

Content available at: <https://www.ipinnovative.com/open-access-journals>

Journal of Preventive Medicine and Holistic Health

Journal homepage: <https://www.jpmmh.org/>

Original Research Article

A retrospective study of the role of Tocilizumab in preventing or controlling cytokine storm in COVID-19 cases

Ajeet Singh Thakur¹, Swapnil Jain^{1,*}, Bhavya Shah¹, Arti Julka¹, J.C. Agrawat¹¹Dept. of Respiratory Medicine, RD Gardi Medical College, Ujjain, Madhya Pradesh, India

ARTICLE INFO

Article history:

Received 04-05-2022

Accepted 12-06-2022

Available online 30-06-2022

Keywords:

Cytokine release syndrome (CRS)

Cytokine Storm syndrome (CSS)

Acute respiratory distress syndrome (ARDS)

Tocilizumab (TCZ)

ABSTRACT

Introduction: In spite of the advancement in science we are still lacking definite specific treatment for Covid-19. And till date (11th April 2022) 6,203,372 and 5,21,722 death occurred globally and in India respectively. The sudden increase of O₂ demand with need for Invasive ventilator is an indicator/ is a warning for cytokine storm Syndrome (CSS) or an over action of the immune system, which can be disastrous. Steroids are still the best anti-inflammatory drugs available thus as soon as a patient shows signs of a 'cytokine storm,' steroids should be used. Other drugs i.e. IL-6 receptor blocker TCZ and Sarilumab and direct IL-6 inhibitor Siltuximab¹ and JAK inhibitors (baricitinib) etc are also been considered in various trials for cytokine storm.

Materials and Methods: A retrospective observational study was performed in hospitalized patients referred from the district hospital to the Dedicated Covid Hospital (DCH), all were diagnosed with COVID-19 with hypoxemia.

Conclusion: The timely detection of CSS & early initiation to controlling management is the key issue. The early identification of cytokine storm with initiation of TCZ may give beneficial result. The Oxygen requirement and CRP showed a significant decline with the use of tocilizumab. Furthermore, the optimal timing, dosage and administration route of TCZ may need to be studied with larger sample or with multicenteric study plan.

This is an Open Access (OA) journal, and articles are distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprint@ipinnovative.com

1. Introduction

Medical science can still recall the deadly Spanish Influenza pandemic outbreak (also referred to as Bombay Influenza/ Bombay Fever in India), almost a century back in 1918-1920. This led to near 75 million deaths globally while India lost more than 15 million that is 5% of the then population. The comparison of 1918 influenza and COVID-19 pandemics has had similarities in the socio-economic implications² also. In spite of the advancement in science we are still lacking definite specific treatment for Covid-19. And till date (11th April 2022) 6,203,372 and 5,21,722

death occurred globally and in India respectively.

Covid-19 pandemic virus is most notorious in respect of rapid mutation, and so far many variants have been identified with different virulence. The clinical manifestations of COVID-19 vary widely among the 1st, 2nd and 3rd wave. The 2nd wave was most devastating with mortality and morbidity involving younger age groups, from mild to severe cases with pneumonia, acute respiratory distress syndrome (ARDS), and some with multi organ dysfunction. These cases often required invasive mechanical ventilation (IMV) but still mortality remained high.³

In several studies, the markedly elevated inflammatory markers (e.g. CRP, D-dimer, ferritin etc) and elevated pro-inflammatory cytokines (including interleukin IL-6, IL-1,

* Corresponding author.

E-mail address: drswapniljain89@gmail.com (S. Jain).

TNF- α) were associated with critical and fatal COVID-19, and while blocking these inflammatory pathway could prevent disease progression,^{1,4}

The sudden increase of O₂ demand with need for Invasive ventilator is an indicator/ is a warning for cytokine storm Syndrome (CSS) or an over action of the immune system, which can be disastrous. Steroids are still the best anti-inflammatory drugs available thus as soon as a patient shows signs of a 'cytokine storm,' steroids should be used.

Apart from symptomatic management & O₂ therapy, the therapeutic options were limited for Covid-19. Neutralizing the virus through passive immunity i.e. monoclonal Antibodies/ Plasma therapy, or inhibiting viral replication (remdesivir), or dealing with the immune response to prevent untoward manifestations such as CSS, acute respiratory distress syndrome, and multisystem organ failure (glucocorticoids, interleukin- 6 antagonists, etc) are some options were tried. In patients with Covid-19, interleukin-6 levels are correlated with viral load, disease severity, and prognosis.⁵ More specific available drug for IL-6 antagonist is Tocilizumab (TCZ). So we have under taken TCZ in this study to better understand the precise use of drugs that have been used to prevent CSS and disease progression along with steroids. Other drugs i.e. IL-6 receptor blocker TCZ and Sarilumab and direct IL-6 inhibitor Siltuximab¹ and JAK inhibitors (baricitinib) etc are also been considered in various trials.

2. Objective

To predict the cytokine storm clinically or with the help of biomarkers and to assess the efficacy of tocilizumab in preventing or controlling cytokine storm induced morbidity and mortality.

3. Materials and Methods

A retrospective observational study was performed in hospitalized patients referred from the district hospital to the Dedicated Covid Hospital (DCH), all were diagnosed with COVID-19 with hypoxemia. Clinical examination for disease severity was assessed and all were admitted to Respiratory Intensive Care Unit (RICU) of R.D. Gardi Medical College. The laboratory investigations including inflammatory Markers i.e. CRP, Ferritin, LDH, NL Ratio, D-dimer etc were performed on the day of admission. All the severe cases with clinical suspicion of CSS who were deteriorating on O₂, corticosteroid and supporting management were given TCZ as an adjuvant therapy.⁴ The Injection TCZ 400 mg was given as a single dose slow intravenously (over 1 h) after dilution in 100 ml of normal saline. A change in hypoxemia/ SpO₂/ vitals/ and biological marker with any untoward or adverse drug reaction was recorded. This study is being done to evaluate the clinical response to drug TCZ.

4. Observations and Result

All the observation and results are presented in a tabular form with gross inference for further interpretation and evaluation.

5. Discussion

The higher rate of infectiousness with development of symptoms specially shortness of breath and the declining Oxygen Saturation rendered hospitalization to be very essential. The rapid increase in mortality has attracted the attention worldwide with detection of a new virus and declaration of Covid-19 pandemic on August 2020. The raised inflammatory biomarker with radiological (Chest X-Ray/ CT Thorax) evidence and declined SpO₂ (< 90) helped in stratifying disease severity without any dispute. The present study included 40 severe case of Respiratory Intensive Care Unit (RICU), all had been referred from district hospital with advanced disease. The median age was 56.4 years and most (82.5 %) were males but no significant association observed between gender and age with the severity of lung involvement.⁶ All had bilateral pneumonia predominantly in the lower and peripheral zones. The biomarkers may be helpful in assessing prognosis i.e. CSS as well the mortality rate. All the cases were already on steroids while injection TCZ was given and this study was to retrospectively evaluate for improvement in O₂ requirement and decline of biomarker values. Preeti Malik et al analyzed 32 studies with 10491 cases of confirmed COVID-19 and found that laboratory biomarkers including elevated CRP, Ferritin, D-dimer, LDH, PCT, CK, AST, ALT, creatinine and lymphopenia, thrombocytopenia were significantly associated with poor outcomes in COVID-19 patients.⁷

CRP is a sensitive biomarker of inflammation, infection, and tissue damage. Studies showed that it increased significantly in severe Covid – 19 patients at the initial stage, and further rose in severe form of interstitial pneumonia, and often evolved into acute respiratory distress syndrome (ARDS) which is a signal of lung damage and disease progression.⁷ Hodges G, et al (cohort of 1310 patients)⁸ mentioned that elevated CRP was independently associated with death/ICU admission after adjusting for age, gender, diabetes, hypertension, ischemic, heart disease or COPD. In our study we observed significantly raised CRP in all the cases and this correlates well with severity and showed reduction in levels in almost all (97.5 %) cases following treatment, however the mortality rate was 25 % among the total cases under trial for tocilizumab.

Besides CRP other inflammatory markers also need to be examined. An initial raised LDH (95%) and Ferritin (52.5) were found in this study. More death among raised LDH during hospitalization was observed while no definite conclusion could be made for ferritin. The ferritin is a

Table 1:

| No. | Parameters | Results | Inference |
|-----|----------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | Total cases | 40 | a) Survived (N=30) 75% b) Died (N=10) 25% |
| 2 | Male | 33 (82.5 %) | Male predominant |
| 3 | M : F ratio | 2.3 | |
| 4 | Mean Age | 56.4 Years | |
| 5 | Bilateral Pneumonia | 40 (100%) | |
| 6 | Hypoxaemia (O ₂ supported) | 40 (100%) | Critical (N=31) 77.5 % |
| | 1. Mechanical Ventilator...22.5 % | Critical 77.5 % | |
| | 2. BiPAP support.40.0 % | | Needed additional supported O ₂ therapy, among them survived 21 (68%). |
| | 3. High flow O ₂ support.15.0 % | 22.5 % | |
| | 4. * NRBM, Mask & Nasal prong. 22.5 % | | |
| 7 | 1. Co morbidity Present 28 cases (70%) | Death among | |
| | 2. None morbid (N=12).30.0 % | None 30% | Morbid/non morbid Proportion of death equal in both group (25%). In co morbid group more death among two or with > two ailments group. |
| | Single morbidity30.0 % | Single 20% | |
| | 3. Double morbidity.....27.5 % | Double 40% | |
| | 4. > two co morbidity12.5 % | >two 10% | |
| 7.1 | Type of Co morbidity N=28 (70%) | Death | |
| | Diabetes (55 %) | DM 60% | More than double the death among co morbid patients while cardiovascular diseases predominated. |
| | Systemic hypertension(44 %) | HT 30% | |
| | Coronary Artery Disease (15%) | CV 40% | |
| 8. | Inflammatory Biomarkers | | |
| 8.1 | CRP: Initially: Raised in all Cases. ... 100 % | CRP declined after treatment with TCZ in (97.4%) cases. In spite 25% death observed | All the cases found with Initial raised CRP. All most all cases including those who died responded to TCZ treatment with decreased of CRP. |
| | Declined with TCZ Treatment ... 97.4% | | |
| 8.2 | Ferritin: | | |
| | Normal.....52.5% | 19.4% (4) Died | |
| | Initial Raised.47.5 % | 15.8% (3) died | |
| | Repeat Test in (9 cases) after treatment of them: | | Could not find any relation to Morbidity & mortality |
| | Normal to Increased (3) | 0 (Death) | |
| | Improved (4) | 1 Died (25%) | |
| | Further Increased (2) | 2 Died (100%) | |
| 8.3 | LDH: Raised values (38 cases).....95% * | 20 % Died 50 % Died | More death among patients with raised in LDH during hospitalization. |
| | After treatment Values declined 37.5% * | | |
| | Further increased values or27.5% no change observed | | |
| 8.4 | D-dimer | Death % | |
| | Normal value. 10 % | 25% | Initial Raised D-dimer was found in 72.5 % of cases with death of only 20 % while Initial Normal value with consecutive sudden increased of D-dimer during hospital stay the death was 40 % |
| | Normal initially then raised during Stay15% | 40 % | |
| | Initially Raised...72.5% | 20 % | |
| 9 | CBC: TLC raised in 50 % cases | | |
| | a) Survived group.....36.6% | | |
| | b) Died group80 % | Further rise of 40% & 63% in survival & died groups. | Death among increasing in TLC is higher Majority have lymphopenia and were more vulnerable to die |
| | Lymphopenia in 73 % cases (29) | | |
| | a)Survived group70 % | | |
| | b)Died group.....80% | | |
| 10 | N/L Ratio: raised in (18) cases. 45 % | | |
| | a) Survival group.10 cases | 33% | Higher N/L ratio have more untoward output |
| | b) Died group8 cases | 80% | |
| 11 | Platelets: Count | Death | |
| | <1.5 Lac (Low)..... 35 % | 28 % | Maximum Patients had normal platelet count & outcome were slightly better in normal count group 77% vs. 72% |
| | >1.5 Lac (Normal)..... 65 % | 23 % | |

key mediator of immune dysregulation that contributes to cytokine storm and it has been implicated in fatal outcomes by Covid – 19 when accompanied by CSS. Thereby those with elevated ferritin have high probability to experience serious complications.⁶ D-dimer is another marker. Initial Raised D-dimer was found in 72.5% of cases with death of only 20 % among them, while initial normal value with consecutive sudden increased of D-dimer during hospital stay, the death was 40 % in our study. Micro embolism, refractory hypoxemia and disseminated intravascular coagulation (DIC) also had contributory factors in mortality among Covid-19.^{6,7} A low initial platelets count (<150000) reported from 17 studies with sample size of 3481 cases of covid-19 showed significantly greater number of poor outcomes.^{6,7} In this reference we observed that maximum patients had normal (65%) platelet count & outcome were slightly better in normal count group 77% vs. 72%, thus the platelet count (<150000) or thrombocytopenia had significant impact on poor outcomes

The other simple routine marker is lymphopenia, or Neutrophil vs. Lymphocyte ratio (NL Ratio). Lymphopenia had nearly threefold higher risk of poor outcomes.⁷ In our study we also observed significantly raised NL ratio in 45 % of cases with 33 % in survival vs. 80 % in deceased group respectively showed more than twofold higher risk with lymphopenia. The association with inflammatory markers and acute phase reactivation likely reflects the CSS associated with severe infection and sequelae of severe sepsis and end-organ damage.^{9,10} Nevertheless, bacterial super infection is an important consideration and a factor in COVID-19; for example, the study by Wang et al,⁹ has reported 81.7% of patients who died with COVID-19 had an associated bacterial infection.^{9–11} Our study also showed a further rises in repeat total leukocyte count in 40 % and 63% percent cases with survivals and deceased group of patients and are more likely to have super infection. However, it is also essential to identify that during acute phase there are non-specific markers of inflammation i.e. procalcitonin secretion is primarily a sensitive marker of bacterial infections.¹⁰ It may help in distinguishing but somehow we have not done this test in all cases.

Associated co morbidity also remained an important contributory factor in the outcome of Covid-19. Most of the studies showed higher vulnerability for those with cardiovascular diseases and Diabetics and we too have observed that 28 cases (70%) had co morbidity while no increase in percentage of death was found. The co morbid patients (70%) in the present study found to have more than doubled the chances to suffer from covid-19 but no difference was found in the proportion of death with co morbid and non co morbid group, while those who had two or more than two simultaneous co morbidity are more vulnerable (>50%) to death. The advance age may be a contributory factor as well. Only 1 case (10% among died)

had multi organ dysfunctions.

TCZ is a humanized monoclonal antibody IgG1 anti-human receptor for IL-6, it is therapeutically been applied in rheumatoid arthritis (RA) and systemic juvenile arthritis but it can be prescribed for COVID-19 patients with severe lung damage and high IL-6. TCZ has shown good efficacy in several clinical trials so far,¹² although mechanism of this drug in respiratory inflammation with COVID-19 is unclear.¹³ The main pathophysiology of covid-19 itself is still unrecognized but increased worsening of inflammation can well be identified clinically with development of pneumonia, O₂ demand and biological marker,^{4,6–8,14} and this has been labeled as cytokine release syndrome (CRS) or Cytokine Storm syndrome (CSS)/ Inflammatory cytokine storm.^{12,13,15} The timely detection of CSS and earlier initiation of controlling management is the key issue.^{16,17} The steroid were invariably been given to all our patients prior to further intervention i.e. O₂ management or add on TCZ therapy. We had used injection methylprednisolone 40 mg twice a day for a short course of 7-10 days. The Horby P. et al warned that high doses or wrong administration timing can be harmful as glucocorticoid delays viral clearance.¹⁸

The Danfei Liu et al mentioned that 58% patients showed a rapid improvement of clinical and respiratory condition and after ten days of TCZ treatment 80 % improved with return of laboratory results to the normal range, while mortality stood at 20%.¹² In our study we also observed rapid improvement in most of the cases with mortality of 25%, (one patient developed sepsis and later died) as against a survey of 137,000 adults, reported (by Jha et al.) 26 to 29% mortality.¹⁹ The most important observation in this study was that Oxygen requirement and CRP regression were observed in all the cases.

In our study a single dose of TZN (400 mg) was used and no side effect were observed. In other studies adverse reaction were observed when higher doses and repeat therapy was followed and found to be in the range around 10%. Some of the studies have reported limited or no significant role of TCZ in respect to clinical improvement or survival in covid-19.^{20–22} The use of TCZ in covid-19 is further need to be explore regarding when to initiate i.e. timing and doses schedule. (16, 18&26) The best result may be obtained to initiate TCZ with early detection of CSS but required further confirmation.

6. Conclusion

The timely detection of CSS & early initiation to controlling management is the key issue. The worsening infection of Covid-19 is clinically well recognized by development of bilateral pneumonia with supplementary demand of oxygenation, which further deterioration with increase in laboratory biomarkers. The early identification of cytokine storm with initiation of TCZ may give beneficial result. The

Oxygen requirement and CRP showed a significant decline with the use of tocilizumab. The Ventilation management may itself be a strategy to reduce the overall mortality. Furthermore, the optimal timing, dosage and administration route of TCZ may need to be studied with larger sample or with multicenteric study plan.

7. Source of Funding

None.

8. Conflict of Interest

None.

References

- Mehta P, McAuley DF, Brown M. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033–4. doi:10.1016/S0140-6736(20)30628-0.
- Sharma A. Comparing the socio-economic implications of the 1918 Spanish flu and the COVID-19 pandemic in India: A systematic review of literature. *Int. Soc Sci J*. 2021;11:1–14. doi:10.1111/issj.12266.
- Roman JMG, García SCR, Vallejo ER, Jiménez AM, Alonso SS, Díaz CF. MD “IL-6 serum levels predict severity and response to tocilizumab in COVID-19: An observational study”. *J Allergy Clin Immunol*. 2021;147(1):72–80. doi:10.1016/j.jaci.2020.09.018.
- Samprathi M. Biomarkers in COVID-19: An Up-To-Date Review “Frontiers in Pediatrics | www. *F Pediatr*. 2021;8:607647. doi:10.3389/fped.2020.607647.
- Chen X, Zhao B, Qu Y. Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin “6 level in critically ill patients with coronavirus disease 2019. *Clin Infect Dis*. 2020;71(8):1937–79. doi:10.1093/cid/ciaa449.
- Gupta P, Halani A, Samuel T, Singh DP. Association of Inflammatory Biomarkers with Radiological Severity in COVID-19 Patients : An Indian perspective”. *Asian J Med Sci*. 2021;12(4):1–7. doi:10.3126/ajms.v12i4.33483.
- Malik P. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and metaanalysis. *BMJ Evid Based Med*. 2021;26(3):1–12.
- Hodges G, Pallisgaard J, Olsen AMS, McGettigan P, Andersen M, Krogager M, et al. Association between biomarkers and COVID-19 severity and mortality: a nationwide Danish cohort study “. *BMJ Open*. 2020;10(12):41295.
- Wang L, He W, Yu X. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect*. 2020;80(6):639–84. doi:10.1016/j.jinf.2020.03.019.
- Mehta P, McAuley DF, Brown M. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033–7. doi:10.1016/S0140-6736(20)30628-0.
- Samsudin I, Vasikaran SD. Clinical utility and measurement of procalcitonin. *Clin Biochem*. 2017;38(2):59–68.
- Liu D, Zhang T, Wang Y, Xia L, et al. The Key to Stop Coronavirus Disease 2019 (COVID-19)-Induced Cytokine Release Syndrome (CRS)?” *Frontiers in Medicine | www.frontiersin.org. Frontiers Med*. 2020;7:1–9. doi:10.3389/fmed.2020.571597.
- Samaee H, Mohsenzadegan M, Ala S, Maroufi SS, Moradimajd P. Hamidreza Samaee et al “Tocilizumab for treatment patients with COVID-19: Recommended medication for novel disease. *Int Immunopharmacol*. 2020;89:107018. doi:10.1016/j.intimp.2020.107018.
- Samaee H. “Tocilizumab for treatment patients with COVID-19: Recommended medication for novel disease. *Int Immunopharmacol*. 2020;89(1):107018.
- Nasa P, Singh A, Upadhyay S, Bagadia S, Polumuru S, Shrivastava PK. Tocilizumab Use in COVID-19 Cytokine-release Syndrome: Retrospective Study of Two Centers”. *J Crit Care Med*. 2020;24(9):71–6. doi:10.5005/jp-journals-10071-23566.
- Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med*. 2020;8(6):46–53. doi:10.1016/S2213-2600(20)30216-2.
- Menzella F, Fontana M, Salvarani C, Massari M, Ruggiero P, Scelfo C. Efficacy of tocilizumab in patients with COVID-19 ARDS undergoing noninvasive ventilation. *Crit Care*. 2020;24(1):589. doi:10.1186/s13054-020-03306-6.
- Horby P, Lim WS, Emberson JR, Mafham M, Bell JL. Dexamethasone in hospitalized patients with covid-19- preliminary report. *N Engl J Med*. 2020;384(8):693–704. doi:10.1056/NEJMoa2021436.
- Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med*. 2022;8(6):46–7. doi:10.1016/S2213-2600(20)30216-2.
- Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Rosas et al “Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. *N Engl J Med*. 2021;384(16):1503–19. doi:10.1056/NEJMoa2028700.
- Salama C, Han J, Yau L, Reiss WG, Kramer B, Cameron ML, et al. Carlos Salama Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med*. 2021;384:20–30. doi:10.1056/NEJMoa2030340.
- Colaneri M, Bogliolo L, Valsecchi P. “Tocilizumab for Treatment of Severe COVID-19 Patients: Preliminary Results from SMATteo COVID19 REgistry (SMACORE)”, *Microorganisms* 2020. *Microorganisms* . 2020;8(5):695. doi:10.3390/microorganisms8050695.

Author biography

Ajeet Singh Thakur, Junior Resident

Swapnil Jain, Assistant Professor

Bhavya Shah, Assistant Professor

Arti Julka, Professor and HOD

J.C. Agrawat, Associate Professor

Cite this article: Thakur AS, Jain S, Shah B, Julka A, Agrawat JC. A retrospective study of the role of Tocilizumab in preventing or controlling cytokine storm in COVID-19 cases. *J Prev Med Holistic Health* 2022;8(1):30-34.