

Case Report

Tocilizumab and Remdesivir in a Pregnant Patient With Coronavirus Disease 2019 (COVID-19)

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BACKGROUND: There are limited data regarding treatment options for pregnant women with severe coronavirus disease 2019 (COVID-19).

CASE: A 35-year-old primigravid patient at 22 weeks of gestation presented with 7 days of fever, cough, anosmia, and dyspnea. Nasopharyngeal swab was positive for the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and a chest X-ray demonstrated bilateral patchy infiltrates. Laboratory evaluation was notable for marked elevation of interleukin-6 and C-reactive protein concentrations. On hospital day 3, owing to increased dyspnea and oxygen requirement, the patient was treated with tocilizumab followed by 5 days of remdesivir. She responded well, recovered to room air, and was discharged home after a 9-day hospitalization.

CONCLUSION: Tocilizumab and remdesivir may be effective for treatment of severe COVID-19 in pregnancy,

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Teaching Points

1. Data regarding treatment of severe coronavirus disease 2019 (COVID-19) in pregnant women are limited and often confounded by concurrent use of multiple investigational therapeutic agents.
2. Remdesivir, a viral RNA polymerase inhibitor, has been shown to reduce time to recovery among nonpregnant adults with severe COVID-19 and may be considered for use in pregnant women.
3. In pregnant women with severe COVID-19 and evidence of interleukin-6-associated cytokine storm, treatment with an interleukin-6 blocker may be considered to mitigate disease.

but additional data are needed to guide risk-benefit considerations.

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The clinical course of coronavirus disease 2019 (COVID-19) in pregnant women is similar to that in the nonpregnant adult population, with approximately 14% of pregnant women with disease having either severe or critical cases.¹ Though the mainstay of treatment for COVID-19 is supportive, clinical trials investigating various potential treatments for infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are underway.

The management of severe COVID-19 in a pregnant woman is challenging. Most studies evaluating novel therapies for COVID-19 exclude pregnant women, limiting data in this vulnerable group. Severe COVID-19 in pregnancy has resulted in high rates of preterm birth and cesarean delivery, similar to other severe viral illnesses in pregnancy.²⁻⁴ Because obstetric complications from infectious disease correlate with maternal disease severity, data are needed to determine whether treatment of COVID-19 in pregnancy improves maternal health and thereby also improves neonatal and obstetric outcomes.

Preliminary data have shown that tocilizumab, an interleukin-6 receptor (IL-6) blocker, and remdesivir, a viral RNA polymerase inhibitor, may help to mitigate the course of disease in nonpregnant adults hospitalized with severe COVID-19.^{5,6} However, data regarding their use in pregnant women hospitalized with COVID-19 are sparse. We describe the case of a pregnant woman hospitalized with severe COVID-19 who was treated with tocilizumab and remdesivir.



CASE

A 35-year-old primigravid patient at 22 2/7 weeks of gestation presented to the emergency department after 7 days of fever, cough, anosmia, and dyspnea. She had underlying hypertension, type 2 diabetes, and intermittent asthma. Her body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) was 28. Outpatient medications included labetalol, metformin, and an albuterol inhaler. Findings from a detailed ultrasound scan for fetal anatomy were normal. The patient was self-isolating because household members had tested positive for SARS-CoV-2 infection.

In the emergency department, her temperature was 39° C, heart rate was 118 beats per minute, respiratory rate was 38 breaths per minute, and oxygen saturation was 95% with nasal cannula oxygen at 1 L/min. She had lymphopenia, and serum concentrations of IL-6 and C-reactive protein were markedly elevated, as seen with cytokine storm syndromes. D-dimer, ferritin, and lactate dehydrogenase levels were increased, but renal and hepatic function were normal (Table 1). Troponin and B-type natriuretic peptide levels were normal. Nasopharyngeal swab was positive for SARS-CoV-2 infection, and a chest X-ray demonstrated bilateral patchy infiltrates. The fetal heart rate was within the normal range. The patient was admitted to the COVID-

19 unit and managed with supplemental oxygen and prophylactic enoxaparin. She was placed in a modified prone position, with supporting pillows beneath the gravid uterus and a slight upward tilt toward the left lateral decubitus position, per published guidelines.⁷

On hospital day 3, her dyspnea and cough worsened, and oxygen was increased to 6 L/min to maintain 95% saturation, the target for pregnant women.⁷ Owing to worsening respiratory status and persistently elevated IL-6 and C-reactive protein levels, tocilizumab 400 mg was given intravenously for off-label use after receiving informed consent. Compassionate use of remdesivir was requested and approved by Gilead Sciences and the U.S. Food and Drug Administration (FDA).

Remdesivir was available the next day, and 200 mg was administered intravenously, followed by 100 mg/d for 4 days. Hematologic, renal, and liver function tests were notable only for a mild thrombocytosis. Serum IL-6 levels increased initially after receptor blockade with tocilizumab but began to decrease by hospital day 6 (Fig. 1). C-reactive protein levels normalized by hospital day 9. At this time, the patient no longer required oxygen supplementation and her cough and dyspnea improved. She was discharged home in stable condition at 23 3/7 weeks of gestation and was advised to self-isolate until she was symptom-free for 7 days. Laboratory values were evaluated 6 days

Table 1. Laboratory Trends, Treatment Course, and Oxygen Requirement During Hospitalization and After Hospital Discharge

	Reference Range	Hospital Day									Day 15 (Outpatient)
		1*	2	3	4	5	6	7	8	9	
Tocilizumab				400 mg IV							
Remdesivir					200 mg IV	100 mg IV	100 mg IV	100 mg IV	100 mg IV		
Oxygen requirement (NC)	None	1 L/min	4 L/min	6 L/min	4 L/min	2 L/min	1 L/min	1 L/min	1 L/min	None	None
Lymphocytes (k/microliter)	1.0–4.5	1.0	1.2	1.0	0.71	0.71	0.94	1.2	1.2	1.9	1.7
WBC count (k/microliter)	4.0–11.0	7.1	6.6	8.5	3.3	5.0	3.8	5.0	6.2	6.7	7.4
Hemoglobin (g/dL)	11.6–15.4	11.6	11.0	11.0	11.3	11.1	11.4	11.9	11.6	11.7	11.9
Platelet (k/microliter)	150–450	309	297	316	322	358	436	474	455	513	467
Creatinine (mg/dL)	0.57–1.1	0.50	0.57	0.58	0.53	0.53	0.53	0.53	0.53	0.54	0.64
AST (units/L)	5–34	21	—	19	—	22	21	22	18	16	13
ALT (units/L)	0–55	11	—	9	—	12	13	14	14	16	11
LDH (units/L)	125–220	336	—	253	256	272	275	295	245	243	163
Ferritin (ng/mL)	4.6–204	262	289	320	342	365	367	367	323	327	232
D-dimer (micrograms/mL)	0–0.50	0.63	0.59	0.66	0.66	0.68	0.95	0.88	0.80	0.52	0.27

IV, intravenous; NC, nasal cannula; WBC, white blood cell; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase.

* Day 1=hospital day 1, symptom day 8.



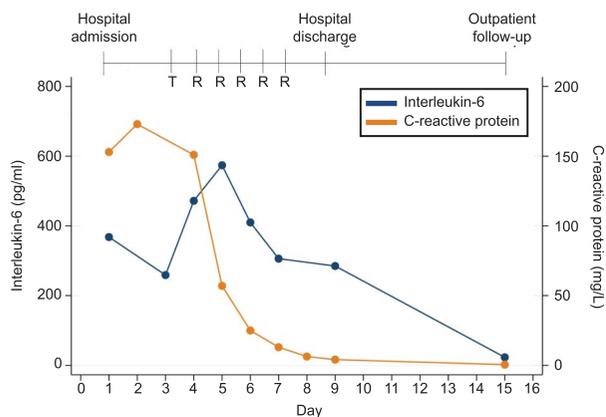


Fig. 1. Laboratory results during hospitalization and after hospital discharge. Normal reference range: C-reactive protein less than 5 mg/L; interleukin-6 less than 14 pg/ml. T, tocilizumab; R, remdesivir.

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after hospital discharge and showed further normalization of both C-reactive protein and IL-6 levels.

DISCUSSION

This report describes detailed clinical and laboratory data before and after the use of tocilizumab and remdesivir for treatment of a pregnant woman with severe COVID-19. We found that, after treatment, our patient had improvement in serum inflammatory markers, oxygen requirement, and clinical symptoms.

Although both tocilizumab and remdesivir have shown potential benefit in the nonpregnant adult population, their concurrent use in a pregnant woman with COVID-19 has not been described previously. We chose these therapeutic agents to specifically mitigate both viral replication and IL-6-mediated systemic inflammation. We did not use other investigational therapies for treatment of COVID-19, such as hydroxychloroquine, lopinavir-ritonavir, azithromycin, or corticosteroids, thus limiting the effect of other agents that could have confounded the interpretation of our patient's clinical course.

Tocilizumab was first approved by the FDA for treatment of rheumatoid arthritis in 2010 and, most recently, chimeric antigen receptor T-cell-induced cytokine release syndrome in 2017. Interleukin-6 appears to be a critical driver of the inflammatory response in COVID-19, and elevated serum IL-6 concentrations have been associated with critical disease and death.⁸⁻¹¹ Dysregulated IL-6 signaling may result in cell injury in COVID-19 through several mecha-

nisms, including increased vessel permeability, vascular endothelial growth factor expression, and T-cell maturation. As such, clinical trials exploring the use of inhibitors of the IL-6 pathway in the treatment in COVID-19 are currently underway.¹² A series describing the use of tocilizumab in 21 patients with either severe or critical COVID-19 found that 75% showed clinical improvement.⁶

Data describing tocilizumab for use in pregnant women with COVID-19 are scarce; however, it has been used in pregnant women with rheumatic disease with no increase in birth defects or miscarriage.¹³ In our case, the patient presented with increasing oxygen requirement and marked elevation of serum IL-6 and C-reactive protein concentrations, meeting internal criteria for treatment with IL-6 blockade at our hospital (Box 1). After a single dose of tocilizumab, C-reactive protein concentrations began to improve and normalized within 6 days. Because tocilizumab blocks the IL-6 receptor, there was an initial rise in serum IL-6 concentrations after treatment, followed by a downtrend within 72 hours. Interleukin-6 blockade during pregnancy is of particular interest when taking into consideration the pathophysiologic connection between elevated IL-6 levels and preterm birth.¹⁴ Though U.S. data suggest that the majority of preterm births associated with severe or critical COVID-19 are iatrogenic, the effect of marked elevation of IL-6 levels on adverse neonatal and obstetric outcomes remains unclear.⁴

In a preliminary report on the compassionate use of remdesivir in nonpregnant adults with severe COVID-19, 68% demonstrated clinical improvement with decreased oxygen requirement.¹⁵ This was followed by a randomized placebo-controlled trial of remdesivir in nonpregnant adults with severe COVID-19, which demonstrated a reduction in time-to-recovery in the remdesivir group when compared with placebo (15 days vs 11 days, $P=.001$).⁵

Remdesivir was recently granted emergency-use authorization by the FDA for the treatment of adults and children with severe COVID-19. Before this emergency-use authorization, access to remdesivir was limited to eligible patients enrolled in clinical trials. However, because pregnant women are considered a vulnerable population and not included in clinical trials for remdesivir, nontrial requests for compassionate use for COVID-19 in pregnancy are granted on an individual basis. In a study by Pierce and colleagues describing the clinical course of COVID-19 in pregnant women with severe or critical



Box 1. Clinical Criteria for Use of Interleukin-6 Blockade at Cedars-Sinai Medical Center for Nonpregnant Patients*

1. Confirmed or high suspicion for COVID-19
2. Acute respiratory distress syndrome, oxygen saturation less than 90% on 4L/min of oxygen, or increasing oxygen requirement over 24 h, in addition to 2 or more of the following predictors for severe disease:
 - IL-6 greater than 10 pg/mL
 - CRP greater than 35 mg/L
 - Ferritin greater than 500–600 ng/mL
 - D-dimer greater than 1 microgram/L
 - Neutrophil/lymphocyte ratio greater than 4
 - LDH greater than 200 units/L
 - Elevation in troponin in patient without known cardiac disease

COVID-19, coronavirus disease 2019; IL, interleukin; CRP, c-reactive protein; LDH, lactate dehydrogenase.

*Pregnant patients meeting clinical criteria for interleukin-6 blockade could receive treatment with tocilizumab if approved by an attending physician in infectious disease or pulmonary critical care.

disease at 12 U.S. hospitals, 16 women (25%) were treated with remdesivir, 52 (81%) were treated with hydroxychloroquine, and 36 (56%) were treated with antibiotics.⁴ Maternal outcomes overall were favorable, and there were no deaths. Before the COVID-19 pandemic, the only other reported use of remdesivir comes from its use during the Ebola virus crisis in 2018, in which six pregnant women were treated with remdesivir; no adverse outcomes were reported in those patients.¹⁶

We treated with a 5-day course of remdesivir, which has shown the same clinical efficacy as a 10-day course in patients with severe COVID-19 not requiring mechanical ventilation.¹⁷ Longer courses may still be considered for critically ill patients. Increases in serum aspartate aminotransferase and alanine aminotransferase concentrations were reported in the initial studies of remdesivir; thus, aspartate aminotransferase and alanine aminotransferase levels were monitored daily during treatment, and levels remained normal. Although other rare adverse events have been reported with use of remdesivir, as well as tocilizumab, our patient did not experience any adverse outcomes during her hospitalization, although longer-term follow-up is needed.

In summary, we describe a case of a pregnant woman with severe COVID-19 treated with tocilizumab and remdesivir with clinical improvement. We are unable to draw definitive conclusions regarding the use of these medications and the patient's recov-

ery, but we are reassured that this patient did well with no short-term adverse outcome. There remains an urgent need to include pregnant women in well-designed, randomized controlled studies of investigational therapies for treatment of severe COVID-19, unless there is a compelling reason that they be excluded.

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