2020

12th, May, 2020

TOCILIZUMAB – An option for Patients with COVID-19 associated Cytokine release syndrome; A single Center experience

IRB# FMH-05-2020-IRB-758-M

Study Protocols, Statistical analysis plan

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Methodology:

Study Design: It was a Quasi-experimental study where participants were allocated using predefined protocol who met the inclusion criteria of study after signing a written & informed consent either by the patient or the person legally authorized to sign.

Study Settings: The study was conducted in Fatima Memorial Hospital, Lahore among in-house patients of COVID-19.

Sample size and technique: our sample size was 93, out of which 33 patients were kept in the experimental group who were offered Tocilizumab and 60 patients were offered Corticosteroids for comparing the efficacy of both modalities of treatment. The sampling technique was consecutive sampling as per the inclusion and exclusion criteria

Data Collection and analysis Procedure: All admitted patients who had moderate to severe disease or who were in a cytokine storm, were studied and data related to Epidemiological, demographic, clinical, laboratory, radiological, and treatment were collected and analyzed. Outcomes were noted and compared.

The response of the patient after Tocilizumab or Corticosteroid administration was recorded. The response was recorded based on clinical parameters (Oxygen requirement, Fever, Need for invasive positive pressure ventilation), biochemical parameters (D-dimers, C-reactive protein (CRP), Ferritin, Lactate dehydrogenase (LDH) levels), Chest X-ray findings, and Repeated PCR test for COVID-19. Any side effects noted after administration of TCZ/ Corticosteroid were recorded.

Tocilizumab administration protocol: Patients received an initial dose calculated as per the body weight (8mg/kg) maximum 800mg/dose) over 1 hour, followed by up to three additional doses if required as per the response after the first dose with 8 hours intervals. Predefined

Parameters of disease severity were assessed 12 to 24 hourly. Injection Paracetamol 1g was administered before infusion.

Corticosteroid administration protocol: Patients received methylprednisolone 80mg/day in two divided doses as per national/local guidelines and predefined parameters of disease severity were assessed on each day.

Data was entered and analyzed using SPSS 25.0. Frequency and percentages were calculated for the qualitative variables like gender, comorbidity, symptoms, radiological findings, response to treatment. Quantitative variables of the study like age, laboratory parameters were expressed as Median (IQR).

Ethical Considerations: Patients were included in the study after written and informed consent Institutional review board IRB approval was taken from the ethical committee. **IRB# FMH-05-2020-IRB-758-M**

Table.1: Baseline characteristics of the participants along with Comorbidities, Initial workup and their Outcomes

Characteristics	All patients (N=93)	Tocilizumab group (N=33)	Steroid group (N=60)
Median age(IQR)-years	58 (21)	60(14)	56(23)
Age category N (%) < 50 years			
50-70 years	30(32.3)	7 (7.5)	23 (24.7)
>70 years	48 (51.6)	20 (21.5)	28 (30.1)
	15 (16.1)	6 (6.5)	9 (9.7)
Male Sex _no(%)	67(72)	22(23.7)	45(48.4)
Female	26(28)	11(11.8)	15(16.1)
Comorbidities			
Diabetes Mellitus	37(39.8)	11(11.8)	26(28)
Hypertension	45(48.5)	17(18.3)	28(30.1)
Chronic kidney disease	9(9.7)	5(5.4)	4(4.3)
Ischemic heart disease	16(17.2)	5(5.4)	11(11.8)
Lung disease	7(7.5)	7(7.5)	0 (0)
Smoker	48(51.6)	16(17.2)	32(34.4)
Malignancy	5(5.4)	2(2.2)	3(3.2)
Symptoms at presentation			
Fever	80(86.0%)	32(34.4%)	48(51.6%)
Cough	75(80.6%)	29(31.1%)	46(49.4%)
Shortness of breath	86(92.4%)	32(34.4%)	54(58.06%)
Vitals on admission			
Respiratory rate_ IQR	26(9)	26(9)	26(9)
Heart rate_IQR	110(19)	109(11)	112(10)
Temperature_IQR	100(99)	101(99)	100(99)
Oxygen saturation at presentation	90(13)	90(13)	90(12)
Highest level of Care			
Intensive care unit	67(72.04)	33(35.5)	34(36.5)
Regular Medical floor	26(28)	0(0)	26(28)
PCR +VE	89(95.7)	33(35.5)	56(60.2) p-value
PCR –VE	4(4.3)	0(0)	4(4.3)
Chest x ray findings			

Bilateral patchy ground glass appearance	22(23.7)	22(23.7)	0(0)
Bilateral Consolidation with peripheral infiltrates	71(76.3)	11(11.8)	60(64.5)
Renal replacement therapy (RRT)	5(5.4)	1(1.1)	4(4.3)
Median hospital stay days(IQR)	7(4)	5(3.5)	9(5)
Outcomes			
Mechanical Ventilation days(IQR)	5(5.4)	3(3.2)	2(2.2)
Death	10(10.8)	6(6.5)	4(4.3)
Recovery	83(89.2)	27(29)	56(60)

IQR, interquartile range; length of hospital stay

Table.2: Comparative analysis, Pre and Post therapy biochemical markers of Tocilizumab group & Steroids group

	Variables	Tocilizumab group (N=33	Steroid group (N=60)	Total N93=)	p-Value between groups
Before	Oxygen requirement in liters_ Median(IQR)	18(5)	18(5)	8(9)	0.911
	Lymphocytes in 109 cells/liter_ Median(IQR)	1.9(9.90)	4.6(4.1)	3.9(4.0)	0.711
	D-dimers micro gram/mL Median(IQR)	2.1(4.4)	2.0(3.60)	2.0(3.75)	0.844
	CRP mg/dl Median_ (IQR)	200(190	202(177)	200(189)	0.800
	Ferritin ng/ml Median(IQR)	1525(1255)	2000(1002)	2000(1200)	0.424
	Trop I ng/ml _Median(IQR)	16(17)	12(11)	13.7(12.85	0.496
	Serum Creatinine mg/dl_ Median(IQR)	1.27(1.34)	1.31(1.9)	1.19(1.1)	0.012
After	Oxygen requirement in liters_ Median(IQR)	8(9)	8(9)	8(9)	0.714
	Lymphocytes in 109 cells/liter_ Median(IQR)	2.9(2.7)	4(4.1)	4.8(4.7)	0.941
	D-dimers micro gram/mL Median(IQR)	1.0(0.89)	1.0(1.16)	1.0(1.16)	0.433
	CRP mg/dl Median_ (IQR)	145(130)	139(90)	145(90)	0.942
	Ferritin ng/ml Median(IQR)	1000(1266)	1000(1000)	1000(1091)	0.884
	Trop I ng/ml _Median(IQR)	16(18)	11(11.0)	18(13)	0.827
	Serum Creatinine mg/dl_ Median(IQR)	1.1(1.2)	1.20(1.6)	1.4(1.3)	0.021

Results: Table 1 summarizes the baseline characteristics of the patients and few important vital signs but few of the important determinants are discussed here. A total of 93 patients were enrolled in our study, two groups were made according to the treatment modality offered and named as Tocilizumab (TCZ) group (case) and Corticosteroid (CS) group (Control), and 33 patients were kept in the TCZ group and 60 patients were enrolled in the corticosteroid group. The median age of all participants was 58 years (IQR-21), TCZ group participants' median age was 60 years (IQR-14) whereas, in the steroid group, it was 56 years (IQR-23). there were 67(72%) male participants and 26(28%) were female. The male predilection of covid-19 was noted down in this study. Regarding age categories, most of the patients 48(51.6%) were falling in the age range of 50 to 70 years, followed by 30(32.3%) and 15(16.1%) in the age categories of < 50 years and > 70 years respectively. Regarding the comorbidities in the participants, there were 37(39.8%) patients with diabetes mellitus, 11(11.8%) in the TCZ group, and 26(28%) in the CS group. There were 45(48.5%) patients having hypertension, 17(18.3%) in the TCZ group, and 28(30.1%) in the CS group. There were 9(9.7%) patients who had chronic kidney disease, 5(5.4%) and 4 (4.3%) in TCZ and CS group respectively. There were 16(17.2%) patients who had Ischemic heart disease, 5(5.4%) and 11(11.8%) in TCZ and CS group respectively. Discussing lung disease, there were a total of 7(7.5%) patients and all belonged to the TCZ group only. 48(51.6%) patients were smokers and 32(34.4%) in the TCZ group and 16(17.2%) in the CS group. Patients who had malignancy were 5(5.40%), 2(2.2%), and 3(3.2%) in the TCZ group and CS group respectively.

Regarding symptoms on presentation, Shortness of breath was the commonest symptom in both the groups, out of 93 patients, 86(92.4%) had it, TCZ group and CS group (34.4% vs 58.06%), Fever was observed in 80(86%), (34.4% vs 51.6%) and cough was seen in 75(80.6%), (34.4 vs 58.06).

Regarding vitals on admission, the median respiratory rate with IQR was 26(9) breaths per minute and the same values were seen in both the groups i-e 26(9) breaths per minute.

The median heart rate was 110(19) beats per minute, 109(11) in the TCZ group, and 112(10) in the CS group.

The median temperature was 100(2) degrees Fahrenheit.

The Median Oxygen saturation (SPO2 %) in liters with the Interquartile range (IQR) at presentation was 90 (13), the same value observed in the TCZ group whereas it was 90(12) in the CS group.

The highest level of care (Intensive care unit, ICU stay) was offered to a total of 67(72%) patients according to their severity of the clinical condition, (35.5% vs 34%) in TCZ and CS group respectively.

26(28%) patients were managed on the medical floor and all these patients belonged to the CS group.

Laboratory & Radiologic Findings:

There were 89 (95.7%) PCR positive patients from their nasopharyngeal swab and only 4(4.3%) had negative PCR reports but radiologically and clinically they were labeled as PCR negative Covid-19 patients as per decisions of senior consultant radiologists of the hospital and senior physicians.

All patients included in the study underwent a chest radiograph on admission, 22(23.7%) patients had the bilateral patchy ground-glass appearance and all belonged to the TCZ group and 71(76.3%) patients had bilateral pulmonary opacities with peripheral infiltrates, 11(11.8%) vs 60(64.5%) patients were in TCZ group CS group respectively.

Total 5(5.4%) patients needed renal replacement therapy (RRT), 1(1.1%) in TCZ vs 4 (4.3%) in the CS group.

On the whole, the total median hospital stay in days was 7 with IQR (4), there was a shorter hospital stay in the TCZ group, 5 with IQR (3.5) days and a longer hospital stay in CS group 9 with IQR (5) days.

The median time in days of patients who remained on invasive positive pressure ventilation (IPPV), was 5(5.4) days with a shorter duration in CS group 2(2.2) and 3(3.20) in the TCZ group.

Total 83(89.2%) patients recovered successfully and discharged, 27(29%) in the TCZ group and 56(60.2%) in the CS group.

Total 10(10.8%) patients died, out of which 6(6.5%) belonged to the TCZ group and 4(4.3%) belonged to the CS group.

Table.2: showing the comparison between the two groups' pre and post-treatment

Important parameters like Oxygen requirement, Lymphocytes count, biochemical markers like d-dimers, C reactive protein(CRP), serum ferritin levels, Troponin-I, and serum creatinine were measured before and after the treatment was offered to both the group.

Before treatment: The median Oxygen requirement with IQR was 18(5) in both the groups and in total it was 8(9).p-value(0.911).The median Lymphocyte count 109 cells/liter 3.9(4.0), TCZ vs CS group 1.9(9.9) vs 4.6(4.1), p-value (0.711), median D-dimers levels microgram/L 2.0(3.75), 2.1(4.4) vs 2.0 (3.60), p-value(0.844), median CRP levels mg/l 200(189), 200(190) vs 202(177),p-value(0.844), median Ferritin levels ng/ml 2000(1200),1525(1255) vs 2000(1002),p-value(0.424), median Trop-I levels ng/ml were 13.7(12.85), 16(17) vs 12(11),p-value(0.496), median Serum creatinine mg/dl was 1.27(1.34), 1.31(1.9) vs 1.19(1.12), p-value(0.012).

 After treatment: The median Oxygen requirement with IQR was 8(9) in both the groups and in total as well, p-value(0.714).The median Lymphocyte count 109 cells/liter was 4.8(4.7),TCZ vs CS group 2.9(2.7) vs 4(4.1), p-value (0.941), median D-dimers levels microgram/L were 1.0(1.16), 1.0(0.89) vs 1.0(1.16), p-value(0.433), median CRP levels mg/l was 145(90), 145(130) vs 139(90),p-value(0.942), median Ferritin levels ng/ml was 1000(1091), 1000(1000) vs 1000(1091),p-value(0.884), median Trop-I levels ng/ml was

18(13), 16(18) vs 11(11.0), p-value(0.827), median Serum creatinine mg/dl was 1.4(1.34), 1.1(1.2) vs 1.20(1.3), p-value(0.021).