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LETTER TO THE EDITOR

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Early remdesivir treatment in COVID-19: Why wait another day?

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that varies from asymptomatic to severe illness and death.[1,2] Old age, hypertension, obesity, diabetes, cardiovascular disease, chronic lung disease, and cancer predict a severe course, risk of hospitalization, and death.[1,2] The US Food and Drug Administration recently approved remdesivir for the treatment of COVID-19 patients requiring hospitalization.[3] However, high mortality persists despite use of remdesivir.[3,4] Remdesivir inhibits SARS-CoV-2 RNA polymerase, hindering viral replication.[5] In patients with COVID-19, peak SARS-CoV-2 concentrations occur on Day 5 and most active replication in the throat during the first 5 days of symptoms onset.[6] In rhesus macaques infected with SARS-CoV-2 and Middle East respiratory syndrome coronavirus, best outcomes were obtained when remdesivir was started early, at 12 h of inoculation.[7,8] These observations suggest that inhibiting viral replication with remdesivir would be more effective if started early after symptoms development. We here report our experience using an early treatment strategy in a high-risk patient with COVID-19 who within 48 h of symptoms onset received remdesivir and experienced an immediate and remarkable clinical response to full recovery.

2 | CASE PRESENTATION

A 77-year-old Caucasian male presented on October 24, 2020, with antigen and polymerase chain reaction proven COVID-19 infection, following a 2-day course of frontal headaches, nasal congestion, myalgia, dry cough, lower lip paresthesia, and temperatures of 37.7–38.9°C treated with ibuprofen. The patient's history included atherosclerotic heart disease, exertional non-sustained ventricular tachycardia, hypertension, hyperlipidemia, toxin-positive *Clostridioides difficile* diarrhea, prostate cancer, and radical prostatectomy. Physical exam revealed a nontoxic, lean patient, in no distress, with normal heart and lung auscultation and pulse oximetry of 96%. When compared with laboratory data obtained the day prior, repeat labs showed a decrease in total neutrophil count (from 2810 to 1190 cells/μl), persistent mild lymphocytopenia, thrombocytopenia, and an elevated C-reactive protein, normal D-dimer, ferritin, and procalcitonin level (Table 1). The chest x-ray and 12-lead electrocardiogram were reportedly normal.

3 | CLINICAL COURSE

Because of the age and clinical risk factors, the patient was admitted for further observation and management. The first dose of remdesivir 200 mg was administered at approximately 8 p.m., 48-h after symptom onset, followed by a daily intravenous dose of 100 mg for three additional days (Table 1). In addition, he received 40 mg of enoxaparin, losartan 50 mg daily, and benzonate as needed. By the second dose of remdesivir (24-h later), the symptoms had markedly improved, as evidenced by the absence of any further fever, chills, weakness, headaches, or muscle aches. Pulse oximetry at room air remained at 96%–99% and unchanged with brisk ambulation. Persistent neutropenia ensued with normalization of lymphocytes, platelet, monocytes, and C-reactive protein levels. There were no changes in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase. Because of the excellent clinical course, the fifth dose of remdesivir was withheld, and the patient was discharged home after 3 days. The patient remained in isolation at home for an additional 7 days. During this time, he was asymptomatic, afebrile, and able to walk long distances and upstairs without dyspnea, reporting only mild tiredness, minimal cough, and residual lower-lip paresthesia that resolved entirely by Day 10. Laboratory results from 2 and 3 weeks later confirmed normalization of all blood counts. The neutropenia, which started before the first-dose of remdesivir, most likely resulted from an idiosyncratic reaction to ibuprofen.

4 | DISCUSSION

Although no meaningful conclusion can be drawn from a single case, the observation that early use of remdesivir in our COVID-19 patient with high-risk features resulted in immediate resolution of symptoms, early discharge and prompt recovery of daily activities, is worth further consideration. Our case report is consistent with data in influenza patients where inhibition of viral replication with oseltaminir (Tamiflu®) achieves best clinical benefits when administered within

TABLE 1 Time and dose of remdesivir administration and laboratory values before, during and after hospitalization in a patient who tested positive for COVID-19 on 10/23/2020

Labs drawn	07/21 Outpatient	10/23 5 p.m. ER	10/24 4 p.m. Hospital	10/25 7 a.m. Hospital	10/26 6 a.m. Hospital	10/27 8 a.m. Hospital	11/11 1 p.m. Outpatient	11/20 1 p.m. Outpatient
Remdesivir administration			200 mg	100 mg	100 mg	100 mg		
			8 p.m.	7 p.m.	7 p.m.	4 p.m.		
WBC (cells/μl)	4700	4640	3290	3930	3320	3270		4500
Platelet (K/μl)	223	139	143	137	146	169		199
Lymphocytes (cells/μl)	1753	860	1290	2200	2210	2360		1976
Monocytes (cells/μl)	456	930	800	790	510	480		423
Neutrophils (cells/μl)	2383	2810	1190	910	580	400		2025
Eosinophils (cells/μl)	89	<30	<30	<30	<30	<30		59
Basophils (cells/μl)	19	<30	<30	<30	<30	<30		18
Hemoglobin (g/dL)	13.9	12.7	12.6	12.8	13.4	14.3		13.5
RDW (%)	13.3	12.7	12.8	12.9	13.0	13.0		12.7
Respiratory panel PCR		Neg						
Blood Cultures		Neg	Neg					
Alkaline-Phosphatase (U/L)		69	68	65	62	64	64	
AST (U/L)		18	18	21	19	21	17	
ALT (U/L)				15	13	14	15	
Sr. Cr (mg/dL)		0.99	1.14	1.17	1.05	0.94	0.85	
CRP (mg/dL)		0.8			0.2		0.4	
D-Dimer (ng/mL)		320	290					
Ferritin (ng/ml)		186	216			335	194	
Pro-calcitonin (ng/mL)			0.07			<0.06		
ESR (mm/hr)						7		6
Anion Gap (mmol/L)		12	9	8	10	9		
Troponin T (ng/ml)			<0.01					

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCR, polymerase chain reaction; RDW, red cell distribution width; WBC, white blood cell.

2 days of symptom onset.[9] Treatment initiation within 48 h of the onset of symptoms may be responsible for the excellent response to remdesivir. Failure to inhibit viral replication at its peak time may allow disease progression, where virus-induced tissue damage, abnormal immunomodulation and inflammation, become determinants of the patient outcomes. We propose that delayed treatment initiation is at least partly responsible for the reported modest therapeutic response of remdesivir.[2,10]

While blanket use of remdesivir in COVID-19 positive subjects is neither desirable nor expectedly cost-effective, in higher-risk patients, early inhibition of viral replication may be clinically impactful and lifesaving. Future studies comparing the effect of time-to-treatment (illness onset to first dose of remdesivir) in this subset population are much needed. Until then, early remdesivir administration among high-risk patients should be considered.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

All authors materially participated in the research, data collection and article preparation. Luigi X. Cubeddu and Robert J. Cubeddu approved the final article.

ETHICS STATEMENT

Written informed consent was obtained from the patient for publication of this case report and accompanying table.

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