Combined effects of Tocilizumab and Remdesivir in severe COVID- 19 patient with cytokine release syndrome: A case-report

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Table of Contents

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Abstract

Background: Novel corona virus (nCoV) or Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is known to cause severe bilateral pneumonia and acute respiratory distress syndrome (ARDS) or Corona virus disease-2019 (COVID-19) in patients that can be debilitating and even fatal. With no drugs or vaccines available yet, a wide range of treatment regimens used are being repurposed. The need of the hour is to analyze various regimens available and devise a treatment plan most effective against SARS-CoV-2.

Objective: Patient concerns: A 68-year-old hypertensive, diabetic male, exhibiting symptoms of cough and shortness of breath presented at the emergency department of our hospital.
Diagnosis: Chest CT revealed bilateral ground glass opacities indicative of COVID-19 and the CT score of 24 indicated severe pulmonary pneumonia. He tested positive for COVID-19.

Methods: Interventions: The treatment regimen included use of convalescent plasma, oxygen therapy, steroids, high dose antibiotics, broad spectrum antiviral Remdesivir, and anti-interleukin-6 monoclonal antibody/Tocilizumab at various stages of the disease.

Results: Outcomes: Oxygen support was required at the time of admission. The patient initially developed cytokine release storm and mechanical ventilation was used to manage his condition. Supportive care and multiple treatment regimens were used to successfully recover the patient's health.

Conclusions: Lessons: With a rapid increase in number of confirmed cases worldwide, COVID-19 has become a major challenge to our healthcare system. With no available vaccines currently, finding a combination of therapeutic drugs which are effective in reducing progression of disease is of utmost importance. Clinical Trial: Abbreviations:COVID-19=Corona virus disease 2019, nCoV=Novel corona virus (nCoV), SARS-CoV-2=Severe acute respiratory syndrome coronavirus 2, ARDS=acute respiratory distress syndrome, RT PCR= real-time polymerase chain reaction, SPO2= oxygen saturation, ICU=Intensive Care Unit, GGO=ground glass opacities, TDS=thrice daily, OD=once daily, BD= twice daily, CRS= cytokine release syndrome, CPAP=continuous positive airway pressure,FiO2= fraction of inspired oxygen, PEEP=positive end-expiratory pressure, PSV= pressure support ventilation.

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Abstract

Rationale**:** Novel corona virus (nCoV) or Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is known to cause severe bilateral pneumonia and acute respiratory distress syndrome (ARDS) or Corona virus disease-2019 (COVID-19) in patients that can be debilitating and even fatal. With no drugs or vaccines available yet, a wide range of treatment regimens used are being repurposed. The need of the hour is to analyze various regimens available and devise a treatment plan most effective against SARS-CoV-2.

Patient concerns**:** A 68-year-old hypertensive, diabetic male, exhibiting symptoms of cough and shortness of breath presented at the emergency department of our hospital.

Diagnosis: Chest CT revealed bilateral ground glass opacities indicative of COVID-19 and the CT score of 24 indicated severe pulmonary pneumonia. He tested positive for COVID-19.

Interventions**:** The treatment regimen included use of convalescent plasma, oxygen therapy, steroids, high dose antibiotics, broad spectrum antiviral Remdesivir, and anti-interleukin-6 monoclonal antibody/Tocilizumab at various stages of the disease.

Outcomes**:** Oxygen support was required at the time of admission. The patient initially developed cytokine release storm and supplemental oxygen was used to manage his condition. Supportive care and multiple treatment regimens were used to successfully recover the patient's health.

Lessons**:** With a rapid increase in number of confirmed cases worldwide, COVID-19 has become a major challenge to our healthcare system. With no available vaccines currently, finding a combination of therapeutic drugs which are effective in reducing progression of disease is of utmost

importance.

Abbreviations:COVID-19=Corona virus disease 2019, nCoV=Novel corona virus (nCoV), SARS-CoV-2=Severe acute respiratory syndrome coronavirus 2, ARDS=acute respiratory distress syndrome, RT PCR= real-time polymerase chain reaction, SPO_2= oxygen saturation, ICU=Intensive Care Unit, GGO=ground glass opacities, TDS=thrice daily, OD=once daily, BD= twice daily, CRS= cytokine release syndrome, CPAP=continuous positive airway pressure,FiO_2= fraction of inspired oxygen, PEEP=positive end-expiratory pressure, PSV= pressure support ventilation.

Keywords: **COVID-19, case report, treatment, Tocilizumab, Remdesivir**

Introduction

Corona virus disease 2019 (COVID-19) is a severe acute respiratory infection that, since the first confirmed case in Wuhan on 31 December 2019 [1], has been traversing the globe as a worldwide pandemic [2].It has since affected 235 countries, areas or territories with 76,900,875 confirmed cases including 1,696,401 deaths as of 20 December 2020 [3].The infectious agent responsible for COVID-19 is a novel encapsulated, positive sense RNA virus that belongs to the beta-coronaviridae family, and has been named as novel corona virus (nCoV) or Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [4]. The gold standard diagnostic test for COVID-19 is a positive a real-time polymerase chain reaction (RT-PCR) test, which confirms presence of viral nucleic acid in blood or respiratory swab samples of a patient. Initial diagnosis of COVID-19 is based on: (1) patient's history; which may indicate possible contact with a confirmed patient, (2) clinical symptoms; which range from mild or moderate (cough, fever, tiredness, shortness of breath) to severe (pulmonary pneumonia, acute respiratory distress syndrome (ARDS)) and (3) radiological findings; consistent with COVID-19 infection [5,6]. The first two cases of COVID-19 in Pakistan were reported on 26 February 2020 with 457,288 confirmed cases including 9,330 deaths till 20th December 2020 [7].

The available treatment options for hospitalized COVID-19 patients with severe or critical disease presentation at the time are limited to use of drugs that aid in the resolution of symptoms and provide supportive care. These include use of convalescent plasma, oxygen therapy, steroids and broad-spectrum, high-dose antivirals and antibiotics [8]. We report the case of an elderly male who presented with cough, shortness of breath and severe pulmonary pneumonia at our hospital during the early months of the pandemic. The patient was admitted after an initial examination and later tested positive for COVID-19. The patient was treated with convalescent plasma, Dexamethasone, high dose antibiotics, broad spectrum antiviral Remdesivir, and anti-interleukin-6 monoclonal antibody Tocilizumab in addition to a number of other drugs. The condition of patient initially worsened after admission, from requiring low flow oxygen to development of ARDS and required mechanical ventilation but then he improved till made full recovery and was discharged after 14 days. The case study is presented to analyze the role of a combination of different drugs on progression of COVID-19 in our patient and highlight its life-saving potential.

Case presentation

On the evening of 10th June 2020, a 68-year-old Pakistani male doctor, with a history of hypertension and diabetes mellitus presented with fever, cough and shortness of breath. Difficulty in breathing had started three days prior to reporting to the emergency department of our hospital and seemed to worsen with time. His vitals at the time of presentation showed a temperature of 98.6°F, pulse 85 beats per minutes, blood pressure 110/70 mmHg and an oxygen saturation (SPO_2) of 87% on room air. After the initial physical exam, the on-duty doctor admitted the patient to the Intensive Care Unit (ICU) for management of possible pulmonary pneumonia and suspecting COVID-19, requested a PCR test and a computerized tomography (CT) scan of the chest. The CT scan revealed bilateral multifocal patchy and confluent areas of ground glass opacities (GGO) on lungs. Associated interlobular septal thickening with crazy paving appearance, subpleural fibrosis and prominent lower lobe bronchi were also noted, bilaterally, with more effect on the right side. The CT severity score was 24 which suggested severe disease. On admission to ICU, Day 1, the patient was initially given a one-time intravenous dose each, of Convalescent plasma (450 ml) and Paracetamol (1g), and given supplemental oxygen through a non-re-breathable mask at 4L O_2/min, to maintain SPO_2 greater than 90%. He was also started on a regimen of intravenous Methylprednisolone (60mg, once daily (OD)) and Enoxaparin Sodium (60mg, OD). On Day 2, the laboratory blood reports indicated lymphopenia, neutrophilia, increased C reactive protein (CRP) and raised serum lactate dehydrogenase (LDH), so a

7-day course of two antibiotics, Meropenem trihydrate (500mg, thrice daily (TDS)) and Moxifloxacin (400mg, OD), was also added to the regimen. On day 3 and 4, the patient's condition deteriorated considerably. He was semiconscious and developed ARDS. The flow velocity of oxygen had to be increased up to 15L O_2/min which was still insufficient to maintain SPO_2 of 90-91%. Serum ferritin levels of the patient were raised along with further increase in lymphopenia, CRP, and LDH and as the patient developed signs of cytokine release syndrome (CRS), Tocilizumab (80mg) was administered intravenously with the dose repeated after 12 hours. On day 5, the patient was put on continuous positive airway pressure (CPAP) ventilation where SPO_2 between 88-92% was maintained at 50% fraction of inspired oxygen (FiO_2), positive end-expiratory pressure (PEEP) of 6, and pressure support ventilation (PSV) of 14. Patient was also brought to a proned position for up to 12 hours to manage the respiratory distress. In addition to ventilator support, Dexamethasone (8mg, twice daily (BD)) was administered intravenously. On Day 8, Remdesivir (200mg) was administered intravenously with dose halved to 100mg for the next four days. A one-time dose of 20% Albumin infusion (50ml) was also administered intravenously and a regimen of intravenous Linezolid (600mg, BD) was also added. On day 10, the condition of patient began to improve and an SPO_2 of 97% was achieved at the same ventilator setting. Serum ferritin, CRP and LDH were also improved. On day 11 patient started to show signs of recovery where an SPO_2 of 97% was achieved with FiO2 reduced to 45%, PEEP of 6 and PSV of 14. On day 12, FiO_2 was further reduced to 40%, PEEP at 6 and PSV of 14. Patient was advised to sit upright for one hour after regular intervals. Since patient was showing signs of improvement, he was gradually weaned off the ventilator and shifted to oxygen mask where he was able to maintain an SPO_2 of 94-96% at 2L O_2/min. On day 13 patient was prescribed oral doses of Dexamethasone (5mg, OD) and Moxifloxacin (400mg, OD) and Linezolid (600mg, BD) for a 3-day course. A reduced intravenous dose of Enoxaparin Sodium (40mg, OD) for the next 7 days was also advised. The PCR for COVID-19 was repeated which came negative and the patient was discharged on Day 14 of admission, i.e., 24th June 2020.

Discussion

The article summarizes the clinical presentation, diagnosis and treatments received by a 68 year old diabetic, hypertensive, male doctor who was presented with fever, cough and shortness of breath at our hospital. Given his age, history (possible exposure at his place of work, presence of underlying conditions like hypertension and diabetes), symptoms (fever, cough, shortness of breath), low oxygen saturation (SPO_2 of 87%) and CT scan findings (CT severity score of 24), our patient was treated as COVID-19 suspect at risk of developing severe disease. A positive PCR test for COVID-19 and later stages of his disease progression during his stay at the hospital confirmed this notion, however timely recognition of risks and provision of immediate, effective treatment most likely ensured his recovery and survival.

In a study describing the clinical characteristics, treatments and outcomes of 138 confirmed COVID-19 cases, Wang *et al.,* [9] reported fever (98.6%), dry cough (59.4%), and dyspnea (31.2%) as the most common symptoms associated with COVID-19. Moreover, all patients showed bilateral ground glass opacities in the chest CT scans. In another study Zhu *et al.,* [10] analyzed the chest CT scans of 72 COVID-19 patients divided into two age groups: 60 years and younger (44 patients) and those older than 60 years (32 patients). They reported GGO in the peripheral areas accompanied by inter lobular septal thickening, subpleural line and pleural thickening. More extensive involvement of the lobes and subpleural line and pleural thickening in the patients older than 60 years was also observed. In another study involving 51 COVID-19 positive patients, Li *et al.* [11] evaluated if chest CT was a reliable tool for rapid diagnosis and management of COVID-19 patients. They concluded that CT had a low rate of miss-diagnosis of COVID-19 and common features characteristic to COVID-19 include presence of GGO and consolidation with or without vascular enlargement, interlobular septum thickening, and presence of air bronchogram. It also appeared that older patients

showed a greater degree of lung involvement as compared to younger patients. The chest CT findings of our patient also indicated presence of severe bilateral pneumonia, a high CT score 24, and characteristic imaging features reported to be consistent with COVID-19 pathology (GGO, interlobular septal thickening, and subpleural fibrosis). In addition to presenting signs and symptoms characteristic to COVID-19, where shortness of breath indicates possibility of developing severe COVID-19, several epidemiological studies have recognized old age, male gender and presence of underlying health conditions such as diabetes, hypertension, and cardiovascular disease, renal and liver diseases etc. as risk factors for development of severe COVID-19 infection [12, 13]. Our patient also had some of these risk factors (old age, hypertension and diabetes) and these indicated the likely possibility of progression to severe COVID-19.

As many of the factors were not indicative of a possibly favorable outcome, the patient was administered a number of therapeutic interventions including convalescent plasma, anti-coagulants, antibiotics, corticosteroids, immunomodulatory drugs and antivirals during his stay at the hospital.

According to the hospital protocol at the time, one of the first interventions our patient received was intravenous convalescent plasma therapy (CPT). Convalescent plasma therapy is being used in different countries to provide passive immunization against SARS CoV-2. It is hypothesized that if CPT is administered in early stages of COVID-19, it reduces overall viral load, improves disease prognosis and increases chances of survival in COVID-19 patients [14]. In a retrospective study [15], the clinical outcomes of 37 critical COVID-19 patients who received CPT were compared with controls who were admitted to the hospital at the same time but did not receive CPT. Patients who received CPT showed greater improvement in oxygen saturation, and better survival rate.

The pathogenesis of SARS CoV-2 and how it affects the physiology of its host is under intense investigation at the moment. In case of severe COVID-19 infections, the progression of viral infection manifests in the form of a massive inflammatory response termed as the cytokine storm or cytokine release syndrome (CRS) which initially affects lungs, causing oxygen insufficiency leading to ARDS, but can also spread to other organs such as heart, kidneys, liver leading to multiple organ failure and eventually death [16, 17].

The hallmarks of CRS include high serum levels of pro-inflammatory cytokines and chemokines especially interleukin 1 family and interleukin 6 (IL-6), which initiate the inflammatory cascade resulting in lung inflammation, fever and fibrosis. These changes can be monitored by laboratory parameters including percentage lymphocyte count which decreases (i.e., lymphocytopenia), and an increase in serum levels of CRP, LDH and ferritin [18]. The presence of these circulating biomarkers have been cited as predictors of severity of COVID-19 and adverse outcomes such as death in COVID-19 patients [19]. So targeting them in order to reduce overall inflammatory cascade i.e. the CRS, is the first logical step to control progression of disease. [16, 20]

Use of glucocorticoid therapy for the management of CRS [21] has been explored and is associated with a reduction in respiratory inflammation and improvement in lung function often eliminating the need for invasive ventilation in severe/critical COVID-19 patients. In a study by Liu *et al.*, [22], administration of a pulse dose of Methyl prednisolone in 101 COVID-19 patients resulted in improved lung function of the 15 patients who were critically affected, with only one patient requiring mechanical ventilation. In an open label, controlled clinical trial [23] of 2,014 COVID-19 patients who received Dexamethasone and 4,321 patients who received usual care, mortality rate in patients who received Dexamethasone was markedly reduced. Moreover among patients receiving Dexamethasone, mortality rates in patients that required invasive and non-invasive mechanical ventilation were significantly reduced whereas no effect was seen in patients who received no respiratory support.

In our case, the initial use of CPT and methyl prednisolone was unable to curtail the cytokine storm and effectively prevent the onset of ARDS. As a result the patient’s condition deteriorated rapidly to the point where he was put on CPAP on day 5. The patient was then administered a combination regimen of twice daily doses of dexamethasone and Tocilizumab, which was repeated after 12 hours.

Tocilizumab is an anti-inter-leukin-6 (anti-IL-6) antibody preparation, which has been shown to be highly effective in improving disease severity by neutralizing IL-6 which has a major role in inflammatory cascades resulting in ARDS [24]. In a retrospective analysis study of 21 critical patients, Xu *et al*., [25] observed a resolution of lymphopenia in 85% patients and decrease in CRP in 84.25% patients within 5 days of administration of tocilizumab. Similar findings were reported by Guaraldi *et al*., [26] where administration of tocilizumab was positively correlated with recovery, and reduced requirement of invasive mechanical ventilation at later stages.
In addition to the above immunomodulation therapies, our patient received Remdesivir on day 8. Remdesivir is a broad spectrum antiviral agent that has previously been investigated for its inhibitory effect on viral replication in case of Ebola virus, severe acute respiratory syndrome (SARS) Corona virus and Middle East respiratory syndrome (MERS) Corona virus. The double blind, randomized, placebo-controlled trial by Beigel *et al.*,[27] concluded that 541 (out of a total 1062) patients who received Remdesivir showed quicker recovery time (10 days as compared to 15 days in control group).Their data also suggests that Remdesivir may also reduce the progression of the disease into more severe stage. Since the results of the trial became public, Remdesivir has become the first antiviral that has been autorized by FDA for emergency use in hospitalized adult patients with likelihood of progression into a severe disease [28]. The effects of the drug are however closely monitored and updated as new evidence surfaces [29].So far, the preliminary results by the more recent Solidarity trial led by World Health Organization (WHO), WHO recommended against the use of Remdesivir for treatment of COVID-19 due to its limited efficacy. [30]. Moreover, in addition to ambiguity regarding its efficacy, remdesivir is also associated with acute kidney and liver injury [31]. Furthermore, it has been suggested that Remdesivir may be more effective in combination with an immunomodulator like dexamethasone or Tocilizumab. A number of trials investigating the use of Remdesivir in combination with Tocilizumab are currently underway and the final verdict regarding its efficacy is still pending [29, 30, 32, 33]

In our patient, however, the combination of Remdesivir, tocilizumab and dexamethasone, administered at a favorable time i.e. during the early stages of the disease when the patient did not yet require mechanical intubation, resulted in timely resolution of cytokine storm, resulting in an improvement in the ARDS symptoms and his subsequent recovery. The reason behind this could be attributed to effective recognition of risks and a timely administration of the available drugs.

Conclusion

Despite being the focus of the medical and scientific research for more than a year, world wide availability of a safe, effective COVID-19 vaccine is still a work in progress. Similarly, a number of antivirals and immunomodulators are being actively tested, yet an effective combination is still unavailable. Therefore, to effectively control COVID-19, there is a need to continuously explore and identify safe, effective combinations of the already available therapeutic agents. In order to ensure safety and survival of the patient, there is a constant need to stay up to date about latest evidence as well. In our patient exhibiting cytokine release syndrome with normal liver and renal functions, combined effect of Tocilizumab, Dexamethasone and Remdesivir helped reduce CRS and the subsequent risk for mechanical ventilation. However, mixed evidence regarding use of Tocilizumab in combination with Remdesivir suggests that caution should be exercised until more evidence is available in support or against this combination for this to become a treatment regimen nationwide.

Acknowledgements

None.

Conflict of Interest

None.

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