Original Research Article

Role of tocilizumab in combating cytokine storm in moderate & severe covid 19 patients- Retrospective observational study

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.

METHODOLOGY:

Study population is sorted by 1:1 matching depending on the HRCT Chest CT Severity Score.Outcome is measured as deaths, discharge with or without LTOTalong with clinical improvement of the patient measured using 9 points ordinary scale score of WHO and length of ICU stay post administration& levels of inflammatory markers (CRP, IL 6) on day of administration- baseline (D0), 1 & 3 days after administration (D+1 & D+3).

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.

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.

KEY WORDS:

COVID 19, Tocilizumab, Standard of Care, Inflammatory markers, 9-point ordinary scale developed by W.H.O.

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[1,3].Since then, the spread of COVID 19 to other countries took place at faster rate reporting mortality associated with COVID 19 as never seen before due to any other illness. The disease is characterized by hyperinflammatory syndrome along with cytokine storm[2]. The disease progresses as early infection followed by moderate pulmonary involvement with or without hypoxia and finally to a severe systemic hyperinflammatory phase[4]. The severe form of disease is characterized with higher levels of proinflammatory cytokines like IL 6, IL2, IL 10, INF γ, C reactive protein (CRP), Ferritin& D- dimer[5,6]. 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. The current study aims at describing the effect of a monoclonal IL 6 inhibitor,

Tocilizumab (TCZ),in combating the cytokine storm in moderate &severely ill COVID 19 patients thereby improving the patient clinically.Tocilizumab is a recombinant humanized monoclonal antibody of IgG1 class that inhibits the IL 6 receptors on the membrane, being the first biologic agent targeting IL 6[7,8]. Evidences suggest that, blocking the key inflammatory mediator IL 6 in severe COVID 19 reduces the disease severity[9]. Use of Tocilizumab is already approved in treating Rheumatoid arthritis, systemic juvenile idiopathic arthritis and giant cell arteritis[7].

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 WHO[10]reduction in the levels of inflammatory markers (CRP, IL 6)on 1 day after administration (D +1)&3 days after administration (D +3) along with the length of ICU stay following administration.

According to the scale, 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 diseases 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[10,27].

METHODS

AIM

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

OBJECTIVES

The primary objective of the study is to evaluate the potential benefits of TCZ in addition to the SoC in reducing mortality &clinically improvement inmoderate & severe ill COVID 19 patients in comparison to the SoC only treated patients.

METHODOLOGY

A retrospective observational study is carried out at Medysis hospitals, LB Nagar, Hyderabad (City), Telangana (State), India (Country) 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 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.

The study included the patients admitted to the ICU from 19-05-2020 to 18-05-2021 in Medisys hospital,RTPCR proven Covid 19 patients and/ or HRCT Severity score $\geq$ 9with partial oxygen saturation (SpO_2) $\leq$ 93% on room airand requiring oxygen of at least 8-10 lit/ min and 9-point ordinary scale score of $\geq$ 4 with the age $\geq$30 years.

INCLUSIVE CRITERIA

- RTPCR proven Covid 19 patients&moderate tosevere on HRCT Chest (CTSS≥9).
- Patients in ICU at the time of TCZ administration.
- Patients in ICU matched with TCZ group.
- Patients whose SpO_2 is ≤ 93% on room air and requiring oxygen support of ≥ 8-10 lit/min.
- Patients with 9-point ordinary scale score of ≥ 4.

EXCLUSIVE CRITERIA

- Immune compromised patients.
- Pregnantindividuals.
- Patients who have an 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.

Comment [MF1]: an deleted.

PROCEDURE

Medical records of all the patients admitted to the hospital between 19-05-2020 to 18-05-2021 due to COVID 19 illness are screenedfor 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 SpO_2≥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 8mg/kg body weight uptomaximum of 400mg.

On the day of administration (D0) and 1 day after administration (D+1), and 3 days after administration (D+3) the test group patient along with the matched patient in control group were given with a score value according to the 9-point ordinary scale and the levels of inflammatory markers were screened along with the final outcome.

MEASURE OF ENDPOINT OF THE STUDY/ OUTCOME

- The outcome of the studywasmeasured asDeath or Discharge with or without LTOT.
- The linear trend of the inflammatory markers (IL-6, CRP) was studied(D0, D +1, D+3).
- The length of ICU stay following administration.

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

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 baseline values of W.H.O. ordinary scale score, CRP& IL 6 with those on D+1 and D+3, which are of numerical variables. The 3 time point values 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 asp≤0.05 indicating the existence of statistically significant difference between the values of 3 time points and vice-versa.

Odds ratio was calculated to determine the odds occurring in the test group in comparison to the control group.

Categorical values are presented as %population and are compared directly between groups.Our study also calculated deaths reported in each group towards the end of their hospital stay. Odds ratio is calculated for each of the final outcome of our study viz; Death, Discharge with or without LTOT.

Following administration, 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 and is presented to compare between the groups.

RESULTS

The test group included 17 patients with mean age of 51.5 ± 9.4, 15 males (88.2%)&2 females (11.7%), and the control

group included 17 patients with mean age of 49.1 ± 10.1,12 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 LTOTwere 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 valuesare graphically presented using 100% stacked column graph, *Figure 1*.

According to the W.H.O. 9-point ordinary scale score value, in the test group, on D0 82.5% population were with 5-point score & 17.65% with 6 score. On D+1 5.88%, 70.59%, 17.65% & 5.88% were with score of 4, 5,6&8 respectively. On D +3 5.88%, 5.88%, 70.59%, 5.88%, 11.76% population were with score value of 3, 4, 5, 6, & 8 respectively, *Figure-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 pointspresented pictographically in the *Figure- 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 of 4, 5 & 6 respectively. On D+3 29.41%, 64.70% & 5.88% population

were with score 4, 5 & 8 respectively, *Figure-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.

Figure-2d represents the individual patient 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 7.32± 1.84 days with p- value 0.07 indicating no statistically significant difference between the two groups. The individual patients stay in ICU is represented in the *Figure 1b*so as to compare between the groups.

The average of CRP baseline values (D0) in test group is 28.56±16.4& in control is 45.45±20.4.

In test groupthe average values on D0 were 28.56±16.4which dropped down to 22.48±13.29 on D+1 &to 19.72±14.12 on D+3. Single factor annova test conducted to check for significant decrease in the CRP values over the 3 time points 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 *Figure 3a*.

In control groupthe average value of CRP on D0 was 45.45±20.4 that dropped to 36.75±15.17 on D+1& to 33.43±17.75 on D+3. Single factor annova test conducted to confirm the significance decrease in the values over 3 time points of the study 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 *Figure-3b*.

Another inflammatory marker studied was IL 6. The average value of IL6 in test group was, on D0: 146±28.96, on D+1136.53±24.67, on D+3 132.06±29.85. Single factor annova test conducted & 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*Figure-3c*.

The average values of IL 6 in control group were; on D0: 141.41±20.66; on D+1: 134.76±22.52 & on D+3: 133.35±25.96. Single factor annova 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 *Figure-3d*.

DISCUSSION

A novel strain of corona virus, SARS-CoV-2, is known to cause Covid-19 disease. First official case of this disease was reported on 31 December 2019 in China and soon spread to all countries and declared as a pandemic disease on March 11th 2020 by WHO[1].

SARS-CoV & MERS CoV are the two known zoonotic corona viruses that cause respiratory track damage. The current pandemic disease COVID-19 is caused by SARS-CoV-2 virus[11]. The elderly patients with age >65 years and with comorbidities are at higher risk of mortality[12]. 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. This cytokine storm is responsible for inflammation seen in COVID 19 disease[13]. Inflammatory cell infiltrates found in the lungs of severe COVID 19 patients made this pathology more evident[14]. Based on these evidences, it is considered that blocking the pathways of inflammatory cytokines 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 sever COVID 19 illness[13,15].

Comment [MF2]: severe

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[16], and in polyarticular-course juvenile idiopathic arthritis, systemic-onset juvenile idiopathic arthritis and Castleman's disease[17]. Tocilizumab is available in the brand names Actemra or RoActemra[18]. It works by inhibiting the IL6/sIL6 complex binding to IL6 receptors and blocking the signalling of IL6 pathway. Elimination of TCZ is dose dependent with non-linear pharmacokinetics[11].

Studies conducted by Qun Li, et al, on 425 population size demonstrated that 55% of cases tested positive were reported to have been to Huanan Seafood wholesale market with mean incubation period of 5.2 days and median age of 59 years of which 56% population are male[19]. The same study estimated the basic reproduction rate (R_0) as 2.2.However meta-analysis conducted by Md. ArifBilla, et al reported an R_0 of 2.8[20].

Initial studies conducted by XiaolingXuet al.[15], 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[21]. 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 levelsare responsible for clinical improvement of the patient[22].

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[23]. The similar results are reported in a prospectivestudy conducted by Marta Colaneri, et al reporting non- statistically significant reduction in mortality and ICU admission in patients treated with TCZ on comparison with patients treated with SoC[24].

Retrospective cohort study conducted on non-ICU admitted patients by CorradoCampochiaro, et al. reported similar results of non-statistically significant decrease in mortality in TCZ treated patients over a 28 day follow up[25].

Rapid beneficial effect of TCZ on fever and inflammatory markers are seen with no effect on clinical outcome in the 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[26]. Depending on these results of the study, TCZ administration could be of higher risk for critically ill patients and careful supervision is required while administration.

SUMMARY

The comparison between the test group (TCZ given group) and control group (TCZ not given group) is carried to find out

the group with better outcome in terms of mortality and discharge with or without LTOT, significant reduction of inflammatory markers & favourable WHO scale scoring over the study time points (as described in the study procedure and statistical analysis section).

Deaths & Discharge with LTOT in the test group were reported slightly higher than those in control group with OR=1.68 & 1.63 respectively & in terms of discharge without LTOT the control group has a higher % population than the test group with OR= 0.2 (corresponding to the odds seen in test group).

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. The overall values of all the factors considered in our study to compare the test group and control group is tabulated in Table 1.

CONCLUSIONS

Retrospective observational study is conducted to postulate the benefits of adding tocilizumab to the standard of carein

treating moderate to severe COVID 19 patients in terms of clinical improvement measured using 9-point ordinary scale developed by W.H.O., and reduction in the levels of inflammatory markers&final outcome. However, our study concludes no marked benefits with the addition of TCZ to the standard of care in treating moderate and severe COVID 19 patients.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 many 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 like its usage in age, severity of the disease, comorbidities, IL6 levels, dose of TCZ required along with no. of doses for its application.

INFORMED CONSENT

No informed consent is obtained since the study is an observational case cohort study.

ETHICAL STATEMENT

Since no intervention is being done and informed consent form is obtained, our study do not require ethical statement.

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FIGURES

FIGURE-1: 1a: Final outcome of the study groups in 100% stacked column graph, 1b: post administration ICU stay of individual patients of both the groups in 100% stacked column graph

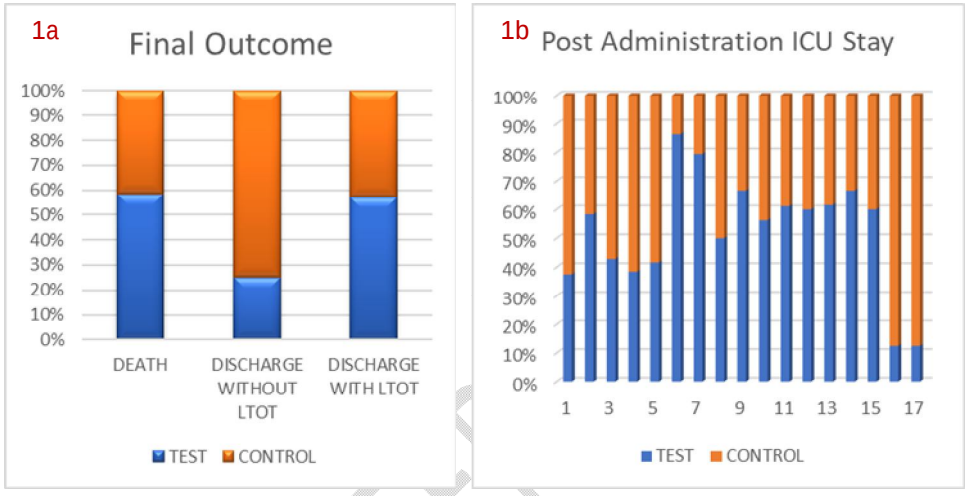

Figure 1: 100% staked column graph representing final outcome (a) and post administration ICU stay (b) in both the groups of study

FIGURE- 2: 2a: % population of test group with each score value on different time points. 2b: W.H.O. score of individual patients of test group on different time points. 2c: % population of control group with each score value on different time points. 2d: W.H.O. score of individual patients of control group on different time points

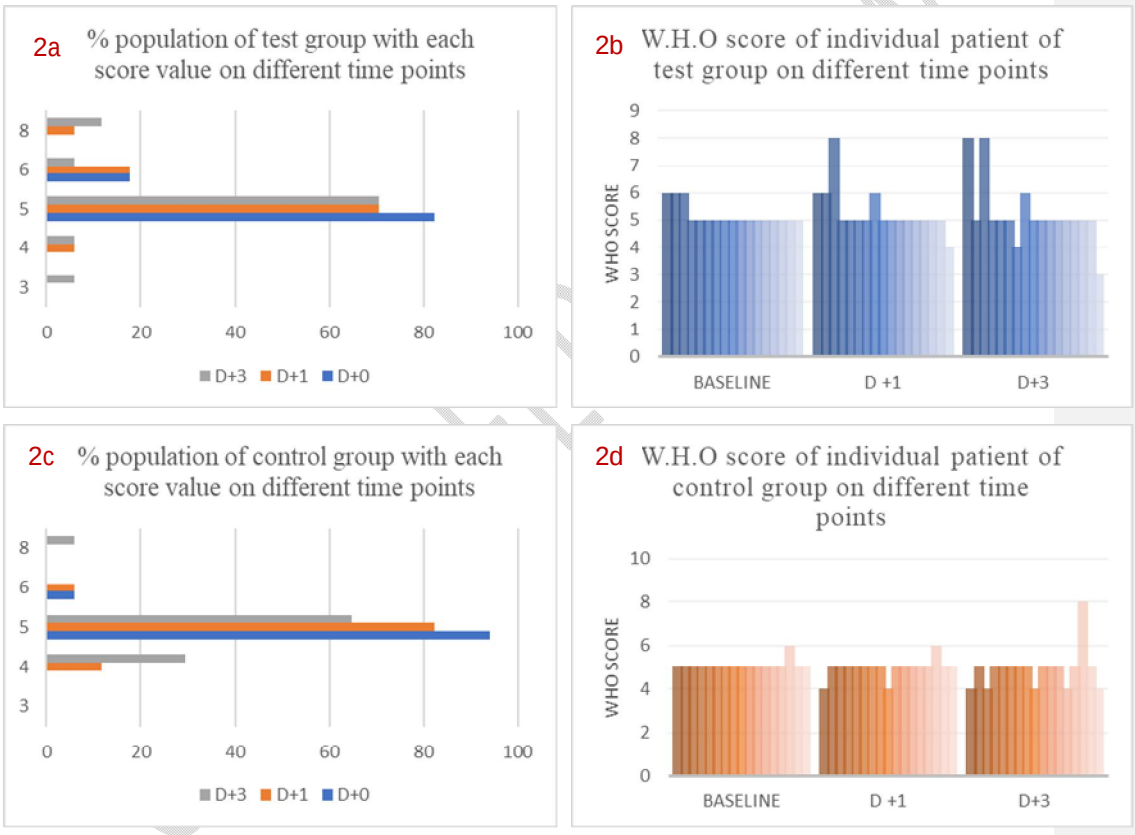

Figure 2: According to the W.H.O. 9 points ordinary scale, % population with each score in test group (a) & control group (c) along with the score of individual patients of test group (b) & control group (d) on different time points

FIGURE-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. 3a: CRP levels of individual patients in test group on different time points. 3b: CRP levels of individual patients in control group on different time points. 3b: IL-6 levels of individual patients in test group on different time points. 3d: IL-6 levels of individual patients in control group on different time points.

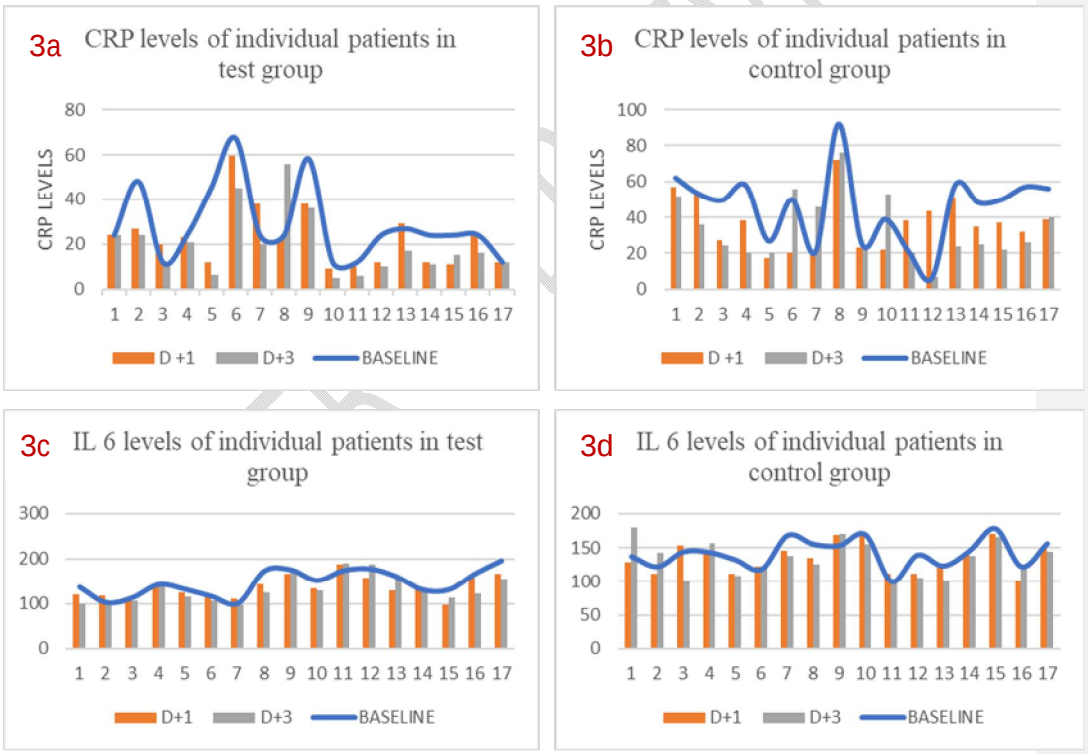

Figure 3: levels of inflammatory markers of our study. baselines values are represented using line so as to compare the values of D+1 and D+3 directly. levels of CRP of test group (a) and control group (b), levels of IL6 of test group (a) and control (b)

TABLE

TABLE-1: Values of all the parameters/ factors of our study in both the groups.

Factor (Measure)		Test group (n=17)	Control group (n=17)
Age in years	Mean± SD	51.5±9.4	49.1±10.1
Males	n (%)	15 (88.2%)	12 (70.5%)
Females	n (%)	2 (11.7%)	5 (29.4%)
Death	%	41.18%	29.41%
	OR	1.68	-
	95% CI	0.79, 13.54	-
Discharge with LTOT	%	47.06%	35.3%
	OR	1.63	-
	95% CI	1.29, 6.46	-
Discharge without LTOT	%	11.76%	35.3%
	OR	0.2	-
	95% CI	0.03, 1.16	-
9-point ordinary scale score	P value	0.92	0.73
Post administration length of ICU stay	Mean± SD	9.06± 6.18	7.32± 1.84
CRP	P value	0.21	0.14
	D0 (Mean± SD)	28.56±16.4	45.45±20.4
	D+1 (Mean± SD)	22.48±13.29	36.75±15.17
	D+3	19.72±14.12	33.43±17.75

	(Mean± SD)		
IL 6	P value	0.34	0.56
	D0 (Mean± SD)	146±28.96	141.41±20.66
	D+1 (Mean± SD)	136.53±24.67	134.76±22.52
	D+3 (Mean± SD)	132.06±29.85	133.35±25.96

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