Successful treatment with Remdesivir and corticosteroids in a patient with COVID-19-associated pneumonia: A case report

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread throughout the world causing significant mortality in high risk patients with severe manifestations. To date, Remdesivir has been the only antiviral authorized by FDA as therapy for emergency use. One of the potential complications of this infection is cytokine storm, which optimal treatment remains unknown. We present the case of a 48-year-old man with no past medical history who presented to the hospital with dyspnea, cough, subjective fever, and diarrhea for 10 days. Nasopharyngeal PCR was positive for SARS-CoV-2. His respiratory status rapidly worsened to the point of requiring supplemental oxygen by high flow nasal cannula with FiO2 of 80%. Chest computed tomography showed confluent ground glass opacities in upper lobes accompanied by patchy airspace opacities in lower lobes bilaterally. He was started on hydroxychloroquine, which was switched to Remdesivir when it became available. Then, methylprednisolone was initiated for suspected cytokine storm. The patient's oxygenation improved significantly over the following days and he was discharged home with no oxygen supplementation and saturating 96% on room air. Our case illustrates the role of Remdesivir for the treatment of severe COVID-19 pneumonia. We also observed a possible clinical benefit of corticosteroids in the context of suspected cytokine storm. Further studies are needed to evaluate this therapeutic strategy.

Resumen

El síndrome respiratorio agudo grave coronavirus 2 (SARS-CoV-2) se ha diseminado rápidamente a lo largo del mundo causando una mortalidad significativa en pacientes de alto riesgo con manifestaciones severas. A la fecha, Remdesivir ha sido el único antiviral autorizado por la FDA para uso de emergencia. Una de las posibles complicaciones de esta infección es el desarrollo de tormenta de citoquinas, para la cual no existe un tratamiento óptimo. Presentamos el caso de un varón de 48 años sin antecedentes médicos que acudió al hospital con disnea, tos, fiebre subjetiva y diarrea durante 10 días. La reacción de cadena polimerasa nasofaríngea fue positiva para SARS-CoV-2. Su estado respiratorio empeoró rápidamente hasta el punto de requerir oxígeno suplementario a través cánula nasal de alto flujo con 80% de FiO2. La tomografía computarizada de tórax mostró opacidades confluyentes en vidrio esmerilado en los lóbulos superiores, acompañadas de opacidades irregulares alveolares en los lóbulos inferiores bilateralmente. Se inició terapia con hidroxicloroquina, la cual se cambió a Remdesivir cuando estuvo disponible. Luego se inició metilprednisolona como tratamiento de una posible tormenta de citoquinas. La oxigenación del paciente mejoró significativamente en los días posteriores y fue dado de alta sin requerir oxigeno adicional y saturando 96% en medio ambiente. Nuestro caso ilustra el papel de Remdesivir en el tratamiento de la neumonía grave por COVID-19. También observamos un posible beneficio clínico de los corticoides en tormenta de citoquinas. Se necesitan más estudios para evaluar la eficacia de esta estrategia terapéutica.

Main messages

- Remdesivir is the only antiviral authorized by FDA for the treatment of COVID.
- Corticosteroids are potential therapies for cytokine storm induced by COVID.
- We observed a possible clinical benefit with the use of Remdesivir followed by corticosteroids in severe COVID pneumonia.
- More studies are needed to evaluate the efficacy of this therapeutic strategy.

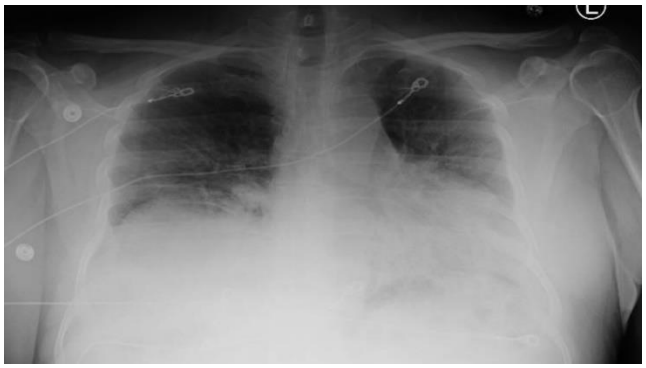
Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) appeared initially in Wuhan, China in December 2009, and since then has spread rapidly around the globe, leading to a pandemic that has not been described for more than a decade. Although most of the patients affected by this virus have good prognosis, approximately 15% can develop severe manifestations that result in high mortality rates[1,2]. At the present time, the optimal treatment of this infection has not been fully determined. Remdesivir, an antiviral targeting the RNA-dependent RNA polymerase of SARS-CoV-2, is the only drug authorized by Food and Drug Administration (FDA) for emergency use in the context of COVID[3]. One of the unique features of this infection is the development of possible cytokine storm induced by the virus, for which there is not a widely accepted therapy[4]. Several immunosuppressants have been considered for treatment of this complication and are currently under investigation through randomized clinical trials[4]. In this report, we present the case of a patient with severe COVID-19 pneumonia treated with Remdesivir and methylprednisolone, the latter used for suspected cytokine storm.

Case Description

A 48-year-old man with no past medical history presented to the hospital with dyspnea, cough, subjective fever, and diarrhea for 10 days. He has been working at the airport selling flowers, he was not aware of any sick coworker or family member. Upon arrival to emergency department, his vitals revealed oral temperature of 38 °C, respiratory rate of 28 bpm, heart rate of 131 bpm, blood pressure of 130/80 mmHg, and oxygen saturation of 90% on room air. He was placed on 4 L/min of oxygen by nasal cannula and his saturation improved to 96%. Physical exam showed labored breathing, but no crackles in lung fields. Laboratory studies revealed a white blood cell count of 16.9 K/uL with lymphopenia of 1.0 K/uL, hemoglobin of 13.9 g/dL, platelet count of 313K/uL, and neutrophil/lymphocyte ratio of 14.3. Complete metabolic panel showed AST of 175 units/L, AST of 164 units/L, and creatinine of 0.6 mg/dL. Inflammatory markers were as follows: ferritin of 3 209 ng/mL, C-reactive protein (CRP) of 34.5 mg/dL, LDH of 1 855 units/L, D-dimer of 2.84 ug/mL, and IL-6 of 81.69 pg/mL. Procalcitonin was 0.343 ng/mL (Table 1). Real time PCR for SARS-Cov-2 was positive (InGenius®). Nasopharyngeal viral respiratory panel (FilmArray®) did not isolate any other respiratory pathogen. Urine Legionella and urine streptococcal antigen were both negative. Chest X-ray demonstrated low lung volumes with bilateral lower lung zone opacities (Figure 1).

Figure 1: Portable chest X-ray showing low lung volumes with bilateral lower lung zone opacities.

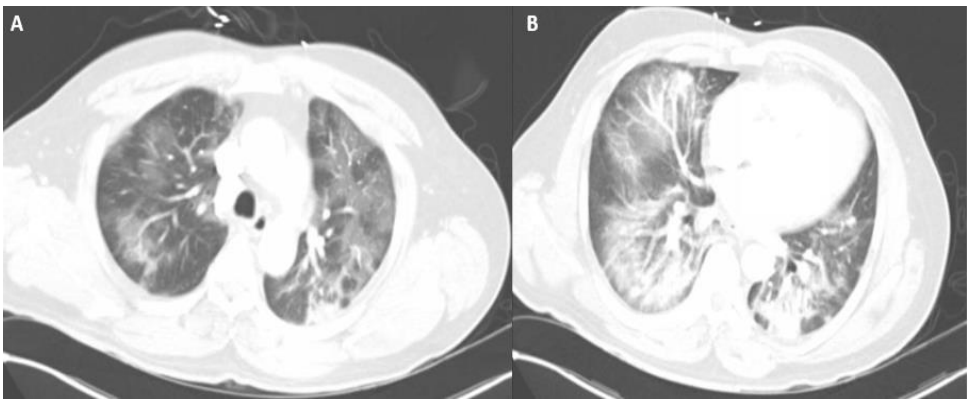


Source: Photographic record obtained by the authors.

He was initiated on ceftriaxone and azithromycin, but later on, azithromycin was discontinued and hydroxychloroquine was added. His oxygen saturation continued to drop and he was started on high flow nasal cannula (HFNC) with FiO2 of 80% to achieve a saturation of 98%. Given his respiratory decompensation, he was transferred to medical intensive care unit (MICU) for close monitoring. Due to poor oxygenation, a chest computed tomography angiography was ordered which was negative for pulmonary embolism; however, it showed confluent ground glass opacities in upper lobes associated with mild patchy airspace opacities mainly in the apical posterior segments. Heterogeneously enhancing patchy airspace opacities were also noted in the medial segment of right middle lobe, and superior, posterior and lateral segments of bilateral lower lobes

(Figure 2 A, B). Echocardiogram did not show right ventricle strain, and left ventricle systolic function was normal. He was started on enoxaparin prophylaxis 40mg subcutaneous daily and was offered to participate in the Tocilizumab clinical trial (COVACTA trial), but the patient refused.

Figure 2: A) Chest CT scan.

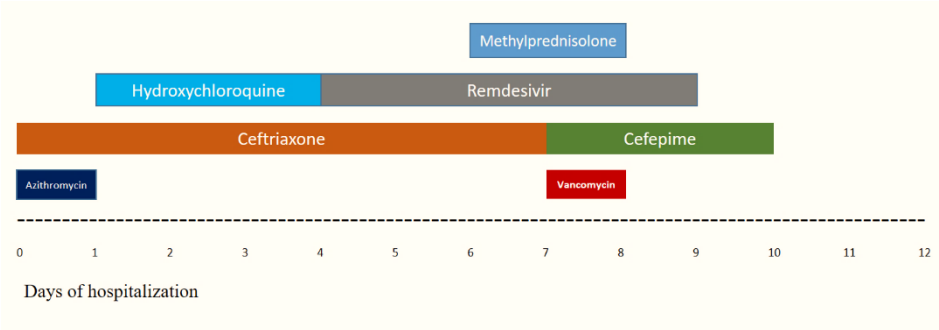


A) Chest CT scan showing prominent confluent ground glass opacities in bilateral upper lobes associated with mild patchy airspace opacities mainly in the apical posterior segments.
B) Heterogeneously enhancing airspace opacities noted in the superior, posterior and lateral segments of bilateral lower lobes.

Source: Photographic record obtained by the authors.

Over the following 3 days, the patient had mild improvement on his oxygenation and was still requiring HFNC with FiO2 of 50% to achieve a saturation of 95%. At this point, hydroxychloroquine was discontinued and Remdesivir was started in a dose of 200 mg IV once and then 100mg IV for 4 days. Two days later, he was started on methylprednisolone 1mg/kg daily for suspected cytokine storm given elevation of inflammatory markers. A chest X-ray was repeated one day later, and showed worsening bilateral perihilar patchy opacities. Due to the concern for superimposed hospital acquired pneumonia, sputum culture was ordered. The gram stain showed gram negative rods, which led to escalation of antibiotics to cefepime and vancomycin, and discontinuation of methylprednisolone after 2 days (Figure 3). As part of work-up for hospital acquired pneumonia, MRSA screen from nares was ordered, which was negative, thus vancomycin was discontinued. Final sputum culture only grew respiratory flora, for this reason, cefepime was also discontinued.

Figure 3: Medications that were administered during hospitalization.



Source: made by the authors.

Over the following 4 days, his oxygenation improved significantly, requiring only 4L/min of oxygen by nasal cannula to maintain a saturation of 97%. His inflammatory markers decreased noticeably, showing a ferritin of 806 ng/mL, CRP of 1,5 mg/dL, LDH of 699 units/L, and D-dimer of 1.30 ug/mL (Table 1). Three days later, he was discharged home in stable condition and saturating 96% on room air.

Table 1: Results of laboratory studies during hospitalization.

Laboratory Parameters	Normal Range	Day 1 Hospitalization Initiation of Hidro-xicloroquina	Day 4 Hospitalization Initiation of Remdesi-vir	Day 6 Hospitalization Initiation of Methylprednisolone	Day 9 Hospitalization	Day 12 Hospitalization Before discharge
Cell blood count						
White blood cell, x 10^3/uL	4.0-10.5	16.9	9.9	11.4	7.4	6.4
Neutrophils, x 10^3/uL	2.0-6.0	14.3	6.6	8.3	4.8	3.5
Lymphocytes, x 10^3/uL	1.1-2.7	1	1.4	1.2	1.5	1.6
Platelets, x10^3/uL	140-400	313	458	421	467	441
Hemoglobin, g/dL	13.3-16.3	13.9	11.9	11.9	12.2	12.2
Arterial blood gas						
pH	7.35-7.45	7.41	7.49	7.41	7.4	
pO2, mmHg	75-100	73	81	78		
pCO2, mmHg	35-45	35	34	24		
HCO3, mmol/L	19-24	22	25	15	26	
Sat O2, %	95-98.5	96	97	95	98	96
Pa/Fi	>300	203	162	156	237	390
Complete Metabolic Panel						
Sodium, mmol/L	137-145	134	136	136	140	140
Potassium, mmol/L	3.6-5	4.4	4.2	4.6	4.8	4.8
Glucose, mg/dL	74-106	115	91	94	94	88
Calcium, mmol/L	8.4-10.2	7.9	8.1	7.9	8.1	8.4
Urea, mg/dL	9.0-20	9	18	19	15	19
Creatinine, mg/dL	0.66-1.25	0.6	0.7	0.6	0.6	0.65
AST	15-46	175	84	52	80	45
ALT	21-72	164	121	91	139	102
Alkaline Phosphatase, U/L	38-126	98	70	89	92	92
Total bilirubin, mg/dL	0.2-1.3	0.3	0.5	0.5	0.3	0.4
Inflammatory Markers						
C-reactive protein, mg/dL	0.0-0.9	34.5	21.7	22	6.1	1.5
LDH, U/L	313-618	1 855	1 299	998	1 036	699
Ferritin, ng/mL	30-400	3209	2341	2083	1451	806
D-dimer, ug/mL	0.0-0.49	2.84	2.55	3.39	<0.27	1.3
IL-6, pg/mL	<5.0	81.69				
Procalcitonin	0.0-0.08	0.343	0.12	0.071		
Troponins	0.0-0.034			<0.012		

Discussion

The optimal treatment of Covid-19 pneumonia is not clearly determined. In terms of pharmacologic therapy, the utility of hydroxychloroquine has been highly questioned by recent publications[5,6]. The retrospective study performed by Geleris et al. in New York-Presbyterian Hospital-Columbia University Irving Medical Center demonstrated that hydroxychloroquine administration was not associated with a significantly higher or lower risk of intubation or death (hazard ratio: 1.04; 95% confidence interval: 0.82 to 1.32) [5]. Moreover, the article published by Mahévas et al. did not obtain positive results either[6]. This observational study was performed in four French tertiary hospitals and evaluated the clinical efficacy of hydroxychloroquine[6]. According to its results, treatment with this drug seemed to have no effect on reducing admissions to intensive care or deaths in patients with COVID pneumonia requiring oxygen[6]. These outcomes from observational and retrospective studies have led to the modification of treatment protocols in different institutions, in which hydroxychloroquine is not considered first line anymore[5]. Up till now the only antiviral that has shown clinical benefit based on results of a randomized clinical trial is Remdesivir[7]. According to the recently published preliminary results, Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory infection[7]. This recovery time was reduced from 15 days in the patients on placebo to 11 days in patients treated with Remdesivir, which corresponded to a recovery rate ratio of 1.32 (95% confidence interval: 1.22 to 1.55; p<0.001). In terms of mortality at 14 days, there was a reduction (7.1% vs 11.9%); with no statistical significance. Of note, results of mortality at 28 days were not shown in this study given the large number of patients that had yet to complete day 29 visits[7]. At present, Remdesivir has been authorized by the FDA only for emergency use, and is undergoing wide distribution to all the hospitals in the United States of America. Our patient was initially treated with hydroxychloroquine given the lack of alternative agents at the moment of hospital admission; however, as soon as Remdesivir became available, his therapy was switched to this new antiviral.

Another important aspect of the pathogenesis of COVID-19 is the possible development of cytokine storm, an immune condition characterized by rapid proliferation and hyperactivation of T cells, macrophages, natural killer cells and overproduction of more than 150 inflammatory cytokines and chemical mediators, which leads to an increased risk of vascular permeability, multiorgan failure, and eventually death[4]. One of the key cytokines implicated in this process is IL-6, which seems to be associated with disease severity[8,9]. For this reason, treatment with Tocilizumab, an IL-6 inhibitor, has been contemplated in patients with respiratory decompensation and inflammatory markers consistent with cytokine storm[10,11]. In our hospital, given its experimental use for COVID-19, Tocilizumab is only offered in the context of a clinical trial, in which our patient refused to participate. Another measure to treat this overwhelming inflammatory response associated with COVID-19 is the administration of corticosteroids[4]. At present, its use is very controversial[4]. Although some studies have reported no real benefit[12,13], others have shown good clinical outcomes with the use of low dose and short term application of methylprednisolone[14,15]. In the study conducted by Wu, C et al. the administration of methylprednisolone appeared to have reduced the risk of death in patients with ARDS (hazard ratio: 0.38; 95% confidence interval: 0.20-0.72; P = 0.003) [14]. Another study led by Wang, Yin et al. revealed better clinical outcomes in patients treated with methylprednisolone in a dose of 1-2 mg/kg/day for 5-7 days. This retrospective cohort study included 46 patients, 26 of them treated with steroids. The analysis of this cohort revealed that patients on methylprednisolone had a faster improvement of the oxygen saturation and a shorter interval of supplemental oxygen therapy when compared with those that did not received corticosteroids. Moreover, the authors found that patients on methylprednisolone were less likely to require mechanical ventilation[15]. A recent publication by Fadel et al. support some of these findings[16]. They conducted a single pre-test, single post-test quasi-experiment in a multicenter health system in Michigan that included patients with moderate and severe COVID infection. A protocol using an early and short course of methylprednisolone (0.5 to 1 mg/kg/day) for 3 days was implemented, and the authors found that this regimen reduced escalation of care and improved clinical outcomes[16].

Our patient was treated with methylprednisolone given the lack of improvement of his respiratory status and elevation of inflammatory markers consistent with cytokine storm. We used a low dose of methylprednisolone (1mg/kg/day) in agreement with the previous published studies. Although our current hospital protocol contemplates the use of methylprednisolone for 5-7 days; this drug was discontinued early in our patient due to the concern for a possible superimposed bacterial infection, which was rule out later. We did not restart methylprednisolone because the patient's oxygenation had already improved significantly after 2 doses.

Conclusions

Our case illustrates the role of Remdesivir for the treatment of severe COVID-19 pneumonia. We also observed a possible clinical benefit of corticosteroids in the context of cytokine storm induced by Covid-19. Although the results of a single case cannot be generalized, we believe that the combination of Remdesivir and methylprednisolone should be considered in cases of severe Covid-19 pneumonia, aiming to counteract the direct viral damage produced by COVID, and at the same time, to control the inflammatory response induced by the virus. Large clinical trials are clearly needed to determine the real value of this therapeutic strategy.

Notes

Roles and contributions

JAGZ participated in the conceptualization and writing. JAGZ, TQ, and ADV reviewed and edited the manuscript.

Source of financial support

None

Conflict of interest

The corresponding author states that there is no conflict of interest.

Ethics

The informed consent requested by Medwave has been signed by the patient and a copy of the signed form forwarded to the editorial board of the Journal.

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