Respiratory Medicine Case Reports 30 (2020) 101139

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: http://www.elsevier.com/locate/rmcr

Case report

Efficacy and safety of tocilizumab in critically ill adults with COVID-19 infection in Bahrain: A report of 5 cases

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A B S T R A C T

Tocilizumab has been recognized as one of the few existing biologic useful for combating COVID-19 infections especially in critically ill patient. We had experience in treating five critically ill patients with severe lung injury who were COVID-19 positive with tocilizumab. In the present case series, we have attempted to summarize their clinical profile, changes in laboratory biomarkers and outcomes.

1. Background

Tocilizumab is a monoclonal antibody to IL-6 receptor and is in widespread use for several auto-immune diseases particularly for rheumatoid arthritis [1]. Use of tocilizumab for treating critically ill adults with COVID-19 infections has been reported in limited numbers of patients. A recent systematic review that has included 10 studies has compiled data on just 29 patients [2]. No conclusion was drawn by the authors as the systematic review was observational without a comparator. However, a registry-based analysis of 21 patients revealed that tocilizumab administration did not influence ICU admission as well as mortality [3]. A retrospective study in 32 patients on tocilizumab therapy revealed no significant difference in the clinical outcomes compared to standard of care [4]. On the other hand, a single-center study from Italy revealed that out of the 43 critically ill patients treated in ICU, 32 (74%) recovered, weaned from the ventilator and were discharged to wards [5]. A vial of 400 mg tocilizumab costs around 2500 USD and not many developing nations can afford. Although several randomized clinical trials are ongoing with tocilizumab in the treatment of COVID-19infections, it is an arduous, time-consuming task with dissemination of results not expected very soon. Our center in Bahrain had experience in treating five patients with proven COVID-19 infection with tocilizumab and so we intend to summarize the characteristics of these patients in the present case series.

2. Case presentation

2.1. Case 1

A 95-year-old male with known history of diabetes mellitus, hypertension, dyslipidemia and benign prostatic hyperplasia was admitted with symptoms and signs suggestive of COVID-19 pneumonia. The patient was put on 5 L facemask with oxygen since admission with SpO_2 of 97%. His acute lung injury score was 2.5 and was classified as having acute respiratory distress syndrome (ARDS). He was administered hydroxychloroquine tablet at 200 mg twice daily and fixed-dose combination of lopinavir/ritonavir once daily. Additionally, he was administered piperacillin/tazobactam injection four times daily. Due to desaturation, the patient was put on venture mask 28% and SpO_2 was maintained between 90 and 94%. As the desaturation continued, he was moved to high flow nasal canula initially at 40% 50 L with SpO_2 of 88% and subsequently to 60% with SpO_2 of 89%. He was moved to non-invasive ventilation at 60%. On the fifth day of admission, he was administered a single intravenous infusion of 400 mg tocilizumab for half-an-hour duration. The patient started to have profuse diarrhea, hematuria and the renal functions worsened. He was initiated on injection metronidazole. The next day following tocilizumab, the patient significantly improved and so the second dose of tocilizumab was not administered. Patient was on HFNC 80% with BIPAP only at night. Two days later, the patient was reverted to 5L/min facemask with oxygen with SpO_2 of 94%. The COVID-19 rt-PCR test was negative after 8 days of ICU admission that corresponds to 4th day following tocilizumab

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https://doi.org/10.1016/j.rmcr.2020.101139
Received 17 June 2020; Received in revised form 20 June 2020; Accepted 21 June 2020
Available online 23 June 2020

administration. A repeat COVID-19 rt-PCR test was also negative after 3 days and the patient was discharged from ICU.

2.2. Case 2

A 54-year-old man with known case of poorly controlled type 2 diabetes mellitus, had history of close contact with a COVID-19 positive patient and on screening with rt-PCR test, he was found to be negative for COVID-19. The patient was quarantined and after thirteen days, he presented with a 3-day history of dry cough and fever along with anosmia. On examination, he had tachypnea. Lung injury score revealed a severe lung injury. He had hypoxemia even with the facemask with 6L/min oxygen. Chest X-ray revealed bilateral infiltrates and nasopharyngeal swab for COVID-19 was positive. The patient was initiated on oral hydroxychloroquine at 200 mg twice daily and injection ceftriaxone. As the patient required an increased requirement of oxygen therapy, piperacillin/tazobactam replaced ceftriaxone and two doses of plasma therapy was infused. As the patient did not show any signs of improvement, injection tocilizumab was administered at 400 mg for two doses. The patient improved significantly on the third day following tocilizumab injection and rt-PCR test for COVID-19 was negative on the fourth day. A repeat rt-PCR test was also negative after 6 days and the patient was discharged from ICU.

2.3. Case 3

A 64-year-old man with known case of bronchial asthma and morbid obesity (body mass index = 58.8 kg/m^2) with reduced glucose 6-phosphate dehydrogenase activity presented with a recent history of travel from Iran and had presenting complaints of dry cough, shortness of breath and fever. Physical examination revealed fine crackles at lung bases bilaterally and chest X-ray showed bilateral pulmonary infiltrates. His acute lung injury score was 2.5 and indicated ARDS. Nasopharyngeal swab for COVID-19 was positive and the patient was initiated on oral hydroxychloroquine 200 mg twice daily along with ceftriaxone, piperacillin/tazobactam, aizthromycin, ribavirin, pegylated interferon (received single dose) and plasma therapy (two doses). The patient did not show any signs of improvement but his oxygen requirement increased for maintaining appropriate oxygen saturation. The patient was shifted to ICU and was administered two doses of 400 mg tocilizumab infusion. Patient improved the following day with a negative COVID-19 test results twice on alternate days and the patient was discharge from ICU.

2.4. Case 4

A 37-year-old man without any significant past medical history presented with a 7-day history of fever along with 3-days duration of shortness of breath with productive cough for 1-day. On examination, the patient had fine crackles at lung bases bilaterally and chest X-ray confirmed bilateral pulmonary infiltrates. Assessment of lung injury score revealed ARDS. Nasopharyngeal test for COVID-19 was positive. The patient received oral hydroxychloroquine 200 mg twice daily along with ceftriaxone, lopinavir/ritonavir, aizthromycin, ribavirin, pegylated interferon (received single dose) and plasma therapy (two doses). Patient did not show any signs of improvement. His oxygen requirement continued to increase. Two doses of tocilizumab 400 mg were administered. Following the second dose of tocilizumab, the patient showed marked signs of improvement and four days later he was found to be negative for COVID-19 test and a repeat test after two days was still negative. The patient was discharged from ICU on day 5.

2.5. Case 5

A 59-year-old man reported with shortness of breath and dry cough with fever. Physical examination revealed bilateral crackles at lung bases. The nasopharyngeal test was positive for COVID-19. Chest X-ray revealed bilateral pulmonary infiltrates and lung injury score revealed ARDS. He was administered injections azithromycin, ceftriaxone, interferon, ribavirin and plasma therapy. As the patient's condition worsened, he was administered two doses of injection tocilizumab at 400 mg intravenously. The patient showed initial improvement followed by deterioration as his requirements for oxygen increased. One day following the second dose of tocilizumab injection, the nasopharyngeal test for COVID-19 was negative and a repeat test after two days confirmed the same. The patient also had positive blood culture (for Methicillin-resistant *Staphylococcus aureus*) with elevated procalcitonin and white blood cell count. The patient went into septic shock with multi-organ dysfunction. Despite active measures, the patient died on 16th day of admission due to refractory hypoxemia and circulatory failure.

All the five patients were initiated tocilizumab therapy following their raised serum interleukin-6 (IL-6) levels (>50 pg/ml). The laboratory profiles of all the above patients with serum ferritin, C-reactive protein, procalcitonin, D-dimer, lactate dehydrogenase and interleukin 6 are shown in Table 1. C-reactive protein decreases steadily in all patients except the one who died. All the patients except case number 5 showed a decline in total white blood cell (WBC) count and an increase in the lymphocyte count following tocilizumab therapy and none of the patients had abnormal liver function test.

3. Discussion

Interleukin-6 is a multi-functional cytokine that can promote the growth of T-cell population, activation and differentiation of B-cells and regulates the acute phase response in cases of systemic inflammation [6]. In critically ill COVID-19 patients with pneumonia, T-cells (GM-CSF$^+$IFN-γ^+) and monocytes (CD14$^+$CD16$^+$) with overexpression of IL-6 were identified in the biopsy specimen from their lungs [7]. Tocilizumab is an IgG1 humanized monoclonal antibody targeting IL-6 receptor and thereby has been theorized to play a significant role in severe critically ill COVID-19 patients. We observed in the present case series that COVID-19 patients with severe lung injury responded dramatically following the introduction of tocilizumab. All our patients had serum IL-6 levels above 50 pg/ml. Until now, the only guidelines recommending tocilizumab therapy in COVID-19 patients is the National Health Commission of China [8]. The guideline recommend tocilizumab in patients with IL-6 levels above 20 pg/ml. The evidence on which this guideline was based is from 21 critically ill patients of which 20 improved and discharged within 2 weeks of tocilizumab therapy. We observed a similar recovery rate with tocilizumab. Of the five patients, four recovered and were discharged from ICU almost within a week. Only one died who had septicemia following secondary bacterial infection. Around 40% of patients with sepsis may have septic shock with a mortality risk of nearly 25% [9]. Only 3.7% of sepsis-associated mortality is preventable [10]. However, COVID-19 related sepsis has been reported in only 2–5% of the patients after 8–10 days [11]. Amongst those who improved with tocilizumab is a 95-year old man with several co-morbid diseases. Our patients also received other drugs such as ribavirin, hydroxychloroquine, azithromycin, lopinavir/ritonavir, pegylated interferon and plasma therapy as a part of the standard of care. Our patients were receiving the standard of care for one or two days and since there was no significant clinical improvement they were administered tocilizumab. We did not observe any specific laboratory-related adverse events following tocilizumab therapy. Although others [12] reported a trend of increased IL-6 immediately following tocilizumab followed by a decrease, we did not perform IL-6 analysis following tocilizumab administration due to cost constraints. However, all the patients had elevated baseline IL-6 levels. Further, except for one all others showed faster clinical improvement following initiation of tocilizumab that it was deemed unnecessary by the treating physicians. In addition, we could not compare our results with only

Table 1
Comparison of biomarkers in patients administered tocilizumab therapy.

Patient number	Before tocilizumab	Days after initiating first dose of tocilizumab therapy									Clinical outcomes
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	
C-reactive protein (mg/L)											
1	124	66.9		26.6		8.77		5.59		3.09	Discharged
2	189		79.9		25.1	14.2		7.02	5.04	3.73	Discharged
3	200.5			61.9		19.1			5.04		Discharged
4	120.5	83.2	36.9	18.9	4.23		5.7	1.9	1.17		Discharged
5	174		91.8	34.5	16.3	8.39	7.16	35.3	44.9		Death
Serum ferritin (μg/L)											
1	1336	1119		1270		2539		1298		905	Discharged
2	1032		1463		1168	1758		1787	1890	1835	Discharged
3	1106			1601		1484			2040		Discharged
4	1257	1407	1501	1705	2371		1386	1634	1631		Discharged
5	1489		2032	1697	1753	1453	1665	1723	1972	1922	Death
D-dimer (μg/ml)											
1	4.28	4.58		5.23		2.43		3.45			Discharged
2	1.02		2								Discharged
3	4.37			31.5		31.71			34.67		Discharged
4	0.65	0.8	0.62	0.8	0.74		0.94	0.39	0.5		Discharged
5	10.99						20.03	15.17	6.26	2.03	Death
Serum procalcitonin (ng/ml)											
1	0.2	0.22		2.61		0.09		0.05		0.02	Discharged
2	0.24		0.11		0.05	0.05		0.02	0.02	0.02	Discharged
3	1.09			0.24		0.09			0.03		Discharged
4	0.02	0.03	0.02	0.02	0.05		0.01	0.02	0.02	0.01	Discharged
5	0.89		0.3	0.22	0.1	0.08	1.06	8.18	4.2	1.9	Death
Lactate dehydrogenase (U/L)											
1	630	294		546		385		210		183	Discharged
2	363		394		350	388		381	317	291	Discharged
3	461			408		350			430		Discharged
4	319	221	290	342	278			180	212		Discharged
5	540		540	594	992	937	1560	1334	1148	532	Death

patients who have received the standard of care. To conclude, tocilizumab appears promising in the treatment of critically ill adults with acute respiratory distress syndrome following COVID-19 infection although large scale clinical trials need to confirm the findings.

Funding

None.

Author statement

Conceptualization & Methodology: Mohamed ElSeirafi, Hasan MSN Hasan, Kannan Sridharan; Data collection: Mohamed ElSeirafi, Alaa Zamoori, Sana Alkhawaja, Sheikh Abdul Azeez Pasha; Writing - Mohamed ElSeirafi, Hasan MSN Hasan, Kannan Sridharan; Revision and approval of final draft - All the authors.

Declaration of competing interest

The authors do not have any conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101139.

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