Compassionate use remdesivir for treatment of severe COVID-19 in pregnant women at a United States academic center

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The authors report no conflicts of interest.

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Condensation: Description of experience using remdesivir to treat five pregnant women with severe COVID-19 requiring hospitalization.

Short title: Compassionate use remdesivir in pregnancy

Keywords: SARS-CoV-2, COVID-19, novel coronavirus, pregnancy, compassionate use, remdesivir

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Objective:

COVID-19, caused by a novel coronavirus SARS-CoV-2, has caused a worldwide pandemic. While early data suggest that pregnant women are not at higher risk for severe COVID-19 infection compared to age-matched nonpregnant counterparts, some pregnant women can become severely ill. There are currently no specific therapies approved to treat COVID-19. Remdesivir (GS-5734), a broad-spectrum nucleotide prodrug that inhibits RNA-dependent RNA polymerase activity in viruses, is an investigational therapeutic agent that has been studied during this pandemic. A report of 61 non-pregnant patients with moderate to severe COVID-19 who received at least one dose of remdesivir showed clinical improvement in 68% of patients.[1] However, this analysis did not definitively demonstrate benefit nor include any pregnant patients.

The safety of remdesivir use in pregnancy has thus far only been evaluated in animal studies and a small clinical trial of treatments for Ebola, which did not demonstrate any maternal, fetal, or neonatal adverse events.[2,3] To date, there are no clinical trials of remdesivir treatment for severe COVID-19 that include pregnant women. As such, Gilead Sciences, Inc. is offering remdesivir through compassionate use for pregnant individuals with severe disease.

Our objective is to describe our experience at the Hospital of the University of Pennsylvania with compassionate use remdesivir in our first five severely ill pregnant patients. This study qualified for institutional review board (IRB) exemption status at the University of Pennsylvania.

Study Design:

This is a retrospective case series of our first five pregnant patients with PCR-confirmed severe COVID-19 treated with compassionate use remdesivir.

Decision to pursue remdesivir:

Pregnant patients with COVID-19 who require hospital admission and supplemental oxygen were considered candidates for compassionate use remdesivir. Treatment decisions were made by Maternal Fetal Medicine (MFM) and Infectious Diseases (ID) teams, as well as shared decision making with the patient and family. The consent reviews the rationale for pursuing the medication and limited data to guide use in pregnancy. Providers applied for approval through Gilead Sciences, Inc. and the Food and Drug Administration (FDA) s contacted to obtain an emergency investigational new drug application (eIND). The IRB was notified. Once approved, the drug was shipped from the manufacturer to the hospital pharmacy within 24-48 hours.

Treatment protocol

A dosing regimen of 200 mg IV on day one followed by 100 mg IV daily for nine days is recommended by the manufacturer.[4] Recommended daily monitoring included a complete blood count (CBC), serum chemistries including aminotransferases and creatinine, and assessment of creatinine clearance. Patients were ineligible if serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) were five times the upper limit of normal, or if their creatinine clearance was <30 mL/min. Abnormalities on daily monitoring labs were carefully assessed, as both COVID-19 infection and remdesivir can cause abnormalities in aminotransferase and creatinine lab values. Patients were discharged prior to completion of the 10-day course if clinically appropriate, in accordance with guidance from Gilead Sciences, Inc.

Lactation considerations:

The manufacturer advises against breastfeeding while taking remdesivir given the absence of information to confirm its safety. Patients who delivered during their treatment course were advised to discard milk until treatment completed.

Results:

Table 1 summarizes key demographic and clinical characteristics. Figure 1 depicts changes in ALT and AST values for each patient. Three required mechanical ventilation. All five ultimately recovered to hospital discharge on room air. Two patients completed the 10-day treatment course. Two were discharged prior to completion. One had treatment halted due to elevated aminotransferases attributed to the medication.

Case 1: A 27 year-old G4P0030 at 16 weeks' gestation with mild asthma who required 3L O_2/min via nasal cannula (NC). Remdesivir was started on hospital day (HD) 4. She was discharged on HD 8. During her hospitalization, she developed abnormal aminotransferases attributed to remdesivir use, which were followed up outpatient.

Case 2: A 39 year-old G4P3003 at 28 weeks' gestation with type 2 diabetes, chronic hypertension, and obesity who developed acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. She received hydroxychloroquine (HCQ) and antibiotics for empiric coverage of pneumonia. Her first dose of remdesivir was on HD 4. After 6 doses, remdesivir was discontinued due to significantly worsening

aminotransferases (Figure 1). On HD 14 she underwent an uncomplicated cesarean delivery at 30 weeks 2 days' gestation of a healthy infant. She was extubated on HD 19 and discharged.

Case 3: A 33 year-old G6P5005 at 26 weeks' gestation with mild asthma who developed severe ARDS requiring mechanical ventilation. She was started on HCQ and antibiotics. She received her first dose of remdesivir on HD 2. She had mild elevation in her aminotransferases, but did not warrant discontinuation of remdesivir. She completed a 10-day course. On HD 28 she had a vaginal delivery of a healthy 30 week infant and on HD 36 was discharged.

Case 4: A 29 year-old G1P0 at 31 weeks' gestation with chronic kidney disease, chronic hypertension, and gestational diabetes initially required 6L O_2/min NC. Remdesivir was initiated on HD 2. She underwent an uncomplicated cesarean delivery under general anesthesia, afterwhich she remained intubated for 14 days. Remdesivir was continued for a total of 10 days with only a mild increase in aminotransferases (Figure 1). She was discharged on HD 21.

Case 5:A 41 year-old G4P3003 at 31 weeks' gestation who required 2L O_2/min NC. Her admission labs were notable for elevated aminotransferases (AST 63 U/L, ALT 35 U/L), thrombocytopenia (106 thousand/uL), and leukopenia (WBC 2.2 thousand/uL), all attributed to COVID-19 infection. She received her first dose of remdesivir on HD 2. After 4 doses, she improved and was discharged. Her initial laboratory abnormalities

normalized (Figure 1). Five weeks later, she had an uncomplicated cesarean delivery of a healthy infant.

Conclusion

We describe our early experience using remdesivir for treatment of severe COVID-19 in five pregnant women. Our small numbers and early experience do not allow us to draw conclusions about the clinical efficacy or safety of remdesivir use in pregnant women. This highlights the urgent need for inclusion of pregnant women in clinical trials to evaluate remdesivir and other treatments for COVID-19.[5]

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Clinical Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	27	39	33	29	41
Gestational age at diagnosis (weeks)	16	28	26	31	31
Coexisting conditions:					
Hypertension		X		X	
Diabetes		X		X	
Asthma	X		X		
Immunosuppression				X	
Other		X			
Highest level of respiratory support:					
Nasal cannula	X				X
Non-rebreather					
Mechanical ventilation		X	X	X	
Days requiring mechanical ventilation	0	>15	>15	16	0
Days of symptoms before remdesivir	8	18	12	9	8
Days of remdesivir received	4	6	10	10	4
Reason remdesivir stopped:					
Completed course			X	X	
Hospital discharge	X				X
Adverse effects		X			
Concurrent hydroxychloroquine	X	X	X	X	X
Pregnancy outcome	ongoing	cesarean	vaginal	cesarean	cesarean
Neonatal COVID-19 status	n/a	negative	negative	negative	negative
Total days of admission	8	13	16	19	5
Total days in ICU	0	12	15	18	0

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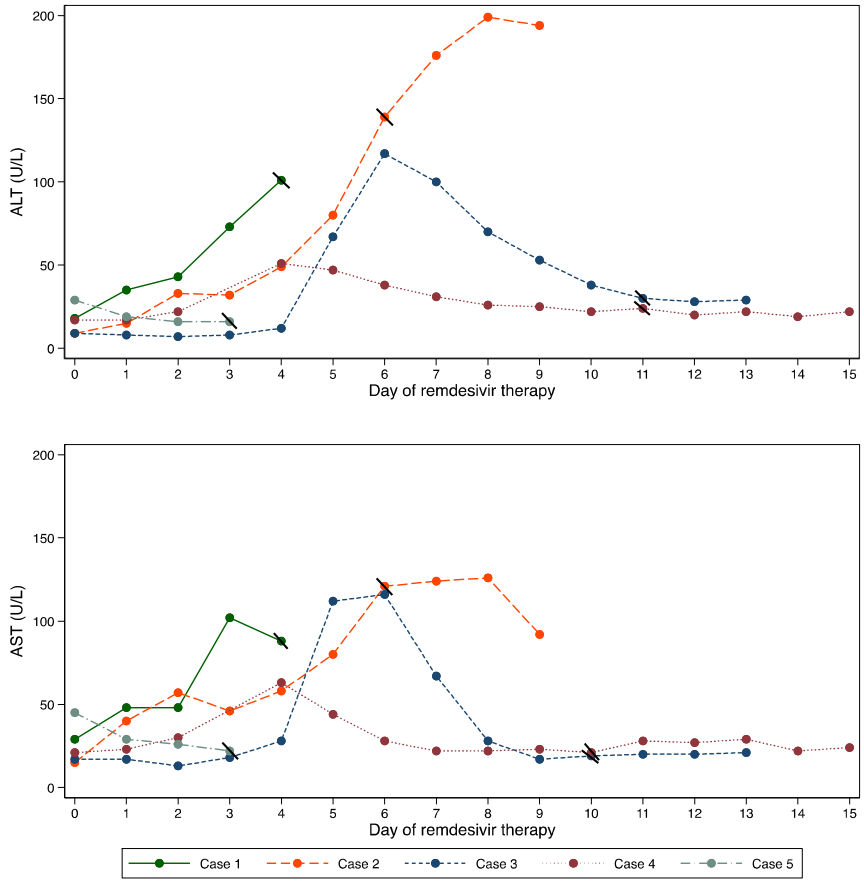
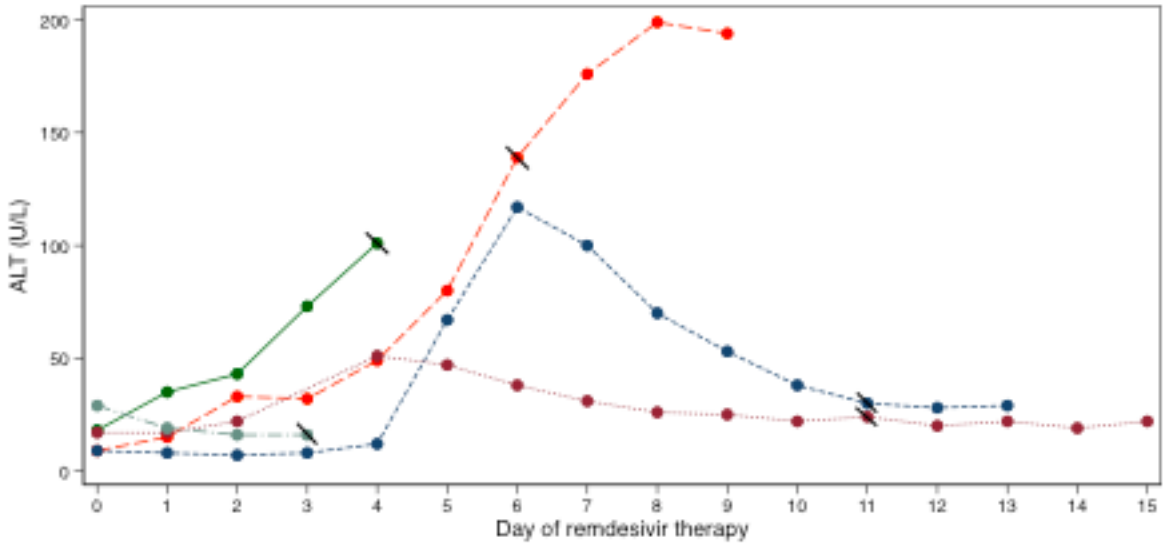
Figure 1. Aminotransferase levels by day of remdesivir therapy. Panel A: Alanine aminotransferases (ALT); Panel B: Aspartate aminotransferases (AST).

Panel A:

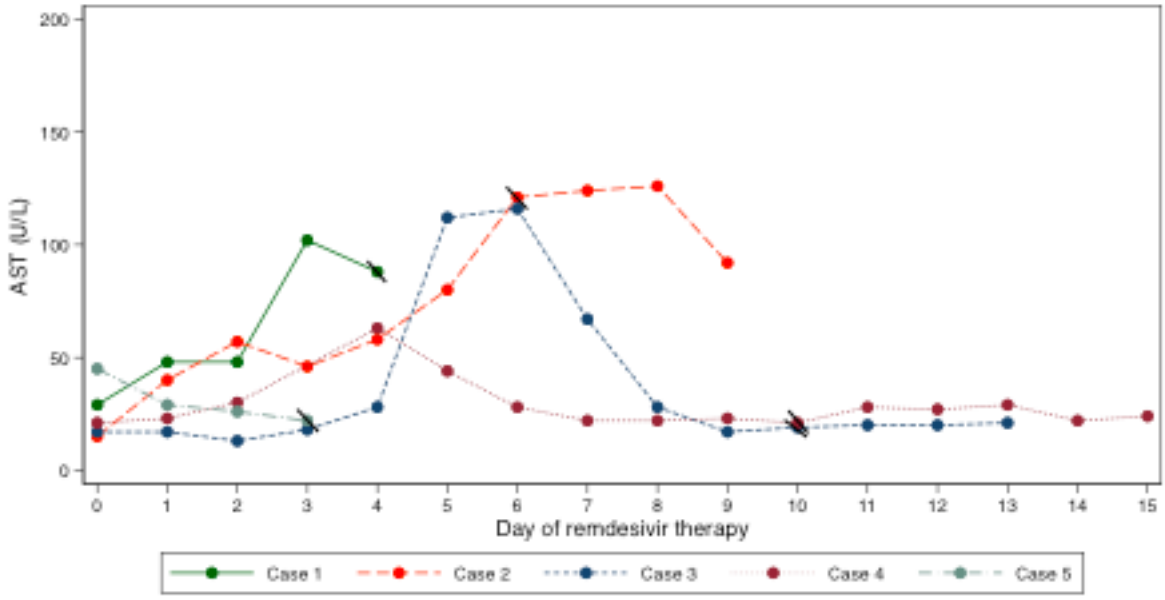


Black bar indicates last day of remdesivir therapy

Panel A:



Panel B:



Black bar indicates last day of remdesivir therapy