Baricitinib in the Treatment of a Critical Patient with COVID-19 Pneumonia: A Case Report

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Abstract

A 72-year-old male presented to the emergency department with a chief complaint of diarrhea after testing positive for COVID-19 two days prior; he initially had minimal respiratory complaints. He was admitted and eventually transferred to the intensive care unit for acute hypoxic respiratory failure. In addition to dexamethasone, Remdesivir, and antibiotics, the patient was treated with Baricitinib. The Food and Drug Administration recently granted this Janus kinase inhibitor Emergency Use Authorization (EUA) to treat hospitalized patients with COVID-19. He had an extensive and complicated hospital course and had to be placed on mechanical ventilation, ultimately undergoing tracheostomy. After 78 days of hospitalization, his family withdrew life-sustaining measures, and the patient died shortly thereafter. This case details the use of Baricitinib for the treatment of COVID-19 pneumonia and demonstrates the need for additional studies regarding the efficacy of this drug.

Introduction

Since the initial reports of SARS-CoV-2 infection, there have been over 100 million confirmed cases of COVID-19.[1] Although many infected with SARS-CoV-2 remain asymptomatic, others can develop severe pneumonia with a fatal illness. Many therapies have been studied to treat COVID-19. As of January 2021, the current standard of care for critically ill hospitalized patients includes dexamethasone and Remdesivir.[2] The Food and Drug Administration (FDA) recently granted emergency use authorization for Baricitinib, a drug typically used to treat rheumatoid arthritis, for the treatment of COVID-19.[3] This report presents the first use of Baricitinib at the University of Louisville Hospital to treat COVID-19 in a critically ill patient.

Case Presentation

A 72-year-old male with a history of hypertension and chronic kidney disease stage 3 presented to the emergency department on December 2, 2020, with a chief complaint of diarrhea. He reported that before this presentation, he and his wife were diagnosed with COVID-19 at an outside facility two and seven days ago, respectively. Two days before presentation, he began having decreased appetite, nausea, diarrhea, and a mild nonproductive cough. He denied fevers, chills, chest pain, shortness of breath, or changes to his ability to taste or smell.

Upon arrival to the emergency room, his temperature was 100.9°F, with all other vitals stable and oxygenation at 95 percent on room air. At this time, he was admitted to the medical floor, where a subsequent chest X-ray showed patchy right infrahilar opacities concerning pneumonia and/or atelectasis (**Figure 1a**). Routine labs were notable for a creatinine increased to 1.9 mg/dL from his baseline of ~1.4 mg/dL. Other pertinent lab values in this patient with COVID-19 are included in **Figure 2**. Given his clinical stability, antibiotics and dexamethasone were deferred on admission. However, the patient spiked fevers up to 103.1°F and had oxygen saturation to 91 percent shortly after admission. Therefore, on day 2 of hospitalization, he was started on dexamethasone, ceftriaxone, and azithromycin for possible superimposed bacterial pneumonia. On day 3 of hospitalization, he continued to have oxygen saturations in the low 90s and required nasal cannula and initia-

Figure 1. Patient chest X-ray on days 1 and 4 of hospitalization.

a) Hospital day 1: Patchy right infrahilar opacities concerning for pneumonia.
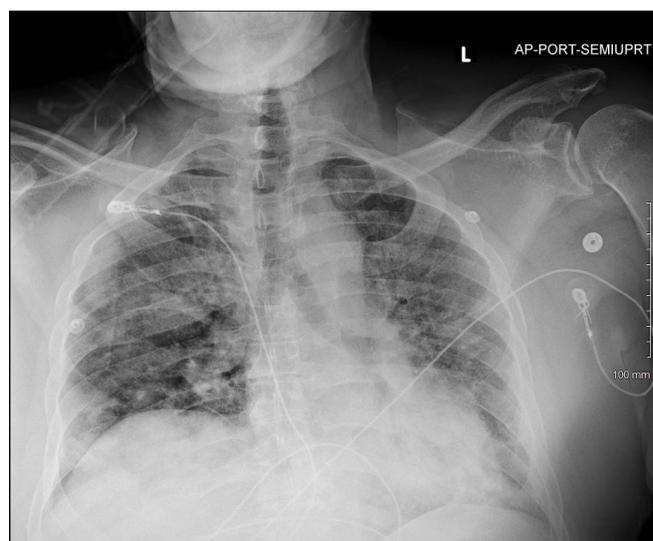
b) Hospital day 4: Interval worsening of the bilateral patchy airspace opacities.

tion of remdesivir. On day 4 of hospitalization, he had acute decompensation from a respiratory standpoint and was placed on a 15L non-rebreather mask. Arterial blood gas was obtained at this time, which revealed pH 7.49, pCO_2 31, and pO_2 38 on 90% FiO_2. Chest x-ray showed worsening of bilateral patchy airspace opacities (**Figure 1b**). He was transferred to the ICU, where he was placed on BiPAP (FiO_2 80%) and maintained oxygen saturations in the upper 90s. However, when an attempt was made to wean the patient to a high-flow nasal cannula (HFNC), he became more hypoxic. Ceftriaxone and azithromycin were discontinued after five days of treatment due to a lack of improvement on antibiotics and low suspicion of a bacterial source.

On day 6 of hospitalization, 4mg oral Baricitinib daily was started. Additionally, the patient was asked to self-prone while in the ICU. On day 8 of hospitalization, he completed a 5-day course of remdesivir and underwent numerous transitions between BiPAP and HFNC for several days. On day 12, a chest x-ray showed a new focal consolidation in the right upper lobe, which required him to start cefepime. Given his low lung reserve and worsening respiratory fatigue, he eventually required mechanical ventilation and was medically paralyzed on day 13 — the same day that his 10-day course of dexamethasone was completed. He went on to develop acute tubular necrosis and became progressively oliguric and azotemic. His creatinine trended up and peaked at 7.6 mg/dL (**Figure 3**). On hospital day 16, he was started on continuous renal replacement therapy due to his worsening renal function and volume overload. Baricitinib was discontinued on the

same day. Therefore, he only received ten days of Baricitinib therapy rather than the planned 14 days. He could not be weaned off the ventilator and underwent placement of a tracheostomy on day 37 of hospitalization.

His subsequent course was complicated by persistent fevers, worsening hypoxia, shock requiring vasopressors, and ventilator-associated pneumonia due to *Serratia marcescens*. Overall, the patient spent 78 days in the hospital and eventually died after the family withdrew life-sustaining measures.

Discussion

Baricitinib is a Janus kinase inhibitor used for the treatment of moderate-to-severe rheumatoid arthritis.[4] In addition to its role as an immunomodulator, it is thought to play a role in inhibiting viral entry.[5] On November 19, 2020, the FDA granted emergency use authorization of Baricitinib, in combination with Remdesivir, for hospitalized patients with COVID-19 requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[5]

This authorization was primarily based on results from the Adaptive COVID-19 Treatment Trial (ACTT-2) study conducted by the National Institute of Allergy and Infectious Diseases (NIAID).[6] This study was a randomized, double-blind, placebo-controlled clinical trial in hospitalized patients with COVID-19 of varying severity who received Baricitinib plus Remdesivir

Figure 2. Patient laboratory values.

a) Trend of inflammatory markers.
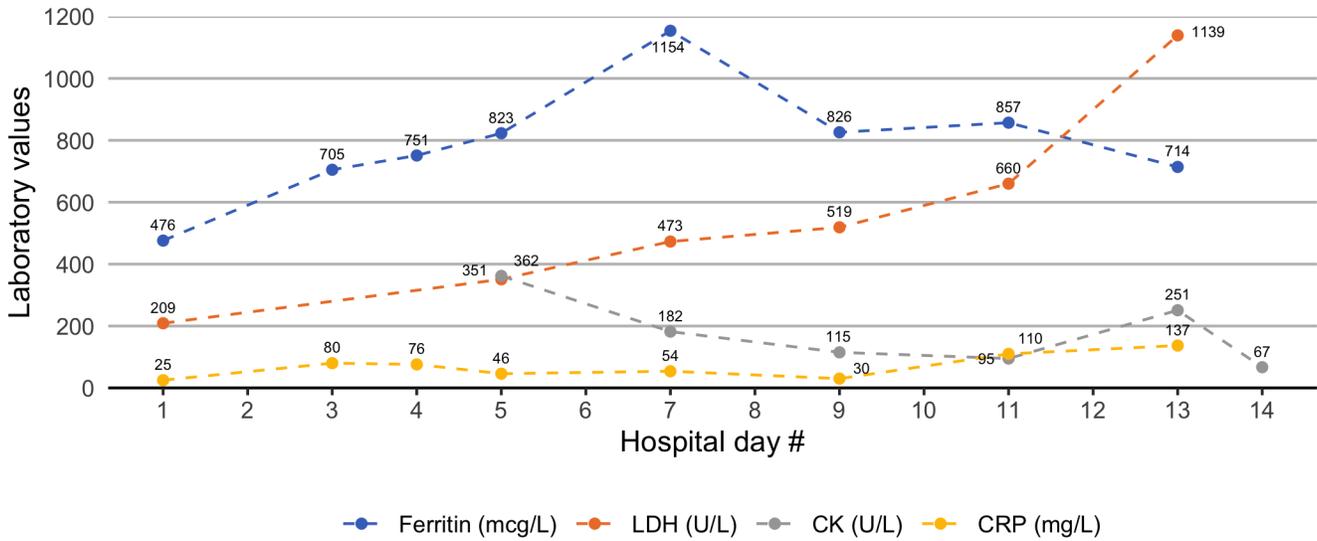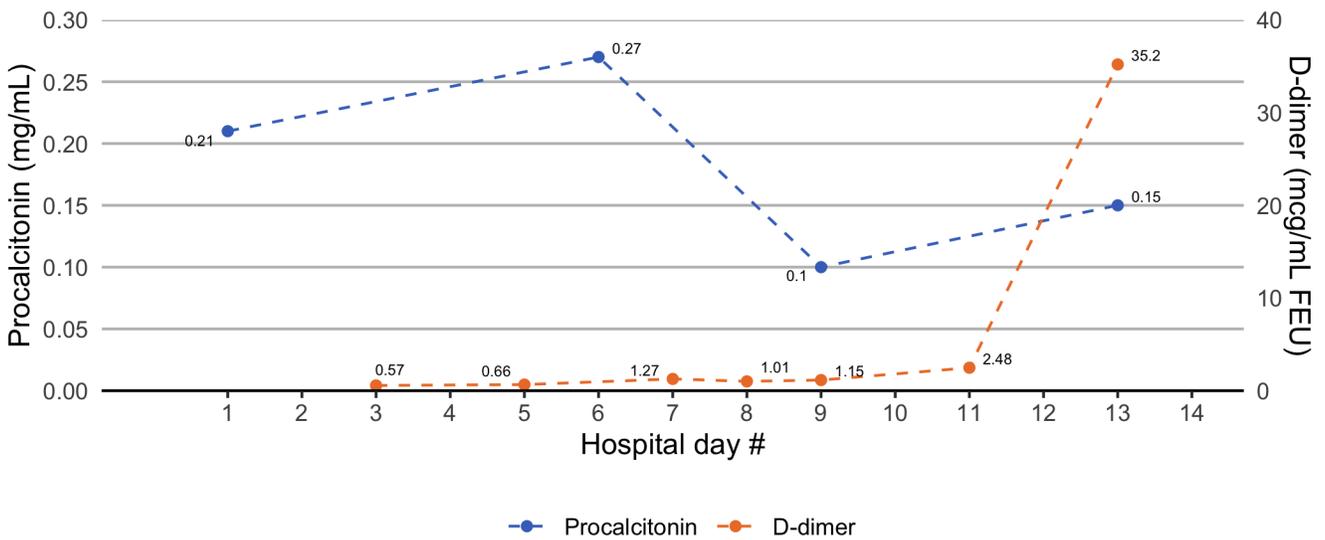

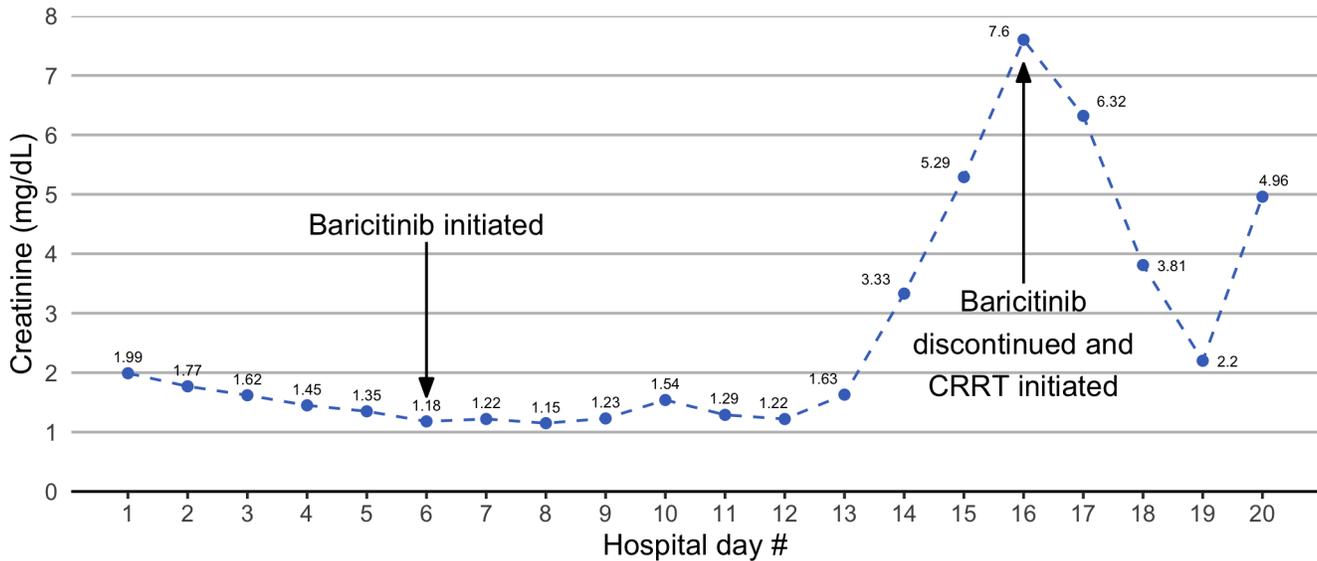**b)** Trend of procalcitonin and D-dimer.

Figure 3. Trend of creatinine.

or placebo plus Remdesivir. The treatment group received oral Baricitinib 4 mg once daily for 14 days or until hospital discharge plus standard-dose Remdesivir for ten days or until hospital discharge. The primary endpoint was time to recovery within 29 days. Recovery was defined as the first day on which one of the following three categories was met: The patient is no longer hospitalized, and without limitations on activities, the patient is no longer hospitalized has some limitations on activities and/or requiring home oxygen, the patient is hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care.

The median time to recovery from COVID-19 was seven days for those treated with Baricitinib plus Remdesivir, and eight days for those given placebo plus Remdesivir [hazard ratio: 1.16 (95% confidence interval (CI) 1.01, 1.32); P=0.03].[6] The odds of clinical improvement at day 15 were also higher in the treatment group versus placebo [odds ratio: 1.26 (95% CI 1.01, 1.57); P=0.044]. Additionally, the proportion of patients who died progressed to noninvasive ventilation/high-flow oxygen or progressed to invasive mechanical ventilation by day 29 was lower in the Baricitinib group (23%) versus placebo (28%) [odds ratio: 0.74 (95% CI 0.56, 0.99); P=0.039]. The overall 28-day mortality was 5.1% for the treatment group and 7.8% for the placebo group [hazard ratio for death, 0.65 (95% CI 0.39, 1.09)]. Given these findings, the FDA granted emergency use authorization for Baricitinib in combination with Remdesivir in hopes of offering an effective treatment option to those hospitalized with COVID-19.

Baricitinib has not yet received FDA approval to be used as a monotherapy for infection with SARS-CoV-2. However, many studies have been conducted to show its efficacy as a monotherapy.[7] Currently, there is no consensus of eligibility criteria of study participants due to the widely varying conditions in which these clinical trials are being conducted.[8] Furthermore, while the previous results demonstrate that the addition of Baricitinib to Remdesivir improves the time to recovery, no data currently exist comparing the addition of Baricitinib to Remdesivir versus the addition of dexamethasone. Large, randomized trials, such as RECOVERY, have shown evidence of a benefit with the addition of dexamethasone to Remdesivir.[9] However, among the 223 patients in ACTT-2 who were also on glucocorticoids during the trial, there was no detected difference in recovery time with the addition of Baricitinib.[6] Currently, the fourth iteration of the Adaptive COVID-19 Treatment Trial (ACTT-4) is underway.[10] This study will directly compare the effects of Baricitinib versus dexamethasone and determine the clinical efficacy of Remdesivir plus Baricitinib versus Remdesivir plus dexamethasone as measured by mechanical ventilation–free survival at day 29.[10] The results of this study will offer clinicians guidance on selecting various treatment options currently available for hospitalized patients with COVID-19.

Some possible side effects in patients with COVID-19 treated with Baricitinib include venous thrombosis, pulmonary embolism, hypersensitivity reactions, and serious infections.[3] However, in ACTT-2, major adverse events were less frequent in the Baricitinib arm

(16.0%) than in the placebo arm (21.0%) [difference -5.0% (95% CI -9.8, -0.3); P=0.03].[6] Additionally, there was a lower rate of new infections in the Baricitinib arm (5.9% vs 11.2%) [difference -5.3% (95% CI -8.7, -1.9); P=0.003]. According to the authors of ACTT-2, the consistently lower incidence of adverse events with Baricitinib may be related to its role in reducing inflammatory-mediated lung injury and improving lymphocyte counts. Moreover, its antiviral properties and the associated shorter recovery time with faster clinical improvement could have reduced the risk of nosocomial infection.

There are no known contraindications for the use of Baricitinib.[11] However, all patients should have laboratory values (i.e., estimated glomerular filtration rate, liver enzymes, complete blood count) evaluated at baseline and thereafter. Dose adjustments may be necessary should abnormal renal, hepatic, or hematologic lab values arise. Baricitinib is not indicated for patients on dialysis or those with end-stage renal disease (eGFR <15 mL/min) and those with acute kidney injury, as there are limited data on the use of the drug in patients with severe renal impairment. Additionally, it is not recommended for patients with active tuberculosis. Baricitinib should be used with caution in pregnant patients, although insufficient data suggests a risk of miscarriage or congenital disabilities. The use of live vaccines should be avoided with Baricitinib. Finally, it is recommended that patients taking strong OAT3 inhibitors (i.e., probenecid) reduce the dose of the OAT3 inhibitor to avoid excessive Baricitinib exposure.

In the present case, the patient's lengthy and complicated hospital course makes it difficult to ascertain the role Baricitinib played in treating his COVID-19 infec-tion. However, he would not have met any of the 29-day outcomes in the ACTT-2 trial. Several factors need to be taken into consideration when reviewing this case. Firstly, this patient was treated only ten days of Baricitinib therapy compared to the recommended 14 days due to his declining renal function. It is unclear whether this shorter course played a role in his lack of clinical response to treatment and eventual death. Secondly, this patient was treated with both Baricitinib and dexamethasone in addition to Remdesivir. It can be challenging to discern the benefits and harms of Baricitinib and systemic corticosteroids when given simultaneously. Since both drugs are immunosuppressants, there is a theoretical additive risk of infection. While this patient developed a hospital-acquired bacterial infection after initially contracting COVID-19, it remains unknown whether this was due to immunosuppression or due to other causes, as his *Serratia* pneumonia developed days after discontinuation of Baricitinib. Following the FDA's emergency use authorization of Baricitinib, the National Institutes of Health COVID-19 Treatment Guidelines Panel recommended using Baricitinib with Remdesivir in cases where dexamethasone cannot be used.[12] More data are needed to clarify the role of Baricitinib in combination with corticosteroids. Still, trials such as ACTT-4 will provide much-needed information to guide the selection of the initial immunosuppressive agent.

In conclusion, the emergency use of Baricitinib in combination with Remdesivir remains an alternative option in treating hospitalized COVID-19 patients. However, Baricitinib had no apparent benefit in this case, as the patient continued to deteriorate even after its initiation clinically. Therefore, more studies are needed to determine its safety and effectiveness.

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