Compassionate use of remdesivir for treatment of severe coronavirus disease 2019 in pregnant women at a United States academic center

OBJECTIVE: Coronavirus disease 2019 (COVID-19), caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2), has caused a worldwide pandemic. Although early data suggest that pregnant women are not at higher risk for severe COVID-19 infection than 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 nonpregnant patients with moderate to severe COVID-19 who received at least 1 dose of remdesivir indicated clinical improvement in 68% of patients.[1] However, this analysis did not definitively report any benefits nor did it 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 indicate 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 was to describe our experiences at the Hospital of the University of Pennsylvania, Philadelphia, PA, with compassionate use of remdesivir in our first 5 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 5 pregnant patients with polymerase chain reaction–confirmed severe COVID-19 treated with compassionate use of remdesivir.

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

TREATMENT PROTOCOL: A dosing regimen of 200 mg intravenous (IV) on day 1 followed by 100 mg IV daily for 9 days is recommended by the manufacturer.[4] Recommended daily monitoring included a complete blood count, serum chemistries including aminotransferases and creatinine, and assessment of creatinine clearance. Patients were ineligible if serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) were 5 times the upper limit of normal or if their creatinine clearance was <30 mL/min. Abnormalities with daily monitoring laboratories were carefully assessed, because both COVID-19 infection and remdesivir can cause abnormalities in aminotransferase and creatinine laboratory values. Patients were discharged before the completion of the 10-day course, if clinically appropriate, in accordance with the guidance from Gilead Sciences, Inc.

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

RESULTS: Key demographic and clinical characteristics are presented in the Table. Changes in ALT and AST values for each patient are presented in the Figure. Notably, 3 patients required mechanical ventilation. All 5 patients recovered and were ultimately discharged from the hospital on room air. Although 2 patients completed the 10-day treatment course, 2 were discharged before completion and 1 discontinued the treatment because of elevated aminotransferases attributed to the medication.

CASE 1: A 27-year-old G4P0030 at 16 weeks' gestation with mild asthma required 3 L O_2/min by 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 in an outpatient clinic.

CASE 2: A 39-year-old G4P3003 at 28 weeks' gestation with type 2 diabetes, chronic hypertension, and obesity experienced acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. She received hydroxychloroquine (HCQ) and antibiotic therapy for

TABLE
Demographic and clinical characteristics

Clinical Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Age (y)	27	39	33	29	41
Gestational age at diagnosis (wk)	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
Nonrebreather					
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 was discontinued					
Completed course			X	X	
Hospital discharge	X				X
Adverse effects		X			
Concurrent hydroxychloroquine	X	X	X	X	X
Pregnancy outcome	Ongoing	Cesarean delivery	Vaginal delivery	Cesarean delivery	Cesarean delivery
Neonatal COVID-19 status	N/A	Negative	Negative	Negative	Negative
Total days of admission	8	13	16	19	5
Total days in the ICU	0	12	15	18	0

X indicates patient had clinical characteristic.

COVID-19, coronavirus disease 2019; *ICU*, intensive care unit; *N/A*, not applicable.

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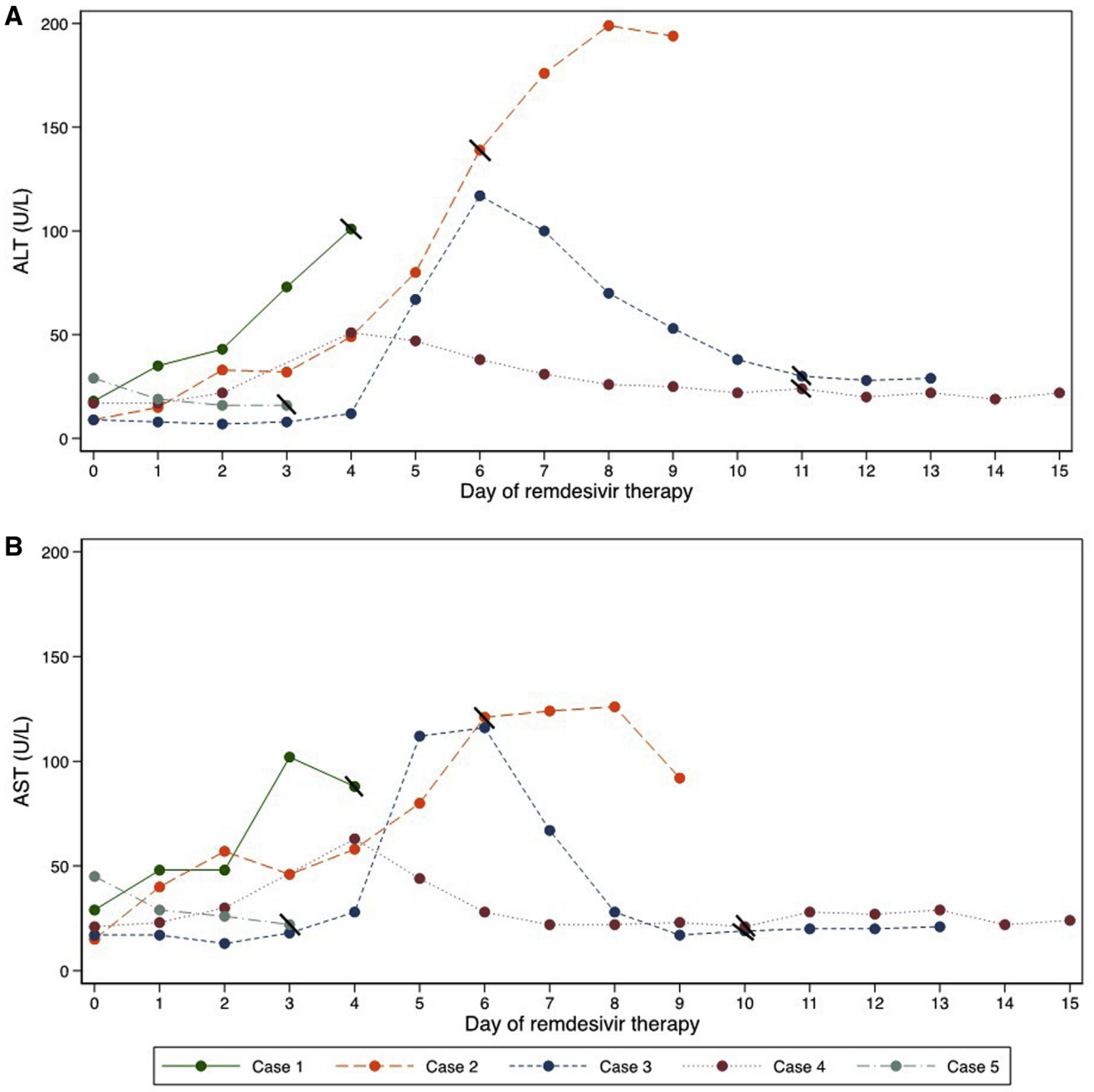
empirical coverage of pneumonia. Her first dose of remdesivir was on HD 4. After 6 doses, remdesivir was discontinued because of markedly worsening aminotransferases (Figure). On HD 14, she underwent an uncomplicated cesarean delivery at 30 weeks and 2 days' gestation of a healthy infant. She was extubated on HD 19 and discharged.

CASE 3: A 33-year-old G6P5005 at 26 weeks' gestation with mild asthma experienced 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 that did not warrant discontinuation of remdesivir. She completed a 10-day course. On HD 28, she underwent a vaginal delivery of a healthy 30-week infant and was discharged on HD 36.

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

CASE 5: A 41-year-old G4P3003 at 31 weeks' gestation required 2 L O_2/min by NC. Her admission laboratories were notable for elevated aminotransferases (AST, 63 U/L; ALT, 35 U/L), thrombocytopenia (106,000/uL), and leukopenia (white blood cells, 2200/uL), all attributed to COVID-19 infection. She received her first dose of remdesivir on HD 2. After 4 doses, she had recovered and

FIGURE
Aminotransferase levels by day of remdesivir therapy



A, Alanine aminotransferases (ALT). **B,** aspartate aminotransferases (AST). *Black bar* indicates the last day of remdesivir therapy.

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was discharged. In addition, her initial laboratory abnormalities normalized (Figure). A total of 5 weeks later, she underwent an uncomplicated cesarean delivery of a healthy infant.

CONCLUSION: We describe our early experiences using remdesivir for the treatment of severe COVID-19 in 5 pregnant women. Our small number of patients and early experience did 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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Jennifer A. McCoy, MD
Department of Obstetrics and Gynecology
Maternal and Child Health Research Center
Perelman School of Medicine
Hospital of the University of Pennsylvania
University of Pennsylvania
3400 Spruce Street
2 Silverstein
Philadelphia, PA 19104-6160
jennifer.mccoy@pennmedicine.upenn.edu

William R. Short, MD, MPH
Division of Infectious Diseases
Department of Medicine
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA

Sindhu K. Srinivas, MD, MSCE
Lisa D. Levine, MD, MSCE
Adi Hirshberg, MD
Department of Obstetrics and Gynecology
Maternal and Child Health Research Center
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA

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