Journal of Investigative Medicine High Impact Case Reports
Volume 9: 1–5
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DOI: 10.1177/23247096211019557
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Tocilizumab for the Treatment of COVID-19-Induced Cytokine Storm and Acute Respiratory Distress Syndrome: A Case Series From a Rural Level 1 Trauma Center in Western Pennsylvania

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Abstract

An outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2, initially in December 2019 at Wuhan, China, subsequently spread around the world. We describe a case series of COVID-19 patients treated at our academic medical center with focus on cytokine storm and potential therapeutic role of tocilizumab. A 59-year-old female admitted for shortness of breath (SOB), productive cough, fever, and nausea in the setting of COVID-19 pneumonia. Oxygen saturation was 81% necessitating supplemental oxygen. She was transferred to intensive care unit (ICU) for worsening hypoxia; intubated and received tocilizumab following which her oxygen requirements improved. A 52-year-old female admitted from an outside hospital with SOB, intubated for worsening hypoxia, in the setting of COVID-19 pneumonia. She received tocilizumab 400 mg intravenous for 2 doses on ICU admission, with clinical improvement. A 56-year-old female hospitalized with worsening SOB, fever, and cough for 8 days saturating 88% on room air in the setting of COVID-19 pneumonia. Worsening hypoxia necessitated high flow nasal cannula. She was transferred to the ICU where she received 2 doses of tocilizumab 400 mg intravenous. She did not require intubation and was transitioned to nasal cannula. A hyperinflammatory syndrome may cause a life-threatening acute respiratory distress syndrome in patients with COVID-19 pneumonia. Tocilizumab is the first marketed interleukin-6 blocking antibody, and through targeting interleukin-6 receptors likely has a role in treating cytokine storm. We noted clinical improvement of patients treated with tocilizumab.

Keywords

tocilizumab, cytokine storm, COVID-19, ARDS, coronavirus

Introduction

An outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during December 2019, initially reported in Wuhan, China, spread around the world and was declared a pandemic.[1]

The initial clinical case series from China largely comprised hospitalized patients with severe pneumonia. Data mainly suggested that about 80% patients have mild disease, 20% require hospital admission, and about 5% require intensive care admission.[2]

We describe a case series on presentation and management of COVID-19 patients treated at our facility with emphasis on cytokine storm and role of tocilizumab (TCZ) as a treatment modality.

Case Series

Case 1

A 59-year-old female with past medical history (PMH) of hypertension, chronic obstructive pulmonary disease, and multiple sclerosis presented to the emergency department (ED) with worsening shortness of breath (SOB), cough,

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Received December 31, 2020. Revised April 21, 2021. Accepted April 29, 2021.

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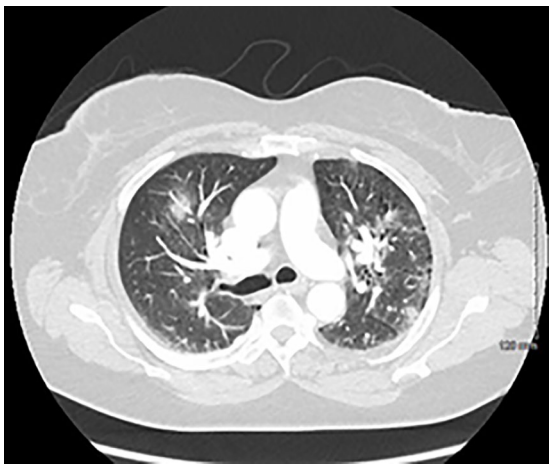

Figure 1. Computed tomography PE showing patchy peripheral ground-glass interstitial opacities.

fever, and nausea. She was admitted to the general medical floor for further management. She was hypoxic with oxygen saturation 81% and was placed on 5 L supplemental oxygen via nasal cannula. Initial computed tomography PE (see Figure 1) was done, which showed interval worsening emphysematous changes with patchy peripheral ground glass interstitial opacities. COVID-19 RNA polymerase chain reaction (PCR) was positive. COVID-19 laboratory tests including D-dimer, fibrinogen, C-reactive protein, lactate dehydrogenase, and triglycerides were trended (see Table 1). Her interleukin-6 (IL-6) level was markedly elevated at 1654.2 (reference: 0-15.5 pg/mL). On day 3 of admission, she continued to remain hypoxic with increasing oxygen requirements and was eventually transferred to intensive care unit (ICU) where she was intubated and on mechanical ventilation. Her COVID-19 treatment regimen included azithromycin 500 mg IV (intravenous) daily ×5 days, hydroxychloroquine 400 mg PO bid ×1 day followed by 200 mg PO bid for an additional 4 days, and zinc sulfate 220 mg PO tid ×5 days. On transfer to the ICU on day 3, she received TCZ 8 mg/kg IV ×1 dose. She was paralyzed with cisatracurium on days 3 and 4. Chemical paralysis was discontinued at the 24-hour mark as her P/F ratio had improved to 235. On day 6, given her increasing D-dimer and FiO_2 requirements, she was transitioned from prophylactic to therapeutically dosed enoxaparin (normal renal function). On day 7, her P/F ratio had subsequently decreased to 170 and she was given an additional dose of TCZ 4 mg/kg IV. Over the next 24 hours, her oxygen requirements improved dramatically. She was extubated, transitioned to nasal cannula, and eventually discharged home.

Case 2

A 52-year-old female with PMH of hypertension, anxiety, and depression admitted from an outside hospital with SOB, intubated for worsening hypoxia. COVID-19 RNA PCR was positive. Her initial chest X-ray (see Figure 2) showed diffuse patchy bilateral airspace opacities, findings consistent with multifocal pneumonia. COVID-19 laboratory tests were trended (see Table 2). Her IL-6 level was elevated at 799.3. Her COVID-19 treatment regimen included azithromycin 500 mg IV daily ×3 days, hydroxychloroquine 400 mg PO bid ×1 day followed by 200 mg PO bid for an additional 6 days and zinc sulfate 220 mg PO tid ×6 days. She received TCZ 400 mg IV every 12 hours ×2 doses on day 1 of ICU admission. Given her severe acute respiratory distress syndrome (ARDS), she also required chemical paralysis and prone positioning on days 1 to 4 of ICU admission. She maintained a stable clinical course until day 11 of her ICU stay. At this point, she acutely decompensated with increasing FiO_2 requirements, hemodynamic instability, an increasing leukocytosis, and high-grade fevers. This abrupt change in her clinical status raised concerns for both a superimposed bacterial pneumonia and pulmonary embolism given the hypercoagulable state associated with COVID-19. She was treated with vancomycin, cefepime, and metronidazole and her deep vein thrombosis prophylaxis was transitioned to a heparin drip. She remained on mechanical ventilation for 15 days after which she was extubated and transitioned to supplemental oxygen via nasal cannula.

Case 3

A 56-year-old female with PMH of hypertension, hyperlipidemia, and diabetes initially presented to the ED with worsening SOB, fever, and cough for 8 days. In the ED, pulse oximeter showed saturation of 88% on room air. COVID-19 RNA PCR test was positive. She required supplemental oxygen via nasal cannula and was transferred to the floor for further management. She became more hypoxic with oxygen saturation in the low 80s and was placed on high-flow nasal cannula. COVID-19 laboratory tests were trended (see Table 3). Chest X-ray showed bilateral interstitial infiltrates (see Figure 3). Her IL-6 level was elevated at 68.9. Her respiratory status continued to worsen, and she was asked to awake prone. On day 3 of hospital admission, she was transferred to the ICU for acute hypoxic respiratory failure in the setting of COVID-19. Her COVID-19 treatment regimen included azithromycin 500 mg IV daily ×5 days and zinc sulfate 220 mg PO thrice daily ×10 days.

Additionally, she was treated with ceftriaxone 1 gm IV q 24 hours ×7 days as coverage for a community-acquired pneumonia. On admission to the ICU, she received TCZ 400 mg IV ×2 doses. She was also started on therapeutic dose enoxaparin at this time. She continued to clinically improve throughout her ICU stay and was transitioned to nasal cannula. On day 8, she was transferred to the general medical floor and was ultimately discharged home on 4 L of oxygen.

Table 1. Trend of COVID-19 labs showing improvement after TCZ administration on Day 3 and further improvement after receiving the second dose of TCZ on Day 7.

	Day 1	Day 3	Day 4	Day 5	Day 6	Day 7	Day 9	Day 11	Day 13	Adm	Peak
D-Dimer (Ref: <0.5 mg/L)		0.6	0.58	0.82	0.85	0.62	0.54	0.86	0.6	0.7	0.85
Fibrinogen (Ref: 163-419 mg/dL)		>600	>600	583	506	379	314	301	249	—	>600
Ferritin (Ref: 2-290 ng/mL)	415	652		1632						415	1632
LDH (Ref: 125-243 U/L)	372	429	557	691	880	766	615	454	367	372	880
CRP (Ref: 0-0.8 mg/dL)	9.4	32	17.8	9.4	5.3	3	1.1	0.5	0.3	9.4	32
Triglycerides (Ref: 0-150 mg/dL)		245	673	562	734	724	364	448	380	—	734
IL-6, serum (Ref: 0-15.5 pg/mL)							1654.2				

Abbreviations: LDH, lactate dehydrogenase; CRP, C-reactive protein; IL, interleukin.

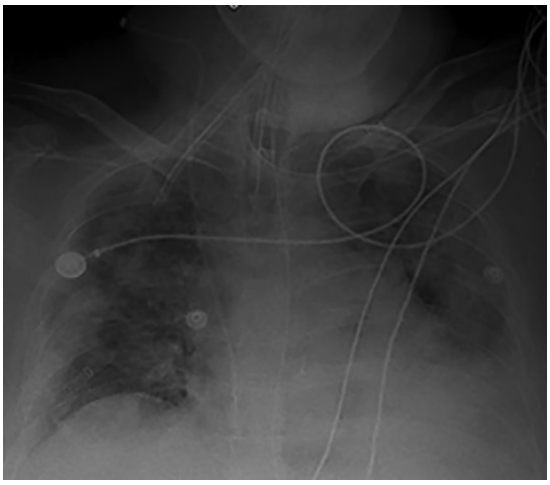

Figure 2. Chest X-ray showing patchy bilateral air space opacities.

Discussion

A hyperinflammatory syndrome (HIS) may cause a fatal ARDS in patients with COVID-19 pneumonia. The limited available evidence suggests that HIS that resembles secondary hemophagocytic lymphohistiocytosis (sHLH) may have a pathogenetic role. The key laboratory features of sHLH are cytopenia, increased levels of ferritin, triglycerides, lactate dehydrogenase, D-dimer, and hypofibrinogenemia.[3]

Cytokine storm is a broad term that encompasses several disorders of immune dysregulation. While it is both a clinical and laboratory diagnosis, at this time, no single definition has been widely accepted. COVID-19 is characterized by heterogeneous symptoms ranging from myalgia and fatigue to cytokine storm and multi-organ failure. Reports of hemophagocytosis and elevated cytokine levels in severely ill patients suggest that cytokine storm may contribute to the pathogenesis of COVID-19.[4]

Cytokine storm is characterized by significant and rapid increase in cytokines, including IL-6, an important inflammatory mediator. Patients with severe COVID-19 infection have high levels of IL-6 and other inflammatory markers suggestive of cytokine storm, unlike those with mild infection.[5]

Similarities between clinical characteristics of sHLH and severe COVID-19 such as multi-organ involvement, cytopenia, and coagulopathy and high levels of ferritin were noted previously,[6] and was also observed in our patients through the labs that were trended.

Among COVID-19 patients, about 25% presented with severe complications including ARDS requiring mechanical or invasive ventilation.[7]

IL-6 plays a prominent role in cytokine storm through various signal transduction pathways. IL-6 binds to IL-6 receptor (IL-6R) and this complex binds to transmembrane glycoprotein 130 (gp130) initiating intracellular signal transduction. These pathways ultimately lead to the promotion of complex biological functions such as proliferation, differentiation, oxidative stress, and immune regulation.[8]

TCZ is an IL-6 blocking antibody that targets IL-6R thus inhibiting IL-6R-mediated signal transduction. It can be administered for a maximum of 2 doses. The first dose is 4 to 8 mg/kg. A single dose administered should not exceed 800 mg.[9]

TCZ seems to effectively treat severe patients of COVID-19, which likely is due to inhibition of the IL-6-mediated inflammatory storm response.[10]

In a series of 100 patients with severe COVID-19 pneumonia complicated by ARDS and HIS, TCZ use was associated with remarkable clinical improvement. In another study by Ramaswamy and colleagues, TCZ used to treat COVID-19 patients with elevated levels of biomarkers (IL-6 and CRP) indicative of cytokine storm provided a short-term survival benefit.[11]

A recent trial published in Stone and colleagues, did not provide support for early IL-6-receptor blockade in moderately ill patients hospitalized with COVID-19[12]; however, intubated patients only comprised 12% of the study population so we need to use caution when extrapolating these results to intubated patients with COVID-19.

In contrast, an observational study of 62 mechanically ventilated, COVID-19-positive patients demonstrated clinical improvement in 36 patients (58%) by 21 days post TCZ.[13]

In another retrospective study by Luo and colleagues,[14] the authors recommended TCZ as an effective treatment option for patients with COVID-19 with high risk of

Table 2. Trend of COVID-19 labs.

	Day 1	Day 2	Day 5	Day 9	Day 14	Day 16	Adm	Peak
D-Dimer (Ref: <0.5 mg/L)	0.62	0.88	2.14		5.74	1.86	0.62	5.74
Fibrinogen (Ref: 163-419 mg/dL)			396	330	309	469	—	469
Ferritin (Ref: 2-290 ng/mL)	2455	1690	2998			276	2455	2998
LDH (Ref: 125-243 U/L)	719	589	1186	702			719	1186
CRP (Ref: 0-0.8 mg/dL)			2	0.3	0.3	2.6	—	2.6
Triglycerides (Ref: 0-150 mg/dL)	326	700	693				326	2142
IL-6, serum (Ref: 0-15.5 pg/mL)	458.5					799.3		799.3

Abbreviations: LDH, lactate dehydrogenase; CRP, C-reactive protein; IL, interleukin.

Table 3. Trend of COVID-19 labs showing improvement after TCZ administration on Day 3.

	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Peak
D-Dimer (Ref: <0.5 mg/L)	3.64	0.34	0.42	0.68	0.83		1.16		0.79		3.64
Fibrinogen (Ref: 163-419 mg/dL)	>600	>600	>600	>600	575		522		396		>600
Ferritin (Ref: 2-290 ng/mL)	1873	2672	3955	3682	3386		3135		1934		3955
LDH (Ref: 125-243 U/L)	413	562	619	547	525		529		381		619
CRP (Ref: 0-0.8 mg/dL)	7.5	10.2	9.9	4.4	2	1	0.6	0.3	0.2	0.2	10.2
Triglycerides (Ref: 0-150 mg/dL)			147	213	244		248		300		300
IL-6,serum (Ref: 0-15.5 pg/mL)	68.9										

Abbreviations: LDH, lactate dehydrogenase; CRP, C-reactive protein; IL, interleukin.

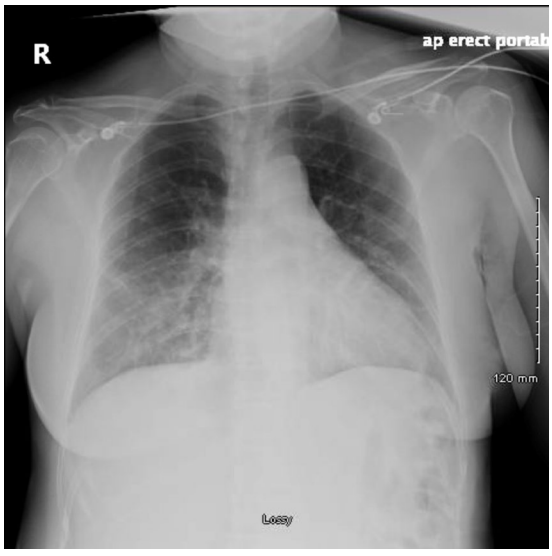

Figure 3. Chest X-ray showing bilateral interstitial infiltrates.

cytokine storm. They also recommended a repeat dose of TCZ for critically ill patients with elevated IL-6 levels.

Potential risks of using TCZ and other biologics include tuberculosis (TB) reactivation, serious infections, and lymphomas.[15] However, we did not note any of our patients who received TCZ to develop any serious infections or reactivation of TB. As their complete blood counts were followed throughout hospitalization concern for lymphoma was ruled out. Another rare complication of TCZ is intestinal perforation.[16]

Hydroxychloroquine (HCLQ) and azithromycin (AZI) drug combination is associated with high risk of QTc prolongation. AZI does not interact significantly with the hepatic cytochrome P450 system and hence not believed to undergo pharmacokinetic drug interactions. HCLQ undergoes CYP mediated metabolism and if co-administered with drugs that are inducers or inhibitors of the isoenzymes CYPs 2C8, 3A4, and 2D6, it may respectively decrease or increase exposure to them. TCZ reverses IL-6 induced suppression of cytochromes, which indirectly increases the metabolism of CYP3A4 substrates. Both HCLQ and AZI are minor CYP3A4 substrates. In theory, the administration of TCZ could potentially decrease the effectiveness of both HCLQ and AZI although this has not been seen in trials.[17] No specific interactions with zinc were noted.

The patients described in our case series were treated early during the pandemic at which time data on management of these patients was evolving. Initially we did use HCLQ and AZI at our facility; however, as more data evolved HCLQ has fallen out of favor although AZI is still used to treat superimposed bacterial pneumonia in these patients. Remdesivir was unavailable in our facility at the time these patients described were hospitalized and thus we did not use them. Through our case series, we noted an improvement in the clinical course and outcomes of patients hospitalized at our facility after they were treated with TCZ, and this case series highlights the key aspects of TCZ in cytokine storm and hence its role in management of COVID-19 patients.

Conclusion

The early, proactive identification of serum acute phase reactants should be implemented in the treatment of COVID-19 to screen for cytokine storm, which is a primary contributor to mortality. This screening, when followed by aggressive early treatment for cytokine storm, may have optimal therapeutic benefits.[18] As IL-6 appears to have a prominent role in mediating cytokine storm, TCZ could mitigate the cytokine storm by blocking the IL-6 pathway.

Based on the current evidence and our case series, at our institution, TCZ is considered on a case-by-case basis in patients with severe COVID-19 and both clinical and laboratory evidence of cytokine storm. Our experience supports the need for continued evaluation of TCZ in the ICU setting.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

The Conemaugh Memorial Medical Center Office of Research Administration reviewed this case series and determined that it does not meet the definition of human subject research as defined in 45 CFR 46; therefore, institutional review board review is not required.

Informed Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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