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LETTER TO THE EDITOR

Management of potential drug-drug interactions with nirmatrelvir-ritonavir and oral anticoagulants: a case series

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Nirmatrelvir-ritonavir (Paxlovid™) is a 5-day oral antiviral therapy given an Emergency Use Authorization by the Food and Drug Administration in late 2021 for the outpatient treatment of COVID-19 infection in adults [1]. The National Institute of Health COVID-19 treatment guideline panel recommends nirmatrelvir-ritonavir for outpatients at high risk of COVID-19 disease progression [2]. Since nirmatrelvir is metabolized by hepatic enzymes CYP3A4 and CYP2D6, ritonavir is co-administered for its CYP3A4 and CYP2D6 inhibitory properties to boost nirmatrelvir plasma concentrations. Ritonavir is a well-known strong combined inhibitor of CYP3A4 and p-glycoprotein (p-gp) [3]. Consequently, it has the potential to interact with all oral anticoagulants, since apixaban, rivaroxaban, and warfarin are CYP3A4 substrates, and apixaban, dabigatran, edoxaban, and rivaroxaban are all substrates of p-gp [4]. The manufacturer-labeled guidance for these potential drug interactions varies by drug (Table 1).

In this case series, we assessed all patients within the University of Utah Healthcare system who had a positive COVID-19 test and were prescribed nirmatrelvir-ritonavir with concurrent use of an oral anticoagulant from December 30, 2021 through June 30, 2022. We describe the drug interaction management strategies undertaken for each patient given their prescribed anticoagulant. We also report bleeding and thromboembolic outcomes 30 days after the nirmatrelvir-ritonavir prescribing date.

Of the 2611 patients who were prescribed nirmatrelvir-ritonavir by a University of Utah Health provider during the study period, we found 72 patients who were also taking an oral anticoagulant (Table 2). Most patients were white (87.5%) males (55.6%) with a mean age of 67 years. The majority of patients were taking apixaban (38, 52.8%), followed by warfarin (23, 31.9%), rivaroxaban (10, 13.9%) and dabigatran (1, 1.4%). The most common indication for anticoagulation was stroke prevention in atrial fibrillation (40, 55.6%) followed by treatment of venous thromboembolism (VTE) (28, 38.9%). Of those treated for VTE, only three had experienced their event in the prior 6 months. One-fourth were enrolled in the Thrombosis Service, and in just under half of patients (34, 47.2%) the Thrombosis Service was consulted by the prescriber for recommendations for the drug-drug interaction management strategy. Concordance with manufacturer drug interaction management guidance (Table 2) was seen in 38 of 72 patients (52.8%). Poor concordance with manufacturer guidance were seen most commonly with dabigatran, rivaroxaban, and apixaban 2.5 mg twice daily primarily due to failing to avoid the combination of use for the duration of nirmatrelvir-ritonavir. Most warfarin-treated patients did receive a guidance-concordant strategy of more frequent monitoring of the International Normalized Ratio (INR) (12/23, 52.2%), and the majority of patients did return with a therapeutic INR following the course of nirmatrelvir-ritonavir (13/23, 56.5%). In this cohort of 72 patients, there were no thrombotic events and three non-major bleeding events in the 30 days following prescription of nirmatrelvir-ritonavir in combination with an oral anticoagulant (Table 3). Two of the bleeding events were in patients taking apixaban, 11 days and 18 days, respectively, after nirmatrelvir-ritonavir completion, and both were dosed in concordance with drug interaction guidance. One patient on warfarin experienced a non-major bleeding event on the third day of nirmatrelvir-ritonavir therapy.

In this case series of 72 patients co-prescribed nirmatrelvir-ritonavir and an oral anticoagulant, approximately half of the patients received drug-drug interaction management that was consistent with the manufacturer

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Table 1 Oral anticoagulant drug interaction prescribing guidance for ritonavir

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Ritonavir Drug Interaction Prescribing Guidance	Reduce apixaban 5 mg BID or 10 mg BID dose by 50% If already using apixaban 2.5 mg BID, avoid combining ritonavir with apixaban	Avoid combining dabigatran and ritonavir if CrCl < 50 mL/min for VTE or CrCl < 30 mL/min for AF	None[a]	Avoid combining ritonavir with rivaroxaban	Use more frequent INR monitoring to adjust the warfarin dose

AF atrial fibrillation, *BID* twice daily, *CrCl* creatinine clearance, *INR* international normalized ratio, *VTE* venous thromboembolism

[a]Edoxaban dose reduction from 60 mg daily to 30 mg daily is recommended for specific p-glycoprotein inhibitors studied in clinical trial setting; this does not include ritonavir since these patients were excluded from clinical trials

recommended strategies. Yet, adverse events were uncommon and potentially unrelated to the drug interaction. This study supplies real-world data to indicate that the recommended drug-drug interaction management strategies may be effective, but that also, provider discretion may be used without patient harm. This study is limited by the small patient population, albeit relatively good size for a novel therapy and a drug interaction study. Initially, supply of nirmatrelvir-ritonavir was extremely limited and thus strict eligibility criteria were implemented, limiting its broader use. Additionally, the short 5-day duration of the nirmatrelvir-ritonavir course could have lessened any serious drug concentration changes as a result of the drug-drug interaction. Reassuringly, even though COVID-19 infection has been associated with thromboembolic events [5], none of these at-risk patients experienced thrombosis while either holding their anticoagulant or while on a reduced anticoagulant dose. Notably, the majority of our observations were limited to apixaban and warfarin, limiting our ability to draw conclusions on how interactions with other oral anticoagulants should be managed. All but three patients with VTE were in the long-term prevention phase of therapy and so we are unable to speak to drug-drug interaction management strategies in those with more acute VTE events. The INRs in the warfarin patients did not seem particularly affected by the potential ritonavir drug interaction, reinforcing the strategy to reactively monitor the INR as opposed to preemptively adjusting the warfarin dose [4].

In conclusion, in this case series, recommended drug-drug interaction management strategies for apixaban, rivaroxaban, and warfarin seemed effective at minimizing adverse events following use of nirmatrelvir-ritonavir with oral anticoagulation. As COVID-19 becomes endemic to our population and nirmatrelvir-ritonavir use becomes more routine, clinicians should remain vigilant to address potential drug-drug interactions and ensure that patients are educated on proper anticoagulant dosing and resumption of therapy at the completion of their antiviral course.

Table 2 Characteristics of patients on oral anticoagulants prescribed nirmatrelvir-ritonavir

Characteristic	Overall N = 72	Concordant with Manufacturer DDI Guidance N = 38
Concordance with Manufacturer DDI Guidance	38 (52.8)	38 (100.0)
Mean age, years (SD)	67 (15.1)	69 (13.5)
Male sex, n (%)	40 (55.6)	19 (50.0)
Race, n (%)		
White or Caucasian	63 (87.5)	33 (86.6)
Black or African American	2 (2.8)	2 (5.3)
Hawaiian/Pacific Islander	1 (1.4)	1 (2.6)
Other	6 (8.3)	2 (5.3)
Mean weight, kg (SD)	91.5 (25.5)	91.5 (25.9)
Mean BMI (SD)	31.2 (8.7)	31.7 (9.4)
Mean CrCl, mL/min (SD)	88.6 (35.3)	89.1 (31.1)
Indication for anticoagulation[a]		
Atrial fibrillation	40 (55.6)	23 (60.5)
Median CHA_2DS_2-VASc Score, (IQR)	4 (2)	4 (2)
Venous Thromboembolism	28 (38.9)	14 (36.8)
< 6 months since VTE	3	1
≥ 6 months since VTE	25	13
Cardiac Valve	3 (4.2)	2 (5.3)
Stroke	3 (4.2)	2 (5.3)
Antiphospholipid Syndrome	3 (4.2)	0 (0.0)
Other	3 (4.2)	2 (5.3)
Anticoagulant prescribed, n (%)		
Apixaban	38 (52.8)	22 (57.9)
2.5 mg twice daily dose	7	2
5 mg twice daily dose	31	20
Dabigatran	1 (1.4)	0 (0.0)
150 mg twice daily dose	1	0
Rivaroxaban	10 (13.9)	4 (10.5)
10 mg daily dose	4	1
15 mg daily dose	1	0
20 mg daily dose	5	3
Warfarin	23 (31.9)	12 (31.6)
INR goal range 2.0–3.0	19	10
INR goal range 2.5–3.5	3	2
Other INR goal range	1	0
Enrolled in the Thrombosis Service, n (%)	18 (25.0)	8 (21.1)
Thrombosis service consulted for drug interaction management guidance, n (%)	34 (47.2)	24 (63.2)

BMI body mass index, *CrCl* creatinine clearance, *DDI* drug-drug interaction, *IQR* interquartile range, *mg* milligrams, *n* number of patients, *SD* standard deviation, *VTE* venous thromboembolism

[a]Indication for anticoagulation percentages exceed 100% due to presence of patients with multiple indications

Table 3 Description of 30-day adverse outcomes

Adverse outcome type	Concordance with Manufacturer DDI guidance?	Prescribed anticoagulation regimen	Date of adverse outcome after starting nirmatrelvir-ritonavir
Clinically relevant Non-major bleeding (rectal bleeding)	No	Warfarin (INR target 2.0–3.0)	3 days later
Clinically Relevant Non-Major Bleeding (vaginal bleeding requiring ED visit)	Yes	Apixaban 5 mg twice daily	16 days later (11 days after DDI discontinuation)
Clinically Relevant Non-Major Bleeding (rectal bleeding)	Yes	Apixaban 5 mg twice daily	23 days later (18 days after DDI discontinuation)

DDI drug-drug interaction, *ED* emergency department, *INR* international normalized ratio

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this letter.

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