: W.H.O. score of individual patient of control group on different time points
Fig. 3. Levels of inflammatory markers of the study at 3 points. Baseline values are represented using line while D+1 & D+3 values as columns so as to compare the values easily on different time points. a: CRP levels of individual patients in test group on different time points. b: CRP levels of individual patients in control group on different time points. c: IL-6 levels of individual patients in test group on different time points. d: IL-6 levels of individual patients in control group on different time points.

Table 1. Overall values of all the factors considered in our study to compare the effect of TCZ+ SoC over Soc alone

<table>
<thead>
<tr>
<th>Factor (Measure)</th>
<th>Test group (n=17)</th>
<th>Control group (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years</strong></td>
<td>Mean± SD</td>
<td>51.5±9.4</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>n (%)</td>
<td>15 (88.2%)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td>n (%)</td>
<td>2 (11.7%)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>%</td>
<td>41.18%</td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td></td>
<td>1.68</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td></td>
<td>0.79, 13.54</td>
</tr>
<tr>
<td><strong>Discharge with LTOT</strong></td>
<td>%</td>
<td>47.06%</td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td></td>
<td>1.63</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td></td>
<td>1.29, 6.46</td>
</tr>
<tr>
<td><strong>Discharge without LTOT</strong></td>
<td>%</td>
<td>11.76%</td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td></td>
<td>0.03, 1.16</td>
</tr>
<tr>
<td><strong>9-point ordinary scale score</strong></td>
<td>P value</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Post administration length of ICU stay</strong></td>
<td>Mean± SD</td>
<td>9.06± 6.18</td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td>P value</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>D0 (Mean± SD)</strong></td>
<td>28.56±16.4</td>
<td>28.56±16.4</td>
</tr>
<tr>
<td><strong>D+1 (Mean± SD)</strong></td>
<td>22.48±13.29</td>
<td>22.48±13.29</td>
</tr>
<tr>
<td><strong>D+3 (Mean± SD)</strong></td>
<td>19.72±14.12</td>
<td>19.72±14.12</td>
</tr>
<tr>
<td><strong>IL 6</strong></td>
<td>P value</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>D0 (Mean± SD)</strong></td>
<td>146±28.96</td>
<td>146±28.96</td>
</tr>
<tr>
<td><strong>D+1 (Mean± SD)</strong></td>
<td>136.53±24.67</td>
<td>136.53±24.67</td>
</tr>
<tr>
<td><strong>D+3 (Mean± SD)</strong></td>
<td>132.06±29.85</td>
<td>132.06±29.85</td>
</tr>
</tbody>
</table>
7. CONCLUSIONS

Our study concludes no marked benefits with the addition of TCZ to the standard of care in treating moderate and severe COVID-19 patients in reducing mortality and improve patient clinically. However, addition of TCZ could be done at the Physician discretion depending upon the patient condition and prognosis of the disease. With varied results in different studies conducted by different researchers in different countries (as detailed in the discussion along with our study results), TCZ has a mixed opinion with both critics and appraisals regarding its usage in COVID-19. Therefore, furthermore clinical trials are needed to establish the safety and efficacy of TCZ in treating severely ill COVID-19 patients with well-defined characteristics of its usage in age, severity of the disease, comorbidities, IL6 levels, dose of TCZ required along with no. of doses for its application.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

I convey my sincere thanks to the managing director of the hospital Dr. Chandrashekar Reddy for allowing us to conduct the project.

I take this space in thanking Dr. Chandrasekhara Rao Baru, Principal, Chilkur Balaji College Of Pharmacy, for allowing the students to participate in the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

use in the management of rheumatoid arthritis.


© 2022 Sattoju et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history: The peer review history for this paper can be accessed here: https://www.sdiarticle5.com/review-history/93673