Experience of Tocilizumab in Patient of Severe COVID-19

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Abstract

Objective: Covid-19 widespread pandemic leading to more than 800 thousand deaths. ARDS remains leading cause of death. Cytokine release syndrome like phenomenon was observed as important contributory factor for death and IL-6 inhibitors showed promising results in multiple case series. We share our experience of Tocilizumab in patients with very severe COVID-19.

Methods: In this prospective non-randomized cohort study conducted in COVID-ICU SIMS/SHL; patients who were given one or two consecutive doses of 400 mg Tocilizumab IV or subcutaneously after fulfilling criteria (Ferritin>700, CRP>70, D-Dimer>1000, FiO2 >10L, pulmonary infiltrates or worsening status) were included. Patient's data was noted on proforma. Patients were given standard treatment including IV dexamethasone, azithromycin and broad spectrum antibiotic, Invasive or non-invasive ventilation and proning from day one.

Results: Twenty one (M=19, F=2) patients having severe or very severe Covid requiring invasive ventilation 17(81%) and non-invasive ventilation 4 (19%)were given Tocilizumab (400mg two doses) along with dexamethasone, antibiotics and general care. Average age was 58.9 + 7. Majority of the patients were below 65 years. Out of 21 patients 4 patients improved and 3 discharged 1still admitted, mortality 81%(n=17). Raised inflammatory marker like CRP, Ferritin, D-Dimer and LDH and these improved after tocilizumab while Oxygen requirement doesn't improved significantly in majority of patients (n=20,95%)apart from 4 patients who improved gradually over next 7-10th day.

Conclusion: In very severe, steroids refractory COVID-Related ARDS Tocilizumab doesn't showed statistically significant improvement in outcome.

Key Words: COVID-19, Cytokine release syndrome, ARDS, Tocilizumab

Introduction

Coronavirus disease 2019 (COVID_19) was initia-lly detected in China in December 2019 and was declared a global pandemic on March 11, 2020 by WHO[1]. It has effected more than 23 million people with more than 0.81 million deaths across the world. Covid related knowledge including clinical presentation, diagnostics and management improved gradually. Now clinical spectrum of this illness ranges from asymp-tomatic infected to life threating acute respiratory distress syndrome (ARDS), circulatory shock, multi organ failure.[2,3] Apart from respiratory system it involved GI, CNS, Musculoskeletal and cardiovascular systems. It remained main burden of hospitalization all over the world and hypoxia was the main reason for hospital admission creating massive demand for invasive ventilation an intensive care unit beds in a short period.[4,5]

Treatment strategy evolved over time started from antivirals (oseltamivir, lopinavir/ritonavir), antimala-rial (Hydroxychloroquine, primaquine), anti-parasi-tic (Ivermite) various antibiotics (azithromycin, ceftriaxone, PIPTAZ, Meropenem) and changed to Remdesivir, dexamethasoneand IL-6 inhibitor with variable benefits. Currently, the standard of care is supportive therapy and there is an urgent need for effective treatment against COVID_19.

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ARDS is the leading cause of mortality in COVID_19 patients and extensive release of pro-inflammatory cytokines is suspected to contribute to poor outcomes in some patients.[6,7] It was hypothesized looking at various inflammatory markers that a cytokine release syndrome (well-established phenomenon in post chemo patients) is the reason for increased mortality in patients of severe covid. This was supported by raised IL-6 levels and various case reports of significant improvement in oxygen demand, need of ventilation and mortality by using IL-6 inhibitor Tocilizumab (interleukin-6 (IL-6) receptor antagonist).

Endogenous IL-6 is induced by inflammatory stimuli and mediates a variety of immunological responses. Inhibition of IL-6 receptors by tocilizumab leads to a reduction in cytokine and acute phase reactant production. Other drugs Siltuximab (direct IL-6 antagonist) Sarilumab, Lenzilumabare also used for treatment of cytokine release syndrome. This study is conducted to share our experience of Tocilizumab in severe covid patients.

Methods

This study was conducted in COVID-ICU SIMS/ SHL Lahore. We included all patients who were given tocilizumab in our ICU during April to August 2020. As a policy Tocilizumab was given to the patients fulfillingcriteria (table 1) and approved by the designated 4 member committee including intensivist, pulmonologist, medical physician and Pharmacist.

After excluding contraindications for tocilizumab (TB, Invasive Fungal infection or sepsis) we gave two doses of 400 mg Tocilizumab IV/Subcutaneously. Patients were followed for adverse effects, special labs, oxygen requirement or radiological improvement till discharge or death. In our ICU all patients were given dexamethasone 4-8mg IV twice a day for 14 days and can be reduced on patient improvement, Azithromycin 500 mg or Moxifloxacin 400 mg OD if intolerant to azithromycin along with broad spectrum antibiotic like PIP+TAZ or meropenem. We didn't gave HCQ but gave Ivermactine initially and Remdesivir if available.

All patients were managed by Oxygen with FM (Face Mask), NRM (Non-Rebreather Mask), NC+NRM according to oxygen increasing requirement respectively. We also used HFNC alone or combined with NRM and CPAP with Face mask via ventilator with 100% FIO in resistant hypoxia and encourage all patients for proning.Patients not improving with NIPPV were ventilated. Data was analyzed by SPSS 19.0.

Table 1: *Criteria for Tocilizumab Administration*

Any one criteria	+Any one Sign	+ Any of two labs
Age >60	Fever >39~C (102~F)	Ferritin levels >700
Cardiomyopathy	Hypotension	CRP>70
ESRD/Organ transplant	>10L Oxygen requirement with FM	D-Dimer level >1000
Lung Disease	R/R >30	
Age <60	As Above	Any 2 of above
Worsening Pulmonary infiltrates and worsening hypoxia		

Results

A total of 21 patients were given Tocilizumab including 19 male and 2 females. Average age was 58.9+ 7. Distribution of age, gender, time to presentation to hospital, time to tocilizumab administration and ICU stay is given in table number 2.

Majority of the patients were below 65 years (76%, n=16). Almost all of the patients had very severe Covid (n=19, 91%)evident by severe hypoxia with high oxygen requirement,>50% lung parenchymal infiltrates and markedly raised inflammatory markers. Only 2 patient had 5L oxygen requirement with Face mask on admission and 7-10L on day of Tocilizumab administration.

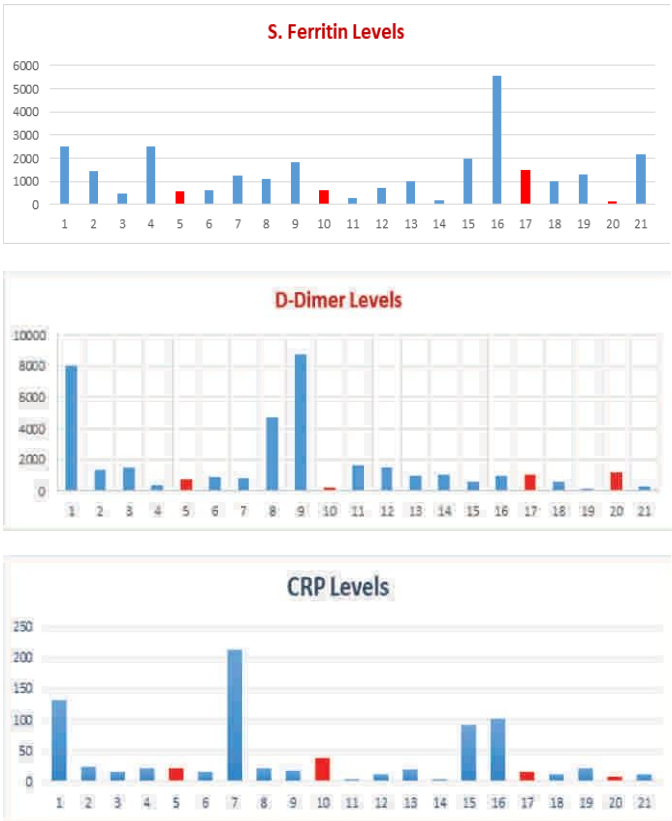
Among 21patients patients improved and discharged 1 patient improving but still admitted, mortality 81%(n=17). Oneout of 3 patients discharged; expired after 3 weeks due to acute worsening of dyspnea possibly due to ACS or Pulmonary Embolism. All patients had raised inflammatory marker (CRP, Ferritin, D-Dimer, LDH) and these improved after tocilizumab but Oxygen requirement doesn't improved significantly after Tocilizumab in majority of patients (n=20,95%) in 1st week. Exception was 4 patients who improved over next 7-10th day. In one patient with relatively mild disease oxygen requirement improved on 3rd day and he was discharged on 7th day. A total of 17 (81%) patients required ventilation, 6 (28.5%) patients were put on ventilation before tocilizumab administration while 11 required invasive ventilation after tocilizumab due to worsening

hypoxia. All of ventilated patients expired and detail along with co-morbitiesis given in table 2.

There was significant interval between start of symptoms and ICU admission 5-7 days (13) and 8-15 days in 8 patients. Majority of patients received Tocilizumab within 48hours of admission and got 2 does of 400 mg each. Three patients got single dose one got Anuria followed by renal shutdown requiring renal replacement therapy and later she expired, other two patients expired after 1st dose. Inflammatory markers were raised in all patients and these improved too after tocilizumab administration (Graph:1) but survivors had comparatively less raised markers favoring a direct correlation.

Table 2: *Demographics, hospital admission, stay, co-morbidities admission hypoxia of total patients is given along with number of patients who survived in each category in given in red on right column. These patients had less severe disease and didn't required ventilation.*

Parameter	Total Number (%)	Survivor (number)
Age	**58.9±7**	
<50	4 (19%)	1
50-60	8 (38%)	2
60-70	6 (28.5%)	1
>70	3 (14.3%)	
PCR +ve	**16 (76%)**	4
Sx. to Admission (day)	**8.1±2**	
5-7	13 (61.9%)	2
8-10	04 (19%)	
11-15	04 (19%)	2
Admission to Toci (Days)	**2.6 ±0.7**	
1-2	12 (57.1%)	2
3-5	07 (33.3%)	1
6-10	02 (9.5%)	1
Sx. To Toci (Days)	**10.48±3**	
Admission FiO2 Required		
5L FM	1 (4.7%)	1
10-15L NRM	7(33.3%)	3
20-25L NRM+NC	13(61.9%)	
Radiological Involvement		
>50% parenchyma	21(100%)	4
Co-Morbidity		
HTN	10 (47.6%)	3
DM	6 (28%)	1
IHD	6 (28%)	2
COPD/Asthma	4 (19%)	1
Nil	7 (33.3%)	1
Ventilation		
HFNC/CPAP	4 (19%)	4
IPPV	17(81%)	0
Post Toci Hospital stay		
1	1(4.7%)	
2	3(14.3%)	
3-5	7 (33.3)	1
6-10	2 (9.5%)	
11-20	4 (19%)	
>20	4 (19%)	3



Graph 1: *Comparative Values of CRP, D-Dimer and S. Ferritin Levels for all Recipients of Tocilizumab. Highlighted in Red Color are the Survivors Who were Discharge. Low Levels of Inflammatory Markers is Evident in this Subset*

Discussion

Covid-19 is new pandemic who spread vastly unlike previous corona related epidemic; SARS inn 2002 and MERS 2012. The knowledge about disease spread, effected organs, management and mortality is emerging and we are learning every day. We are reading multiple articles with different and conflicting results, making decision making difficult for the treating physicians. But few points are evident for the data that ARDS is the most fatal and prevalent implication followed by cardiac and renal involvement. Aged with multiple co-morbidities, with high viral load and late presenters has high mortality.

A subsets of patients who developed acute worsening of hypoxia, persistent fever and hypotension was

consider to have cytokine release syndrome like phenomenon due to raised inflammatory markers. Cytokine release syndrome is frequently associated with chimeric antigen receptor (CAR)-T cell therapy in B- cell malignancies. Itoccurs when large numbers of white blood cells are activated and release inflammatory cytokines, which in turn activate yet more white blood cells. CRS is also an adverse effect of some monoclonal antibody medications, as well as adoptive T-cell therapies.[7,8] Its clinical spectrums varies from mild fever and tachycardia to life threatening ARDS and shock grade as 1-5 according to Common Terminology Criteria for Adverse Events classifications for CRS as of version 4.03 issued in 2010[9]. Most the times it improves with Steroids and few cases required IL-6 inhibitors for steroid refractory cases.

Tocilizumab showed improved outcome in patients of COVID in case reports, small studies and few case control trials as compared to other drugs like HCQ, Azithromycin,[10] antivirals both in ventilated and non-ventilated patients.[11,12,13] But in these studies steroids weren't used.

In our study relative younger age group with less co-morbidities showed good outcome that is same for most of the studies.[14,15] The prognosis also depends on severity of disease as all patients who survived had less severe disease (5-10L FiO_2) and doesn't required ventilation. As contrast to other studies we don't observed significant reduction in oxygen requirement post tocilizumab and those of who improved had longer hospital stay 20 days on average. This phenomenon may be due to selection of the patients as we gave tocilizumab to very severe cases with full blown ARDS and worsening clinical status despite of steroids. As steroid can treat and delay the cytokine release storm those who doesn't improved with steroids they didn't improved to tocilizumab. This question will remained unanswered till a RCT with head to head comparison of tocilizumab with steroids done. Short comings of our study is a control group and small sample size with single center data. Large trial with multicenter data will answer many question and help is decision making.

Conclusion

In very severe, steroids refractory COVID-Related ARDS Tocilizumab doesn't showed statistically significant improvement in outcome.

Authors Contribution

1. **MH:** Study design, data collection, manuscript writing, data analysis and patients care.
2. **KKC:** Study design, manuscript writing, data analysis and patients care.
3. **MG:** Radiological input, data collection, results

4-6: DR, ZK, MM: Data Collection

Conflict of Interest: None

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