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Outcome of COVID-19 patients with use of Tocilizumab: A single center experience

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ABSTRACT

COVID-19 pandemic has become a global concern. Cytokine release syndrome (CRS) complicates acute respiratory distress syndrome (ARDS) and causes multi-organ failure which can subsequently lead to mortality in COVID-19 patients. Tocilizumab, an interleukin-6 antagonist, has shown to salvage patients with cytokine release storm. In this study, we aim to evaluate therapeutic response of Tocilizumab in COVID-19 patients. A single-arm retrospective review of 40 patients with COVID-19, admitted to The Aga Khan University Hospital Karachi, from March 2020 to May 2020 was performed. Selection of patients for use of Tocilizumab was based on severity of disease, rapid clinical deterioration, presence of CRS and absence of any absolute contraindication to Tocilizumab. Improvement after Tocilizumab was defined as improvement in oxygen requirement and inflammatory parameters. Serum levels of inflammatory cytokines like C-reactive protein, ferritin, D-dimer and lactate dehydrogenase levels were monitored before and after administering Tocilizumab. Mean age was 62.4 years and 33 (82.5%) were male. 19 (47.5%) patients were critically sick, 18 (45%) were severely sick and 3 (7.5%) were moderately sick. 29 (77.5%) patients showed significant improvement in oxygen requirement, inflammatory parameters and chest x-rays, out of which 28 patients were discharged home. The mean duration between administration of Tocilizumab and overall improvement was 4.3 ± 3.2 days. Hence, Tocilizumab can be used as a possible treatment option in patients with COVID-19 induced CRS but needs monitoring for its adverse effects.

1. Introduction

Coronavirus family consists of enveloped RNA viruses which usually caused mild respiratory diseases in the past. Four such strains had been identified previously, named as HKU1, NL63, 229E and OC43 [1]. A human coronavirus (*SARS-CoV*) precipitated severe acute respiratory syndrome coronavirus (SARS) epidemic in 2003 [2]. *SARS-CoV-2* is a novel coronavirus that originated in Wuhan city, Hubei province in China which was notified to World Health Organization (WHO) on December 31, 2019 and was declared a pandemic causing global concern [1,3]. Till June 6, 2020 total of 6,663,304 cases have been reported of which 392,802 have died [4]. The disease is highly infectious. Infected droplets can spread up to 1–2 m and can settle on surfaces. Spread of disease can occur either by inhalation of these droplets or by coming in contact with these surfaces and then touching eyes, face and nose [5].

Clinical features of COVID-19 have a wide spectrum with majority of cases being either asymptomatic or have mild symptoms while few present as acute respiratory distress syndrome (ARDS) and respiratory failure along with multi-organ dysfunction [1,6]. Studies have reported that around one fourth patients require intensive care, while overall mortality rate has been reported as 2–3% [1].

The immune mechanism behind this viral infection revolves around the production of α-interferon, TNF-α and secretion of IL-6 and IL-12. This leads to the formation of CD8 + specific cytotoxic T-cells, which along with CD4 + helper T-Cells are involved in the production of antigen specific B-cells and antibody production [7–8]. Hence, when the body is unable to mount an adequate immune response against the virus, this state of persistent inflammation results in a cytokine release syndrome (CRS) causing ARDS and multi-organ dysfunction [7,9].

ARDS is the primary cause of poor outcomes in majority of these patients in terms of mortality and morbidity [10]. The initial pathological examination demonstrated bilateral diffuse alveolar injury with cytomyxoid fibroma exudate while a peripheral flow cytometry analysis showed a reduction in CD4 and CD8 cell count with an increase in T-Helper-17 cell population which is primarily stimulated by Interleukin

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6 (IL-6) and Interleukin 23 (IL-23) [11,12]. Furthermore, the release of pro-inflammatory markers causes increased vascular permeability resulting in fluid and blood extravasation into the alveoli leading to respiratory failure [13].

CRS is systemic inflammatory response caused by various viral infections, connective tissue diseases and organ transplantation. It is specified by a rapid increase in levels of inflammatory cytokines [11]. *SARS-CoV-2* is associated with development of CRS and this inflammatory response causes initiation and worsening of ARDS [14]. CRS is also a key regulator in causing multi-organ failure and death [15]. It is believed that managing inflammatory responses by immunomodulators is an effective measure to improve outcomes in COVID-19.

Although therapeutic options for *SARS-CoV-2* are evolving rapidly, as of yet no specific antiviral therapy has proven to be effective in treating *SARS-CoV-2* patients [10]. Studies and experiences from China showed that use of antiviral drugs for treating these patients was based on past experiences with Ebola, Middle East respiratory syndrome (MERS), SARS and other viral infections [6]. In addition to these studies related to antiviral drugs, clinical trials are being conducted on chloroquine, hydroxychloroquine and azithromycin as they have shown some benefit through their action on immune system [7].

Tocilizumab is a recombinant humanized monoclonal antibody which is an antagonist of IL-6 receptor of immunoglobulin IgG1 subtype [11]. As previously described, IL-6 plays an important role in this viral infection which can lead to ARDS and subsequent respiratory failure. Two studies from China have reported their findings of using Tocilizumab in patients with *SARS-CoV-2* and both studies have shown improvement and stability in clinical condition as well as a decrease in inflammatory markers [7,16]. A multicenter, single arm, open label trial is also underway to assess the efficacy and tolerability of Tocilizumab in COVID-19 pneumonia and is currently in phase 2 [7].

The aim of this study is to report our experience with a series of COVID-19 patients treated with Tocilizumab. Although several other studies have reported these findings, most of them are case reports and series from China and Italy. Our study is the first from South Asia and will help in providing some evidence for use of Tocilizumab in these patients.

2. Materials and methods

This single-arm retrospective study was conducted in the department of Medicine of The Aga Khan University Hospital Karachi, Pakistan. The Aga Khan University Hospital Karachi is a JCIA accredited academic tertiary care medical institute with around 750 beds. To manage the surge of COVID-19 patients in our city, our hospital has assigned a 100 bed unit for management of COVID-19 patients. The objective of this study was to determine the response of Tocilizumab in patients with *SARS-CoV-2* in terms of clinical parameters and inflammatory markers. An institutional ethical review committee approval was obtained before starting the study (ERC 2020-4752-10750). All adult patients with a diagnosis of COVID-19 admitted from March 15, 2020 to May 15, 2020 were included in the study. Any patient who had a positive nasopharyngeal or oropharyngeal swab for *SARS CoV-2* through real-time reverse transcription PCR was labeled as having COVID-19. Patients were classified into mild, moderate, severe and critically ill categories according to CDC (Centres for Disease Control and Prevention) USA [17]. Those patients who had confusion, shock or respiratory failure requiring mechanical ventilation were labelled as having critical disease. Those patients who were hypoxic with oxygen saturation $< 93\%$ on room air or having a respiratory rate ≥ 30 per minute, without meeting the criteria for critical disease, were labelled as having severe disease. Patients with only fever, cough and mild infiltrate on chest x-ray were labeled as having mild to moderate disease. Improvement after Tocilizumab administration was defined as decrease in FiO_2 to at least half of that of the highest value of FiO_2 before Tocilizumab administration, and improvement in inflammatory parameters including C-reactive protein (CRP), ferritin, D-dimer and lactate dehydrogenase (LDH).

The data regarding patients' demographics, comorbidities, treatment, laboratory parameters, radiological investigations, and outcomes were retrieved from medical records. Tocilizumab was administered mainly to patients who were having severe disease or were critically ill and had developed CRS. Selection of patients for compassionate use of Tocilizumab was based on severity of disease, rapid clinical deterioration, need of mechanical ventilator support, presence of CRS and absence of any absolute contraindication to Tocilizumab which included a suspected or a confirmed bacterial infection signified by raised procalcitonin or positive cultures (blood, urine or sputum). Written informed consent was taken from next of kin before administration of Tocilizumab and risks and benefits were explained to them in detail. Majority of the patients who received Tocilizumab also received standard treatment protocol in the form of antibiotics (azithromycin, and ceftriaxone or piperacillin/tazobactam), intravenous steroids (methylprednisolone) and hydroxychloroquine depending upon QTc interval. Tocilizumab was administered at a dose range of 4–8 mg/kg.

Serum levels of inflammatory cytokines like CRP, ferritin, D-dimer and LDH were recorded before and after administration of Tocilizumab. Other parameters like change in oxygen requirement and chest x-ray findings before and after Tocilizumab administration were also recorded. Regarding inflammatory marker values, the highest levels of inflammatory markers before administration of Tocilizumab and the lowest value of inflammatory markers, after Tocilizumab administration were noted. The clinical outcomes in terms of mortality, weaning from mechanical ventilator, weaning from oxygen support, improvement in laboratory parameters including inflammatory cytokines and length of hospital stay were also documented.

3. Results

In our study total of 40 patients received Tocilizumab. The mean age was 62.4 ± 12.8 years and 33 (82.5%) were males. Most prevalent symptom at the time of admission was cough which was present in 31 (77.5%) patients. The dose of Tocilizumab used was 320–680 mg. Out of 40 patients, 35 received single dose of Tocilizumab while 5 received two doses which were given at least 24 hours apart. The mean duration of hospital stay was 14.5 ± 8.4 days. Regarding severity of illness, 19 (47.5%) patients were critically sick, 18 (45%) were severely sick and 3 (7.5%) were moderately sick. Out of 40 patients 11 (27.5%) patients were on mechanical ventilator while 29 (72.5%) were in monitored setup (special care unit). The mean duration of these 11 patients to be on ventilator was 9.0 ± 5.5 days. All 40 patients had bilateral pneumonia. Hypertension was the most prevalent comorbidity and was present in 57.5% of patients. Out of 40 patients, 11 (27.5%) had no prior comorbidities while 23 (57.5%) had 2 or more comorbidities. Baseline characteristics of all 40 patients are summarized in Table 1.

HTN: Hypertension, DM: Diabetes, IHD: Ischemic heart disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease

Mean values of NLR (neutrophil to lymphocyte ratio) and inflammatory markers before and after Tocilizumab administration were recorded (Table 2). Almost all inflammatory markers including CRP, ferritin, LDH and procalcitonin showed significant improvement after Tocilizumab administration. NLR also significantly improved in our patients.

Out of 11 patients who were on ventilator, 7 were weaned off from ventilator and subsequently extubated, however, 2 of them later expired. All of the 40 patients received antibiotics, 30 (75%) received azithromycin, 28 (70%) received hydroxychloroquine and 33 (82.5%) received glucocorticoids.

Out of 40 patients, 29 (77.5%) patients showed improvement in terms of oxygen requirement (Table 3) while 23 (79.3%) out of these 29

Table 1
Baseline characteristics of all 40 patients who received Tocilizumab.

Characteristics	N = 40
Age (years)	62.4 ± 12.8
Gender	
Male	33 (82.5%)
Female	7 (17.5%)
Comorbidities	
HTN	23 (57.5%)
DM	20 (50%)
IHD	12 (30%)
COPD	8 (20%)
CKD	7 (17.5%)
Others	9 (22.5%)
None	11 (27.5%)
Symptoms	
Cough	31 (77.5%)
Fever	30 (75%)
Shortness of Breath	27 (67.5%)
Sore throat	5 (12.5%)
Others	2 (5%)

showed improvement in chest x-rays. Out of 29 patients who showed improvement, 28 patients were discharged home safely while one patient was admitted in hospital at the time of our study. Out of 11 patients who deteriorated, 9 patients expired and 2 left against medical advice. The mean duration between first day of Tocilizumab administration and overall improvement was 4.3 ± 3.2 days. Although, only one of our patients had chronic kidney disease as a known comorbidity, 4 patients required renal replacement therapy.

Regarding development of infections after Tocilizumab administration, most common organisms found in tracheal aspirate were *Aspergillus* in 6 (15%) patients, *Pseudomonas* and *Stenotrophomonas* in 3 (7.5%) each and *Klebsiella* and *Acinetobacter* in 2 (5%) patients. Moreover, 2 (5%) patients developed candidemia.

4. Discussion

Majority of our patients who received Tocilizumab showed improvement in terms of oxygen requirement, chest x-rays, weaning from ventilator, improvement in CRP, ferritin, LDH levels, NLR and safe discharge to home. The early clinical and biochemical improvement following single dose Tocilizumab administration indicates that it may be a possible therapeutic option in critically ill patients with COVID-19-induced CRS. The response to Tocilizumab in majority of our patients is fairly rapid and sustained as those patients in our study who improved after Tocilizumab continued to recover in subsequent days. It is worth mentioning that majority of critically ill-patients got extubated from mechanical ventilator. They were eventually shifted to general care and were discharged home.

The rationale of use of Tocilizumab in COVID-19 is based on our knowledge of the role of IL-6 in this disease and the experience of this drug in the treatment of CRS [16]. Due to lack of specific anti-viral drugs, available host-directed therapeutics may have a potential to manage COVID-19 patients [18]. Tocilizumab has been used by several healthcare professionals for COVID-19 as a compassionate drug. Large number of clinical trials of Tocilizumab are underway in patients with COVID-19 across the globe. Three of these trials have been completed. However, none of these trials have been published and results of these trails have not been announced till date [19]. Tocilizumab has also been included in the current Chinese national treatment guidelines [20]. To date two largest case series of patients who were treated with Tocilizumab are from Italy and China with a total of 100 and 21 patients, respectively [21,22]. Like our case series majority of their cases also showed improvement after Tocilizumab. It is noteworthy that Infectious Disease Society of America (IDSA) has recently published guidelines

Table 2
Median and interquartile ranges of inflammatory markers and neutrophil–lymphocyte ratio (NLR) before and after Tocilizumab administration.

	Overall (Number of patients = 40)			Patients who expired (Number of patients = 9)			Patients who improved (Number of patients = 29)		
	Before Tocilizumab	After Tocilizumab	P value*	Before Tocilizumab	After Tocilizumab	P value*	Before Tocilizumab	After Tocilizumab	P value*
C-Reactive protein (mg/L)	198.5[164.7–248.4]	5.7[1.6–18.9]	< 0.001	227.2[140.9–308.4]	13.3[2.2–98.1]	0.012	197.2[165.5–233.2]	4.6[1.7–11.9]	< 0.001
Ferritin (ng/ml)	1185.7[765.3–1502.5]	712.8[375.2–1414.4]	0.002	1191.5[604.6–1705.8]	1285.1[465.9–1736.3]	0.889	1185.7[817.7–1450.6]	585.8[401.0–1293.3]	0.001
D-Dimer (mg/L)	1.4[0.7–6.2]	1.4[0.8–6.9]	0.925	4.9[1.5–16.1]	8.4[3.1–13.5]	0.327	1.2[0.6–2.2]	1.0[0.6–1.9]	0.446
Lactate dehydrogenase (IU/L)	531.0[421.8–603.8]	331.5[276.8–481.0]	< 0.001	600.5[517.5–638.3]	669.5[428.5–795.0]	0.484	513.5[397.8–584.0]	309.5[264.3–352.3]	< 0.001
Procalcitonin (ng/ml)	0.281[0.16–0.59]	0.68[0.04–0.15]	0.004	0.27[0.24–1.1]	1.3[0.09–6.3]	0.123	0.28[0.11–0.59]	0.05[0.04–0.11]	0.001
NLR †	10.6[6.9–15.2]	4.6[1.7–13]	0.021	15.2[12.9–18.1]	20.4[9.7–30.5]	0.161	9.2[6.5–13.0]	3.3[1.3–5.4]	< 0.001

* Based on Wilcoxon Signed Ranks Test, † NLR: Neutrophil-Lymphocyte ratio.

Table 3
Oxygen requirement before and after Tocilizumab administration.

	Overall (Number of patients = 40)			Patients who expired (Number of patients = 9)			Patients who improved (Number of patients = 29)		
	Before Tocilizumab	After Tocilizumab*	Pvalue†	Before Tocilizumab	After Tocilizumab	P value†	Before Tocilizumab	After Tocilizumab	P value†
Oxygen requirement [FiO_2%]	48.0 ± 16.2	29.8 ± 6.8	< 0.001	56.3 ± 9.2	64.4 ± 11.2	0.06	45.2 ± 15.7	29.9 ± 6.9	< 0.001

* This is the first significant decrease in oxygen after Tocilizumab, †Based on Paired samples *t*-test.

regarding use of Tocilizumab in COVID-19. According to them, due to gap in knowledge regarding use of Tocilizumab, it should only be used for the purpose of clinical trial [23].

Apart from these larger case series, there are several case reports in literature showing favorable response to Tocilizumab. Michot et al reported a patient of sarcomatoid clear cell renal cell carcinoma who responded dramatically to Tocilizumab [24]. Zhang et al reported a patient of multiple myeloma who responded well to Tocilizumab [25]. Another case report from Italy has been published with good outcome in COVID-19 after Tocilizumab [26]. Overall, these case reports have showed improvement in condition of patients as was shown by majority of our patients.

While interpreting our results we should not ignore the fact that an important portion of our study subjects, nine out of forty, did not improve and died. This showed that Tocilizumab did not work in them despite blockade of the IL-6 pathway, suggesting that blockade of the IL-6 pathway will not be successful in all patients.

Toniati and Luo, in their case series followed IL-6 as an outcome measure in addition to other parameters [16,22]. Similarly, we followed several outcome measures in our patients including chest X-ray, oxygen requirement, weaning from ventilator, ferritin, CRP, D-dimer, LDH and NLR. However, we did not follow IL-6 as it is not available in our institute. As oppose to our case series, the patients in case series from China received lopinavir/ritonavir as a part of their standard treatment regimen [21]. While none of our patients received lopinavir/ritonavir.

The dose of Tocilizumab used by majority of case reports and series is 8 mg/kg [24,25,27,28]. Dose mentioned in case series by Luo et al ranged from 400 to 600 mg [16]. Similarly, the dose used in our study was 320–680 mg. As per literature review, many patients received two or more doses of Tocilizumab [16,21,24,28,29]. Though, single dose administration has also been mentioned in case reports [21,25,27]. In our case series only five patients received two doses while rest received a single dose.

An interesting finding in our study is that patients who died showed significant decrease only in CRP after Tocilizumab administration while other inflammatory markers showed a paradoxical rise. This showed that Tocilizumab has a more profound effect on CRP as compare to other inflammatory markers. However, in our study, this proved true only for those patients who died. Similarly, Tinoti et al showed that in their series of patients LDH increased in those patients who worsened [22]. However, Luo et al showed that CRP did not decrease in one of their patients in which there was deterioration of the disease [16].

Tocilizumab is associated with risk of infections. In our series several of the patients developed bacterial infections. Interestingly, six of them developed *Aspergillus* in tracheal cultures while two of them developed candidemia. Although, candidemia is not a commonly associated infection with Tocilizumab [30], however, in a case series by Antinori et al, three patients developed candidemia after Tocilizumab [30]. This is very important in terms of overall survival of patients as candidemia by itself is a poor prognostic marker. Patients being treated with Tocilizumab should be observed and investigated for this important and potentially fatal complication of treatment. Apart from candidemia mentioned by Antinori et al, none of the case series and case reports mentioned development of any opportunistic infections in their patients treated with Tocilizumab [21–27].

Other than risk of infections, an interesting adverse effect of Tocilizumab was acute hypertriglyceridemia developed in two patients who received concomitant propofol with Tocilizumab. Since many patients of COVID are managed in intensive care units with propofol being used as a means of sedation, the potential adverse effect of acute hypertriglyceridemia should be kept in mind by the treating physician.

Our study is not free of limitations. In the current scenario, when whole world is in search for definite treatment option for COVID-19, a clinical trial is need of the hour rather than presentation of data in the form of case series. A major limitation of our study is the lack of control arm of patients who received standard of care. As compared to other case series, our study had adequate sample size but still a larger number of participants would be required to establish the therapeutic role of Tocilizumab in COVID-19. Due to lack of guidelines, the specific indications for COVID-19 patients receiving Tocilizumab, could not be defined by us. We could not monitor IL-6 levels as this test is not available in our institute. Moreover, this is a single center study. Large multicenter randomized controlled trials are required to see the effectiveness of this treatment modality for patients with COVID-19.

5. Conclusion

Tocilizumab seems to be a potential treatment option for COVID-19 induced CRS and may repress further clinical deterioration of critically ill patients. Clinical improvement was shown by majority of our patients after receiving Tocilizumab. However, use of Tocilizumab should be done judiciously and adverse effects should be monitored after its administration.

6. Financial disclosure

The authors have no relevant financial interest in this article. The authors declare that they have no conflict of interest.

Declarations of interest: None

CRediT authorship contribution statement

Muhammad Zain Mushtaq: Conceptualization, Methodology, Data curation, Writing - original draft, Validation, Resources. **Saad Bin Zafar Mahmood:** Conceptualization, Methodology, Data curation, Writing - original draft, Formal analysis, Validation, Resources. **Bushra Jamil:** Supervision, Resources, Writing - review & editing. **Adil Aziz:** Writing - review & editing, Resources. **Syed A. Ali:** Writing - original draft, Supervision, Project administration, Validation.

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