Original Work

Baricitinib (Olumiant®) Thromboembolic Event in Patient Receiving Full-dose Anticoagulation

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Abstract

We describe the case of a 69-year-old male on baricitinib for COVID-19 treatment who developed bilateral deep vein thromboses while on full-dose anticoagulation with apixaban. Patients should be closely monitored for signs of venous thromboembolism while on baricitinib, even while on anticoagulation.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), better known as the coronavirus disease 2019 (COVID-19), is an infectious disease impacting public health globally. As the disease continues to spread, treatment options are emerging. Baricitinib has demonstrated improved time to recovery in patients with COVID-19, along with standard of care.[1] Baricitinib is a selective and reversible Janus kinase (JAK) 1 and 2 inhibitor. It has known anti-inflammatory effects in patients with autoimmune diseases, such as rheumatoid arthritis.[2] Its anti-cytokine properties and ability to target host proteins give it potential for the treatment of COVID-19.[3]

Baricitinib has a black box warning for thromboembolic risk; that is, deep vein thrombosis (DVT) and pulmonary embolism (PE)]. It also has a warning for cardiovascular risk (stroke).[1] There have been higher incidences of venous thromboembolic events (VTE) reported in patients on baricitinib versus placebo, even in those on prophylactic anticoagulation. However, there have not been any reports of thromboembolic events noted with baricitinib use while on therapeutic anticoagulation dosing. Due to these reactions, it is not considered a first line agent for the treatment of COVID-19. It is reserved for patients with progressive oxygen requirements despite standard of care.[3]

A literature search was conducted in MedLine and PubMed using the following search terms: (baricitinib and thrombosis) and (baricitinib and thromboembolism). No results returned involving reports of baricitinib use during COVID-19 treatment and occurrence of VTE, while also on therapeutic anticoagulation. The following case is a report of a patient who developed bilateral DVTs while on baricitinib, along with therapeutic anticoagulation. The Research Subject Protection Program at our health institution determined that this report does not constitute as human subject research and does not require Institutional Review Board oversight.

Case Presentation

In August 2021, a 69-year-old white male was admitted to the hospital with a chief complaint of worsening shortness of breath. He first tested positive for COVID-19 11 days prior to admission. He received casirivimab and imdevimab three days prior to admission, completed 10 days of dexamethasone, and was on oxygen at home for the treatment of COVID-19. He received two doses of the Pfizer-Biotech COVID-19 vaccine series in March of 2021 (booster doses were not approved at that time). Upon admission, a chest CT was completed, and no PE was detected. An ultrasound was not completed at this time as there were no signs of DVT.

Pertinent past medical history included

TABLE 1. Patient Lab Values During Admission

Lab Value	*Reference Range*	*ED Admission*	*Week 1* *Prior to start of baricitinib*	*Week 2* *Day ultrasound showed bilateral deep vein thrombosis*	*Week 3* *After discontinuation of baricitinib*
Creatinine	0.67-1.17 mg/dL	0.87	0.71	0.56	0.54
Creatinine clearance	97-137 mL/min	108	>120	>120	>120
Aspartate transaminase	≤37 Units/L	19	34	59	26
Alanine aminotransferase	<64 Units/L	22	54	199	118
Alkaline phosphatase	45 – 117 Units/L	88	76	106	84
Total bilirubin	0.2 - 1.0 mg/dL	0.4	0.4	1.4	1.4
Platelets	150 – 450 K/mcL	392	373	252	126
Hemoglobin	13.0 - 17.0 g/dL	12.8	11.7	12.4	9.3
Hematocrit	39-51%	38.1	34.9	36.3	27.3

interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), and atrial fibrillation. He had no relevant allergies. The patient was a former smoker (40 pack year history), and reported rare alcohol use and no illicit drug use. At the time of admission, his weight was 96 kilograms and he was 1.88 meters tall. Current home medications included alendronate 35 mg weekly, cetirizine 10 mg daily, cholecalciferol 2000 units daily, doxazosin 4 mg daily, fish oil 1000 mg twice daily, montelukast 10 mg daily, multivitamin daily, pantoprazole 40 mg daily, metoprolol tartrate 25 mg twice daily, apixaban 5 mg twice daily, mycophenolate 1500 mg twice daily, and psyllium 2.6 g daily. The patient was adherent to his medications and reported no missed doses. Significant labs are seen in Table 1. Labs were notable for an elevated serum creatinine upon admission and mild transaminitis while taking baricitinib and remdesivir.

At the time of admission, the patient was started on remdesivir 200 mg once followed by 100 mg daily for 5 days and baricitinib 4 mg daily for 14 days for COVID-19 treatment, due to his worsening respiratory status. Valacyclovir 500 mg twice daily for 28 days was also started for herpes simplex virus (HSV) prophylaxis. The patient was already taking apixaban 5 mg twice daily for stroke prevention following his atrial fibrillation diagnosis in July of 2021. The apixaban was continued inpatient for stroke prevention and venous thromboembolism prophylaxis. Ten days into treatment with baricitinib, it was noted that the patient had swelling in both legs and an ultrasound confirmed that the patient had developed bilateral lower extremity DVTs. Given this finding, baricitinib was discontinued, as well as apixaban due to possible treatment failure. The patient was instead started on enoxaparin 100 mg subcutaneously twice daily for DVT treatment, with the addition of warfarin. Enoxaparin was able to be discontinued after INR was therapeutic (2.0–3.0) for 48 hours. He was admitted for a total of 26 days.

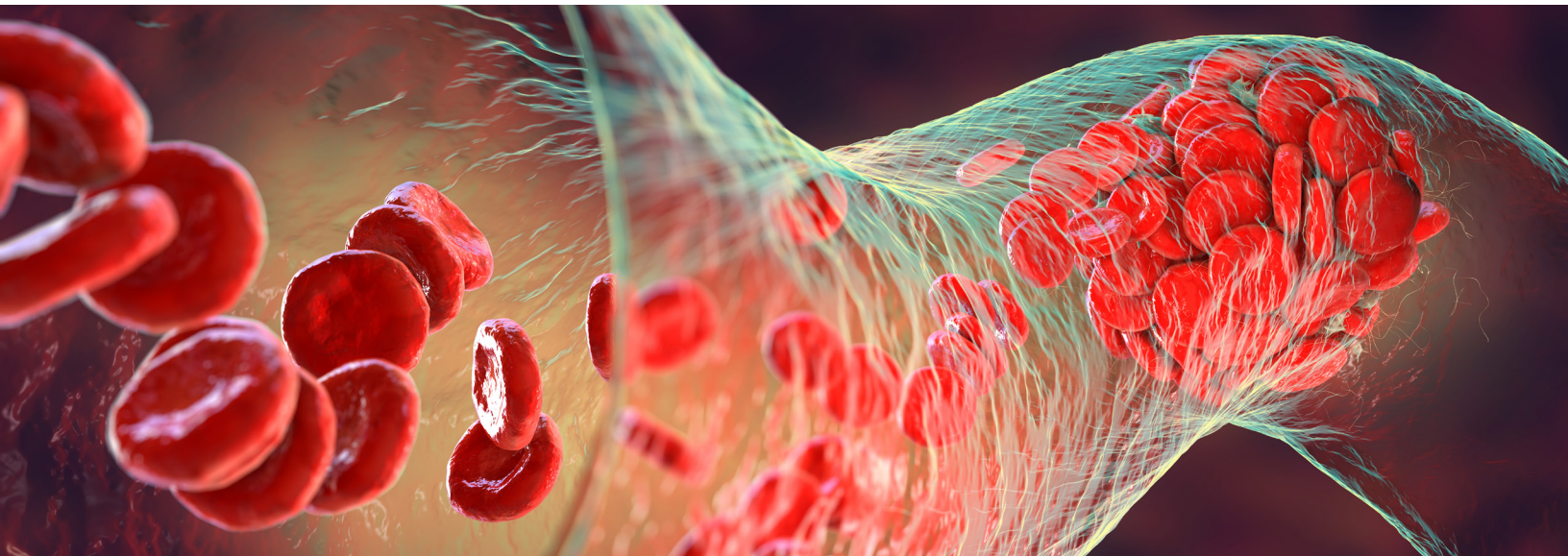
Discussion

Multiple scenarios were evaluated for our patient when searching for a cause of his bilateral DVTs. VTE is a well-known side effect of baricitinib. VTE has been appearing in patients with COVID-19 as well.[1,4] Studies have also reported coagulation abnormalities in patients with COVID-19. A systematic review found a 14% incidence of VTE across all patients with COVID-19, with VTE occurring in almost 23% of patients in the intensive care unit (ICU).[4] Current guidelines from the National Institutes of Health recommend thromboprophylaxis anticoagulation dosing in patients with severe COVID-19, in the absence of high bleed risk.[5]

Baricitinib was originally approved in 2018 for rheumatoid arthritis.[6] In November 2020, the FDA granted Emergency Use Authorization (EUA) of baricitinib for use in COVID-19 patients for 14 days, or until hospital discharge.[7] It is thought that baricitinib inhibits the intracellular signaling pathway of cytokines, which are often elevated in patients with severe COVID-19. Two phase 3, randomized, double-blind controlled clinical trials evaluated baricitinib use in patients with COVID-19.[2,8] Despite COVID-19 and baricitinib both being risk factors for increased VTE, treatment with baricitinib did not show an increased risk compared to placebo.

There are a few aspects that may have led to treatment failure in this particular patients; however, most of those were able to be ruled out. While it is recommended to decrease the dose of baricitinib to 2mg daily for patients with estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73m2, this patient's eGFR was >90 mL/minute/1.73 m2; thus, baricitinib was dosed appropriately.[1] Additionally, VTE prophylaxis is required with the administration of baricitinib; however, this patient was on full-dose anticoagulation with apixaban when he developed bilateral DVTs. There is limited data regarding the dosing of apixaban in obese patients (> 120kg), as previous studies have noted a decrease in maximum concentration (Cmax) and area under the curve (AUC) in this patient population. Yet there are still no specific dosing adjustments recommended.[9] Importantly, the patient in this case had an actual body weight of 96 kg; therefore, this was not likely a reason of his treatment failure.

Other potential causes of treatment failure could have been due to medication interactions. There was a notable interaction between apixaban and diltiazem, with the potential to increase apixaban concentration. We would expect this to increase the risk of bleeding, not clotting as experienced by this patient, making baricitinib the likely culprit. There was also a drug-drug interaction between baricitinib and the patient's home medication of mycophenolate, with the potential to enhance immunosuppression. However, this did not play a role, because mycophenolate, used in this patient for interstitial lung



disease, was not continued during the hospital stay.

Conclusion

This patient case demonstrates that the overlapping pharmacodynamic risk factors for VTE, including hospitalization, active COVID-19 infection, and concomitant use of baricitinib therapy, resulted in breakthrough thrombosis despite full dose anticoagulation with apixaban for underlying atrial fibrillation. Providers should be aware of this adverse reaction and monitor early and often, even if a patient is on full anticoagulation. Additional reports of VTE occurrence on full dose anticoagulation may be expected, as baricitinib is used for COVID-19 therapy in more patients as the pandemic continues. Further studies to define the optimal anticoagulation regimen for patients requiring baricitinib for COVID-19 infection are still needed.

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