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ORIGINAL RESEARCH **CORONA EXPERIENCE**

Efficacy of tocilizumab in critically ill COVID-19 patients: a retrospective cohort

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Abstract

Background & Objective: Covid-19 is a complex disease with unpredictable blended pattern, and it resembles the cytokine release syndrome (CRS), marked with vasculopathy, coagulopathy, ARDS, multi-organ failure, and aggressive rise of inflammation markers in the serum. Tocilizumab (TCZ) has been in use as an off-label drug due to its antagonist activity on IL-6 receptor. This study compared the efficacy of standard of care (SOC), and SOC along with TCZ, in critically ill COVID-19 patients.

Methodology: In this retrospective cohort, we included 74 critically ill COVID-19 patients, aged between 18 to 90 y. Those who received only SOC were placed in the SOC group, while patients who received TCZ in addition to SOC, were placed in the TCZ + SOC group. The SOC included low molecular weight heparin (LMWH) 60 mg S/C OD, dexamethasone 6 mg IV OD, remdesivir (antiviral) 200 mg IV stat then 100 mg IV OD for 5 days and when needed 10 days, antibiotics for secondary infection e.g., Azithromycin 500 mg IV OD, in the presence of High flow Oxygen (HFO) or CPAP. X-rays chest, serum levels of lactate dehydrogenase (LDH), D-Dimers, ferritin, pro-BNP, C-reactive protein (CRP), total leukocyte count (TLC), renal and liver markers, serum electrolytes, sugar levels, and ABGs were obtained from the data, at the time of admission in ICU and on the 7th day of ICU stay.

Results: 57% patients received only SOC while 43% received TCZ in addition to SOC. Improvement in hypoxia and radiological findings on day-7 was more in SOC' group than TCZ+ SOC' group (52% vs. 34% and 52% vs. 31% respectively), but it was not statistically significant. Overall improvement in inflammation markers on day-7 was similar in both groups with p = 0.925. Survival was 45% vs. 37.5% in SOC' vs. TCZ+ SOC' group respectively (p = 0.504).

Conclusion: Tocilizumab does not alter the overall survival of critically ill COVD-19 patients.

Key words: COVID-19; Tocilizumab; Standard of care; Efficacy; Survival

Abbreviations: TCZ – Tocilizumab; HFO - High flow Oxygen; LDH - lactate dehydrogenase; CRS - cytokine release syndrome; CRP - C-reactive protein; SOC - standard of care; LMWH - low molecular weight heparin; COVID-19 - Coronavirus Disease 2019; SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2

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1. Introduction

In this past year, COVID-19, the global pandemic, has proven to be calamitous to the human population; leading to a total of 87.2 million infected cases and 1.88 million deaths all over the world.[1] While in Pakistan it took more than 10,000 lives by infecting 495,000 people, since March 2020.[2]

Covid-19 is a complex of symptoms involving multiple body systems, exhibiting an unpredictable pattern of blended clinical scenarios. In severe cases, it shows patterns that resemble the "cytokine release syndrome" (CRS), marked with vasculopathy, coagulopathy, acute respiratory distress syndrome (ARDS), multi-organ failure, and aggressive rise of inflammation markers in the serum.[3-8]

Although some countries have come up with the vaccine against COVID-19 virus, efficacy of these different vaccines is still unknown. And their availability in our country is unspecified. So until the availability of the vaccine and even afterwards, we need to assess and evaluate the available treatment options against COVID-19. Among these options, Tocilizumab (TCZ) is one under trial in COVID-19 patients, due to its antagonist activity on IL-6 receptor.[9] Its efficacy is yet to be established in these patients, as fewer studies are available until today which are indecisive.[10,11] TCZ has been used with 'standard of care' (SOC) treatment which includes steroids, antiviral, and anticoagulation agents in these patients.

In our country, no study has been published yet emphasizing the role of TCZ in critically ill COVID-19 patients. Especially its efficacy is needed to be compared with other treatment options in critically ill COVID-19 patients. Our hospital is following the policy made by our provincial advisory committee and thus SOC is being given to COVID-19 patients since June 2020. TCZ was also incorporated in the guidelines as an experimental drug to treat the CRS-like symptoms in critically ill COVID-19 patients. We conducted this study to establish its role in critically ill patients with COVID-19, who are taking SOC, as no treatment modality has been authenticated yet, not only in Pakistan but all over the world.

This study compared the efficacy of SOC, and SOC plus TCZ in critically ill COVID-19 patients.

2. Methodology

For our retrospective cohort study, after approval from the Institutional Review Board of Sheikh Zayed Hospital Rahim Yar Khan (IRB No. 146/IRB/SZMC/SZH), we retrieved data from COVID-19 ICU patients' records. A total of 170 COVID-19 patients were admitted in COVID-19 ICU through the COVID-19 isolation ward and flu filter, between 14th June 2020 and 2nd December 2020. Informed written consent had been taken from patients and their attendants for all kinds of treatment. Identities of patients were concealed for privacy.

In our study, after excluding the patients who were received dead, in severe shock due to sepsis, multi-organ failure, or in gasping state, a total of 74 patients were included in the study with a positive PCR for COVID-19 after a throat or nasal swab along with radiographic evidence of chest infiltrates, severe hypoxia as evident through SpO_2 (O_2 saturation < 90% on 10 L of O_2) and/or PaO_2 (arterial O_2 < 60 mmHg), aged between 18 to 90 y of both genders. Basic information such as age, gender, and presence of co-morbidities was obtained from the retrieved data, and two categories of patients were identified. We labeled them as 'SOC group' and 'TCZ + SOC group' as per treatment they received. Those who received only SOC were placed in the SOC group, while patients who received TCZ in addition to SOC, were placed in the TCZ + SOC group.

TCZ was not given to the patients with coagulation abnormalities, known hypersensitivity to TCZ, deranged liver parameters five times the normal, renal impairment, history of gastric perforation, and pregnancy. The SOC included low molecular weight heparin (LMWH) 60 mg S/C OD, dexamethasone 6 mg IV OD, remdesivir (antiviral) 200 mg IV stat then 100 mg IV OD for 5 days and when needed 10 days, antibiotics for secondary infection e.g., Azithromycin 500 mg IV OD, in the presence of High flow Oxygen (HFO) or CPAP.

X-rays chest, serum levels of lactate dehydrogenase (LDH), D-Dimers, ferritin, pro-BNP, C-reactive protein (CRP), total leukocyte count (TLC), renal and liver markers, serum electrolytes, sugar levels, and ABGs were obtained from the data, at the time of admission in ICU and on the 7th day of ICU stay.

Investigations retrieved at the time of admission were labeled as baseline.

Efficacy of treatment was the main outcome of our study, which was assessed by improvement in inflammation markers and/or in SpO_2 and/or reduction in chest infiltrates on radiographs within one week of initiation of treatment in COVID-19 ICU. This was labeled as primary outcome variable, while the secondary outcome variable was overall survival, in the two groups.

Statistical analysis: Data were entered into SPSS version 16. String variables like gender, presence of co-morbidities, presence of chest infiltrates, survival outcome, improvement in inflammation markers and chest infiltrates, correction of hypoxia was presented as percentages and frequencies. The primary and secondary outcome variables were analyzed using crosstabs and chi-square test. Survivors and non-survivors were compared in regard to age, for presence/absence of co-morbidities, and their inflammation markers plus TLC at the time of admission and at 7th day of ICU stay. The duration of ICU stay and all laboratory data were presented as Mean ± Standard Deviation.

3. Results

According to the results (Table 1**)**, it is evident that more than 50% of patients coming to Covid-19 ICU were having moderate to severe radiological findings, severe hypoxia (<45% SpO2), severe ARDS (low P/F ratio), and male gender was more affected than female (72% vs. 28% respectively). At the time of admission, basic characteristics in the two groups were similar regarding mean age, hypoxia, p/f ratio, and radiological findings. Although patients in the 'SOC' group were shown to have more co-morbidities than the 'TCZ + SOC' group (71% vs. 56%), this difference was statistically insignificant (p = 0.175).

After receiving treatment, improvement in hypoxia and radiological findings on the 7th day was more obvious in the 'SOC' group than the 'TCZ + SOC' group (52% vs. 34% and 52% vs. 31% respectively), but it was not statistically significant. Overall improvement in inflammation markers on the 7th day after treatment was similar in both the groups with a p-value of 0.925. Our secondary outcome, the survival, was 45% vs. 37.5% in 'SOC' vs. 'TCZ + SOC' group respectively. Although it showed that more patients have survived in the 'SOC' group but this finding was statistically insignificant p = 0.504.

In Table 2, the important laboratory data, before and after treatment, is presented in the form of Mean±SD and is compared between the two groups as well as within each group. If we see the impact of treatment on the individual markers, we will get the evidence that the treatment with SOC alone was quite effective in reducing the inflammation response in these patients. While with the addition of TCZ, reduction in inflammatory response was enhanced (see the left columns in Table 2). There is a statistically significant difference found in day-1 vs. day-7 markers after the addition of TCZ. But there is also a persistent rise in D-dimers in the 'TCZ + SOC' group on Day-1 vs. Day-7 (696 vs. 805), while in the 'SOC' group D-dimers showed little improvement on the 7th day. Similarly, Pro-BNP was not improved in the 'TCZ + SOC' group (694 vs. 1011 at Day-1 vs. Day-7 respectively). While in the 'SOC' group, there is improvement in Pro-BNP at Day-7 (Table 2), though statistically this is not significant (p = 0.341).

Although, when the effect on inflammation markers was analyzed individually in each group, it showed that TCZ was an effective addition to SOC (Table 2). But when the overall efficacy was compared in the two treatment groups, we found no statistically significant difference (Table 2).

We also compared the basic characteristics of survivors and non-survivors in our study (Table 3). Though the male population was more affected than females, survival was not different for the two genders (p = 0.677). Survival of patients without co-morbidities was similar to the patients having co-morbidities, showing no statistical differences.

Non-survivors had elevated CRP, LDH, D-dimers, and Pro-BNP more than the survivors at the time of admission. Even after treatment, CRP, LDH, D-dimers, and Pro-BNP though showed an improvement but were still on a higher side in the non-survivors group than the survivors (Table 3).

Table 1: **Demographic data, co-morbids and outcomes of both groups of patients in COVID-19 ICU**

Characteristics		Total	Groups		p value
			SOC	TCZ + SOC	
Gender	Male	53 (72)	24 (57)	29 (90.6)	0.002
	Female	21 (28)	18 (43)	3 (9.4)	
	Total	74	42 (57)	32 (43)	-
Chest infiltrates	Basis	22 (30)	15 (35.7)	7 (22)	0.218
	Up to mid	40 (54)	19 (45)	21 (65.6)	
	Above mid	12 (16)	08 (19)	04 (12)	
Age (Mean ± SD) y		59.4	60.76 ± 15.6	57.72 ± 14	0.390
SpO2 (baseline) Mean ± SD		77.5 ± 13.8	76.8 ± 13.4	78.8 ± 12.4	0.446
Median (IQR)		78 (42-96)	80 (42-94)	81 (45-96)	
Diabetes		37 (50)	21 (50)	16 (50)	1.000
Hypertension		37 (50)	25 (60)	12 (37)	0.060
Ischemic Heart disease		10 (13.5)	6 (14)	4 (12)	0.824
Asthma		3 (4)	2 (4.8)	1 (3.12)	-
CRF		3 (4)	2 (4.8)	1 (3.12)	-
CVA		2 (2.7)	2 (4.8)	0 ()	-
CLD		1 (1.4)	1 (2.4)	0 ()	-
Hypothyroidism		1 (1.4)	0 ()	1 (3.12)	-
Co-morbidities (Overall)	Yes	48 (65)	30 (71)	18 (56)	0.175
	No	26 (35)	12 (29)	14 (44)	
Duration (days) Mean		9.36	9.00	9.84	0.540
Improvement in SpO_2		33 (45)	22 (52)	11 (34)	0.123
Improvement in chest films		32 (43)	22 (52)	10 (31)	0.069
Improvement in inflammation markers		25 (34)	14 (33.33)	11 (34)	0.925
Survival		31 (42)	19 (45)	12 (37.5)	0.504

Data given as n (%), unless specified otherwise

4. Discussion

In our study, we tried to determine the efficacy of TCZ through its effects on inflammation markers, correction of hypoxia, ARDS, and overall survival. We compared the results in two groups, one being treated with SOC and the second being treated with TCZ in addition to SOC to establish their efficacy in critically ill patients with COVID-19. As per our analysis, it is found that with the addition of TCZ to the standard of care treatment (SOC), no significant improvement was seen and it did not alter the outcome in critically ill COVID-19 patients.

Searching through literature we found some retrospective studies favoring our results. Campochiaro et al. in their retrospective study on 65 severe COVID-19 patients, have compared the efficacy of TCZ with SOC within 28 days of admission.[10] Clinical improvement in 69 vs. 61, and mortality in 15 vs. 33 was found in TCZ vs. SOC

Table 2: Comparative inflammation markers and other labs at admission and at 7th Day of COVID-19 ICU stay (*Data given as Mean ± SD unless specified otherwise)*

Laboratory Data	Day	Groups		p	95 % CI	
		SOC	TCZ + SOC		Lower	Upper
CRP (mg/L)	Day 1	79 ± 85	99 ± 69	0.303	-56.16	17.71
	Day 7	41 ± 60	38 ± 54	0.818	-23	30
Sr. Ferritin (ng/ml)	Day 1	772 ± 856	734.66 ± 628	0.835	-321	396
	Day 7	519.5 ± 728	441.56 ± 547	0.614	-229	385
Sr. LDH (U/L)	Day 1	591 ± 676	851 ± 713	0.114	-584	63
	Day 7	302.45 ± 406	421.41 ± 533	0.280	-336	98
D-Dimers (ng/ml)	Day 1	348 ± 712	696 ± 1714	0.244	-938	242
	Day 7	326 ± 842	805 ± 204	0.173	-1172	214
TLC (per mm^3)	Day 1	11000 ± 4768	11550 ± 3492	0.603	-2518	1472
	Day 7	12417 ± 7188	13475 ± 6000	0.504	-4198	2082
Pro-BNP (pg/ml)	Day 1	1247 ± 5407	695 ± 1492	0.577	-1410	2515
	Day 7	393 ± 1706	1011 ± 4270	0.396	-2060	823

group respectively. But these differences were statistically insignificant in terms of overall outcome.

Tsai et al. did a retrospective study on 132 COVID-19 patients, compared the in-hospital mortality in these patients with and without TCZ administration, and found no statistical difference in the outcomes in both the groups thus favoring our study results.[11] They compared the basic characteristics and laboratory data in survivors and non-survivors, and it was found that CRP was significantly elevated in the non-survivor group. And this was a similar finding in our study.

Colaneri et al. in their retrospective study, included 112 COVID-19 patients with severe pneumonia and ARDS.[12] They compared two groups similar to our study and according to their results; though administration of TCZ was associated with a decline in CRP it did not alter the mortality rate of these patients as compared with standard of care treatment. This finding is consistent with our results.

We found a few RCTs (randomized controlled trials) in the context of our study. One such RCT by Stone et al. has evaluated 243 COVID-19 patients in the USA, by comparing the effects of TCZ with placebo.[13] Their results show that there was no significant difference found among the two groups regarding O_2 requirement, intubation, invasive ventilation, and mortality. They concluded that TCZ was not effective in COVID-19 patients in preventing death or intubation.

In two other studies by Salvarani et al. and Rosas et al. TCZ was found to be ineffective as compared to standard of care treatment, in regards to disease progression, clinical improvement, and death in COVID-19 patients.[14,15] These results are comparable to our study results.

Then there are few observational studies found which show data, favoring the use of TCZ in COVID-19 patients. Ramaswamy et al. in their observational study as case-control, have compared the effects of TCZ treatment vs. no treatment, on 86 COVID-19 patients, and their results showed a 75 reduction in in-patient deaths after treatment with TCZ.[16] Well, basing their results on untreated patients leading to death has raised controversies in this study. Guaraldi et al. in their retrospective cohort study, compared two groups of 544 patients in total: one group treated with SOC and the other with TCZ in addition to SOC.[17] Their results show a significant reduction in deaths among the TCZ group as compared to SOC group 7 vs. 20 respectively. Salvati et al. have compared two similar groups comprising only 33 COVID-19 patients in total, and their results favor the use of TCZ in regards to improvement in the pulmonary vasculature as evident from X-ray chest.[18]

Table 3: Comparative patient characteristics between overall survivors and non-survivors

Characteristics		Survivors (n = 31)	Non-Survivors (n = 43)	p value
Gender n (%)	Male (n = 53)	23 (43.4)	30 (56)	0.677
	Female (n = 21)	08 (38)	13 (62)	
Age (Mean ± SD)		56 ± 18.2	62 ± 11.9	0.128
Co-morbidities n (%)	(n = 48)	20 (41.6)	28 (58.4)	0.957
Diabetes n (%)	(n = 37)	16 (43)	21 (57)	0.814
HTN n (%)	(n = 37)	14 (38)	23 (62)	0.480
IHD n ()	(n = 10)	4 (40)	6 (60)	0.896
CRP (mg/L)	baseline	79.8 ± 87.63	93.5 ± 72.70	0.466
Sr. Ferritin (ng/ml)	baseline	796.8 ± 868.57	726.5 ± 684.24	0.698
LDH (U/L)	baseline	618.23 ± 620.52	764.84 ± 773.11	0.378
D-D (ng/ml)	baseline	348 ± 698	606 ± 1552	0.391
Pro-BNP (pg/ml)	baseline	1474 ± 6254	672.4 ± 1449	0.419
TLC (per mm^3)	baseline	10910 ± 4747	11500 ± 3880	0.558
CRP (mg/L)	7^{th} Day	25 ± 42	50 ± 64	0.064
Sr. Ferritin (ng/ml)	7^{th} Day	499 ± 647	476 ± 665	0.883
LDH (U/L)	7^{th} Day	397 ± 452	322 ± 479	0.497
D-D (ng/ml)	7^{th} Day	354 ± 1061	661 ± 1737	0.386
Pr0-BNP (pg/ml)	7^{th} Day	568 ± 2058	727 ± 3663	0.827
TLC (per mm^3)	7^{th} Day	10800 ± 4455	14370 ± 7622	0.02

They did not comment on overall survival in these patients and their sample size was extremely small.

Biran et al. have conducted a retrospective study in 18 hospitals in the USA and represent data of 630 COVID-19 patients in their study.[19] Their results are in favor of TCZ in COVID-19 patients who require ICU care, as TCZ showed a reduction in mortality.

Somers et al. in their observational study on 154 patients, have concluded that the use of TCZ is associated with a reduction in death, though there are higher chances of superinfection.[20] And this observation is causing uncertainty regarding the use of TCZ in COVID-19 patients.

A large observational multi-center study done by Martinez-Sanz et al comprises a total of 2047 COVID-19 patients, has studied the interaction between TCZ and high levels of CRP.[21] And their results show the effectiveness of TCZ in such patients, in regards to reduction in mortality.

Mikulska et al. in their observational study, have compared the efficacy of TCZ with SOC treatment in 196 COVID-19 patients.[22] And they concluded that the efficacy of TCZ is superior to SOC based on improvement in overall survival (86 vs. 72 respectively).

We did not find any randomized controlled trial so far, favoring the use of TCZ in COVID-19 patients. These were few observational studies and mostly have controversies in their results which we have discussed here.

5. Limitations

The first limitation of our study is that it's a retrospective cohort study and not a randomized controlled trial. A lot of bias and confounding factors cannot be removed from such study designs. Secondly,

our sample size was small which can produce by chance results.

We suggest more randomized controlled trials in this regard to establish the veracity and to reach an authenticated conclusion.

6. Conclusion

From the results obtained through statistical analysis, and comparing our results with other available studies, we conclude that administration of tocilizumab does not alter the overall survival of the critically ill COVD-19 patients.

7. Conflict of interest

None

8. Authors' contribution

SS: Conceived, designed and did statistical analysis editing and writing of manuscript
BB: Data collection
SSH: Designed & Editing
GM: Statistical analysis
SAAN: Conceived & Designed

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