Case Report

SAGE Open Medical Case Reports

SAGE Open Medical Case Reports
Volume 10: 1–5

DOI: 10.1177/2050313X211069023
journals.sagepub.com/home/sco
SAGE

Use of tocilizumab, remdesivir, and high-dose methylprednisolone prevents intubation in an ESRD patient with COVID-19 pneumonia

Ramzan Judge[1], Stephanie Kolaski[2] and Farhan Qadeer[1]

Abstract

Coronavirus disease 2019 (COVID-19) has affected over 200 million patients worldwide. COVID-19 is transmitted through respiratory droplets from patient to patient or by touching a surface that has been contaminated by an infected patient. Many COVID-19 patients have other comorbidities, such as end-stage renal disease. Currently, management of COVID-19 in patients with end-stage renal disease is unclear. Some studies have shown improvement in this population with the use of tocilizumab, a humanized interleukin-6 monoclonal antibody, in addition to the standard therapy as per guidelines published by the National Institutes of Health. In this case report, we present a patient case where the use of remdesivir, tocilizumab, and pulse-dose methylprednisolone significantly improved symptoms and inflammatory biomarkers associated with COVID-19 in a patient with end-stage renal disease.

Keywords

Critical care/emergency medicine, nephrology, infectious diseases, COVID-19, steroids, remdesivir, tocilizumab, end-stage renal disease

Date received: 31 August 2021; accepted: 7 December 2021

Introduction

Coronavirus disease 2019 (COVID-19) is caused by a Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) transmitted through respiratory droplets from patient to patient. SARS-COV-2 is made up of four structural proteins, including spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins.[1] The S protein is responsible for viral binding to the host cell receptor and entry into the host cell membrane. Once in the membrane, the viral contents are released and begin to replicate through RNA polymerase activity creating new strands of positive RNAs. The N protein binds to the new RNA, forming nucleocapsids that are enclosed in the endoplasmic reticulum and eventually transported to the extracellular space via exocytosis.[2] This progression ultimately leads to an uncontrolled inflammatory response due to a rapid increase in proinflammatory cytokines, mainly interleukin (IL)-6, causing a cytokine storm and acute respiratory distress syndrome (ARDS). Several other inflammatory markers have been detected with COVID-19, which include elevated levels of serum ferritin, C-reactive protein (CRP), procalcitonin, alanine transaminase (ALT), and aspartate aminotransferase (AST).[1]

With the rising death tolls due to COVID-19, clinicians have used a wide variety of combinations of medications to curtail the mortality rate. Despite ongoing clinical trials and retrospective publications, there is no current consensus on pharmacotherapy. Currently, clinicians have used remdesivir, corticosteroids, and tocilizumab for treatment. Remdesivir, Food and Drug Administration (FDA)-approved in October 2020, is a broad-spectrum antiviral that inhibits the RNA-dependent RNA polymerase.[2] Glucocorticoids exhibit an anti-inflammatory effect that can decrease IL-6, IL-8, and TNF receptor 1, which are all inflammatory markers that were found to be elevated in COVID-19 patients.[3] Finally, tocilizumab, a humanized anti IL-6 monoclonal antibody, selectively and competitively binds to soluble expressing IL-6 preventing a cytokine storm (see Figure 1).[4]

[1]Shore Medical Center, Somers Point, NJ, USA
[2]Thomas Jefferson University, Jefferson College of Pharmacy, Philadelphia, PA, USA

Corresponding Author:
Ramzan Judge, Shore Medical Center, 100 Medical Center Way, Somers Point, NJ 08244, USA.
Email: ramzanjudge@gmail.com

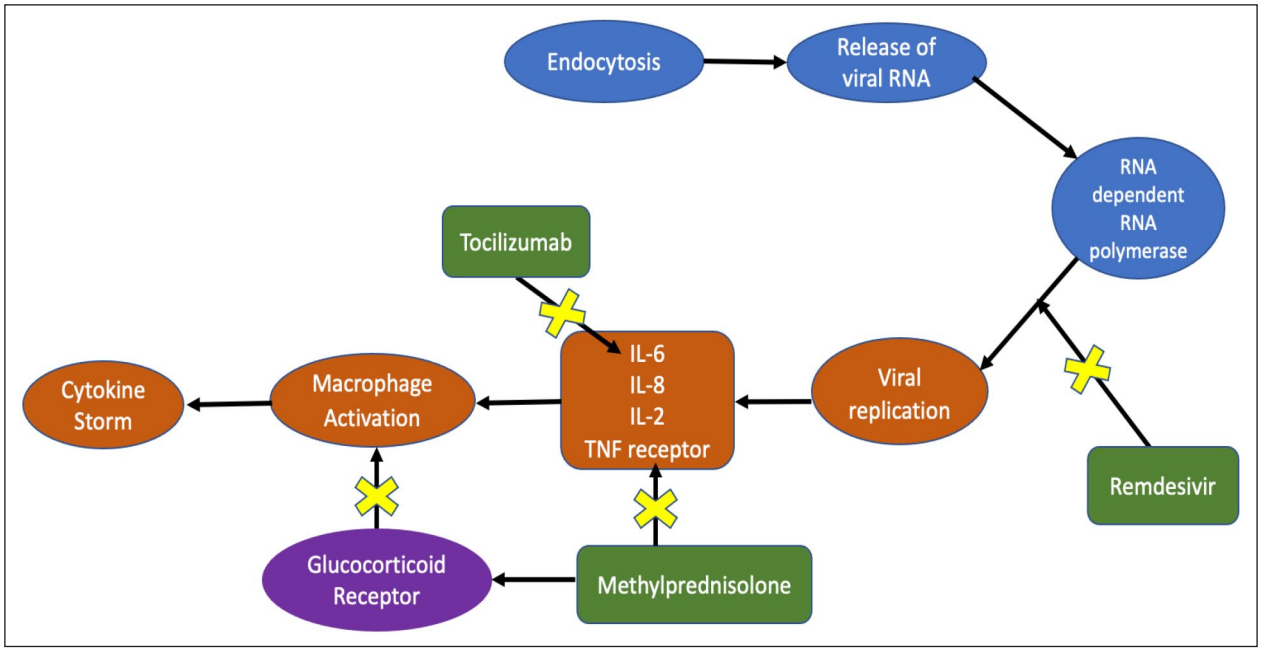

Figure 1. Mechanism of action of tocilizumab, remdesivir, and methylprednisolone in COVID-19. Tocilizumab binds to the IL-6 binding site of human IL-6R and competitively inhibits IL-6 signaling, thereby interfering with the cytokine storm.[5] Remdesivir inhibits RNA-dependent RNA polymerase, preventing new RNA strands.[6] Methylprednisolone binds to glucocorticoid receptors after diffusing across the cell membrane, where it causes a conformational change in the receptor and restricts macrophage activation. Methylprednisolone also inhibits TNF-alpha receptor, which downregulates activation of cytokines, preventing a cytokine storm.[7]

Case presentation

Our patient was a 75-year-old Caucasian male with a prominent past medical history of ESRD, hypertension, diabetes, and benign prostatic hyperplasia who provided written informed consent. The patient had a recent surgery for spinal stenosis and was recuperating at a nursing home where he contracted COVID-19. Patient noted that he has been compliant with his dialysis schedule. When he was brought to the emergency department due to worsening shortness of breath, he was found to be hypoxic with an 87% SpO_2 on room air. The initial chest X-ray revealed bilateral infiltrates consistent with multifocal bronchiolitis pneumonia (see Figure 2). His SARS-COV-2 antigen and PCR test were both positive upon admission, and his CRP was elevated. On day 1, the patient was admitted to the general hospital ward on 4 L of oxygen with an SpO_2 of 91%. However, his respiratory status worsened on day 2 and oxygen requirement escalated to 15 L with saturation in the high 90's. His arterial blood gas showed a pH of 7.43, $PaCO_2$ of 42.0 mmHg, PaO_2 of 78.0 mmHg, and SO_2 of 96.2 while on 15 L high flow nasal cannula (HFNC). He was then transferred to the intensive care unit (ICU) for closer monitoring.

Initially, the patient was treated with one dose of dexamethasone 10 mg IV push and bamlanivamab and etesevimab. However, upon ICU transfer, the patient was started on methylprednisolone 1 g for 3 days per our ICU COVID-19 protocol. Originally, remdesivir and tocilizumab were held due to the patient's history of ESRD and concern for toxicity. After deliberation with other specialties, the patient was started on remdesivir 200 mg for 1 day, followed by remdesivir 100 mg for 4 days, as well as tocilizumab 8 mg/kg for 1 dose on day 2. After the pulse dose of methylprednisolone was completed, the patient was started on methylprednisolone 40 mg twice a day. Within a few days of

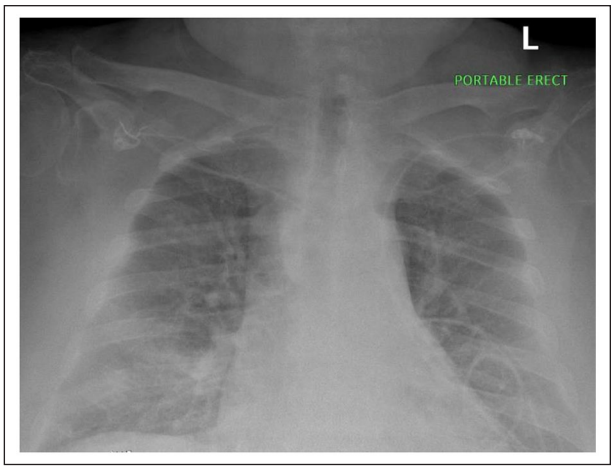

Figure 2. The chest X-ray showed multifocal bilateral patchy interstitial and alveolar infiltrates. No pneumothorax was present. Findings were consistent with multifocal bronchiolitis pneumonia consistent with the history of COVID-19 pneumonia.

Table 1. Progression of biological parameters from day 1 of hospital admission to discharge.

Measure	Day 1	Day 2[a]	Day 3	Day 4	Day 5	Day 6[b]	Day 7
White cell count (109/L)	5.14	8.39	8.03	8.46	10.39	14.27	18.44
Neutrophil count (%)	77.7	89.4	89.4	86.7	82.7	81.1	80.8
Lymphocyte count (%)	10.7	5.2	6.5	5.1	4.9	4.9	5.6
Hemoglobin (g/dL)	8.4	9.7	9.8	9.1	9.5	9.8	9.9
Hematocrit (%)	26.3	30.1	29.5	27.4	28.4	28.9	29.6
Platelet count (109/L)	179	238	277	295	346	314	349
CRP (mg/L)	136	NA	120.6	76.3	53.8	38.6	27.6
Ferritin (µg/L)	NA	NA	5340	5047	4480	3882	3803
ALT (U/L)	NA	9	9	10	15	24	26
AST (U/L)	NA	19	18	18	18	23	20
FIO2% (L/min)	4 L NC	15 L HFNC	100 % @ 50 L	40% @ 40 L	2 L NC	Room air	Room air

CRP: C-reactive protein; NA: not available; ALT: alanine transaminase; UL: units per liter; AST: aspartate aminotransferase; FIO: fraction of inspired oxygen; NC: nasal cannula; HFNC: high flow nasal cannula.
The patient received hemodialysis on days 3, 4, 5, and 7 of his hospital stay.
[a]Remdesivir day 1 and tocilizumab administration.
[b]Completion of remdesivir treatment.

treatment, the patient had substantial improvement in oxygen requirement as well as inflammatory biomarkers. He was discharged on day 7 after being hemodynamically stable for more than 48 h (see Table 1). His liver function tests were within normal limits (shown in Table 1) throughout the duration of therapy and hospital stay. Patient has end-stage renal disease (ESRD), therefore, creatinine clearance was not trended. No liver necrosis or acute kidney injury was seen during or after completion of triple combination therapy in our patient. Due to the available resources at our community hospital, we did not have access to measure interleukin (IL)-6, IL-8, IL-2, and transferrin receptor (TF) receptor. We did analyze CRP and serum ferritin. Patient was observed for any adverse events related to remdesivir and tocilizumab, including hypersensitivity reactions, bradycardia, and increased hepatic effects.

Discussion

Shortly after first being reported in Wuhan, China in December 2019, COVID-19 became a global, ongoing pandemic that has been linked with high mortality. According to the World Health Organization, as of early August 2021, there have been over 200 million cases of COVID-19 confirmed worldwide, including 4.2 million deaths.[4] Signs and symptoms of COVID-19 include shortness of breath, cough, fever, nausea, vomiting, or loss of taste and smell. These can appear anywhere from 2 to 14 days post exposure, whereas some patients have no symptoms but can still spread the disease. It has been noted that patients have a higher risk of contracting COVID-19 with risk factors such as old age, immunosuppression, diabetes, ESRD, or cardiac and pulmonary disease.[2] At the time of this patient case in July 2021, there were no case reports which showed the use of this triple therapy regimen in a patient with ESRD that resulted in successful recovery. Unfortunately, the treatment for COVID-19 patients, specifically with ESRD, is poorly understood due to lack of data or evidence at this time.

Although there is literature to support the safe use of remdesivir and tocilizumab in individuals with normal liver and kidney function, there have been concerns in using it in patients with ESRD. Remdesivir is a prodrug mainly metabolized by hepatic enzymes to remdesivir triphosphate, which is a nucleotide analog that prevents replication of SARS-COV-2.[4] The plasma half-life of the parent drug remdesivir is 1–2 h. However, the half-life of the active metabolite remdesivir triphosphate is about 20–25 h.[4] Remdesivir also contains the inactive ingredient, sulfobutylether-β-cyclodextrin (SBE-β-CD), which is a large, cyclic oligosaccharide mainly excreted through glomerular filtration that has an elimination half-life of less than 2 h. SBE-β-CD has been shown to accumulate in patients with a creatinine clearance less than 50 mL/min.[6] Hence, there is concern for liver necrosis and renal tubule obstruction with using remdesivir in ESRD patients.[5] Currently, manufacturer's labeling does not recommend its use in this population.[7]

However, there was an observational prospective study published in March 2021 with 48 dialysis-dependent patients diagnosed with COVID-19 who received remdesivir. During the treatment period, 100 mg of remdesivir was given 4 h before hemodialysis sessions. In this study, the researchers did not see a significant alteration in liver function tests and CRP levels improved. This study concluded no liver necrosis or acute kidney injury and if remdesivir is initiated within 48 h of hospitalization in ESRD patients, it reduces recovery time.[5] There have also been several case reports on the use of remdesivir in a patient with ESRD. One case report initially used dexamethasone, and 10 days later administered remdesivir due to worsening symptoms. There were no signs of drug-related toxicity and oxygen parameters improved on day 5 of treatment with remdesivir.[8] Another single-center trial of 157 COVID-19 patients with ESRD studied the use of remdesivir

and dexamethasone. The authors reported that no clinically significant ALT elevations were observed, and no patients needed early discontinuation of therapy due to adverse effects.[9] Although there are retrospective studies to demonstrate the safety of the remdesivir in ESRD patients, there are no reports of using the triple therapy as noted in our study.

In regard to tocilizumab, it is known to have biphasic elimination from the circulation following intravenous administration. Its pharmacokinetics show a volume distribution of 6.4 L at steady state. The concentration-apparent half-life is 11 days for 4 mg/kg and 13 days for 8 mg/kg.[10] No large, randomized controlled trial has been conducted with the use of tocilizumab in ESRD patients. Hence, the manufacturer recommends against use in this population. However, there are a few case reports that show efficacy of tocilizumab in renally impaired patients. In November 2020, a case report involving tocilizumab for a 52-year-old COVID-19 patient with ESRD on hemodialysis showed rapid improvement and became afebrile 24 h after administration.[11] In another case report, an Australian patient on long-term hemodialysis with severe COVID-19 was treated with tocilizumab on day 7 of her hospital stay. The case report showed a significant and immediate decrease in her inflammatory markers.[12] Tocilizumab also has the approved indication for rheumatoid arthritis, where it also has limited data regarding safety with ESRD patients. In 2015, a study that took place in Japan analyzed the effect between tocilizumab and methotrexate, another rheumatoid arthritis agent, in patients with ESRD. Efficacy parameters in the renal insufficiency group with tocilizumab were like those in the methotrexate group. There were also no significant differences in rates of dropout, adverse events, or severe adverse events between the two groups for patients with and without renal insufficiency.[13]

Finally, corticosteroids have become the mainstay of treatment for COVID-19. A cohort study published in May 2021 with 216 COVID-19 positive patients compared dexamethasone and methylprednisolone. The patients received methylprednisolone 250–500 mg IVPB for 3 days followed by prednisone 50 mg orally for 14 days or dexamethasone 6 mg orally for 7–10 days. The maximum amount of methylprednisolone given was 1 g IVPB for up to 7 days. Both groups were shown to decrease recovery time and severity markers, including CRP and ferritin.[14] This use of corticosteroids was also studied in the RECOVERY trial that included 2104 patients hospitalized with COVID-19. The patients received either dexamethasone 6 mg orally or intravenous once daily for up to 10 days plus usual care or usual care alone. The results showed that the dexamethasone group had a lower 28-day mortality rate in patients who received invasive mechanical ventilation or oxygen therapy alone.[14,15] Due to the current available published data, our patient was given methylprednisolone 1 g IVPB for 3 days followed by methylprednisolone 40 mg twice a day, remdesivir for 5 days, and one dose of tocilizumab 8 mg/kg.

We believe that this is the first reported case of COVID-19 pneumonia in an ESRD patient who was treated with the combination of pulse dose methylprednisolone, tocilizumab, and remdesivir. Our case report shows that a single dose of tocilizumab (8 mg/kg), along with remdesivir and methylprednisolone, reduces the symptoms and decreases inflammatory biomarkers in a patient who tested positive for COVID-19 with ESRD. While there is a plethora of data for the use of the three agents (steroids, remdesivir, and tocilizumab) in non-ESRD patients, there has not been published guidelines regarding their use in ESRD COVID-19 patients. In addition, our case report included the use of the pulse-dose methylprednisolone (a dose larger than the currently suggested by the RECOVERY trial). Hence, our study proposes the need to investigate the role of higher doses of steroid in combination with remdesivir, and tocilizumab in this patient population.

Conclusion

In light of COVID-19 delta variant and growing population of ESRD patients, a triple therapy consisting of pulse dose methylprednisolone, tocilizumab, and remdesivir can be considered as a treatment option. However, randomized controlled trials are warranted to assess its safety and efficacy of the noted regimen.

Acknowledgements

We would like to thank the patient who entrusted us to be part of his care and permitted us to share his case.

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.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

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

ORCID iD

Ramzan Judge https://orcid.org/0000-0001-5800-5478

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