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BRIEF REPORT

High Prescription Rate of Medications With Rifampin Drug–drug Interactions in Patients With Diabetic Foot Osteomyelitis: Should Rifabutin Be Included in Clinical Trials for Adjunctive Therapy?

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Rifampin may improve diabetic foot osteomyelitis outcomes, but its extensive drug–drug interactions could hamper its use. Here, through a review of the medications prescribed to a cohort of 190 persons with diabetic foot osteomyelitis, we show that rifabutin, a rifamycin with fewer drug–drug interactions, would be easier to implement in practice.

Keywords. diabetic foot osteomyelitis; drug-drug interactions; rifamycins.

Diabetes is a leading cause of preventable limb loss globally and diabetic foot osteomyelitis (DFO) is one of the strongest risk factors for lower extremity amputations [1–3]. However, DFO antibiotic management is highly variable and there are few data to guide antibiotic management, including whether or not to use a rifamycin-containing regimen [4–6]. The VA INTREPID is an ongoing randomized clinical trial investigating whether adjunctive rifampin improves DFO outcomes [7]. The trial population consists of persons with definite or probable DFO according to international guidelines and the identity of the infecting organism(s) is not included in the study's selection criteria [7, 8]. A preliminary VA observational study found higher rates of amputation-free survival among those who received adjunctive rifampin therapy [4]. Patients who received rifampin were younger and had fewer comorbidities compared to those who did not receive rifampin. The authors speculate these significant differences might be related to drug–drug interactions (DDIs), which highlights one of the most important barriers to the use of this drug. As such, there has been increased interest in evaluating rifabutin, a rifamycin with less potent induction of CYP3A4 and p-glycoprotein and thus fewer DDIs compared to rifampin [9]. There is limited yet promising evidence that rifabutin may serve as an alternative to rifampin for bone and joint infections. These data include *in vitro* [10, 11], animal model [12], and small case series [13, 14] suggesting rifampin and rifabutin exhibit similar activity against staphylococcal bone and joint infections. The question of whether adjunctive rifampin therapy improves outcomes in DFO is essential, but implementing rifampin in clinical practice may be challenging given the high number of DDIs between rifampin and commonly used medications. Here, we sought to evaluate the extent to which DDIs could be barrier to using rifampin compared with rifabutin for DFO.

METHODS

Study Design and Definitions

We performed a retrospective cohort study of all patients hospitalized with DFO between 2017 and 2019 in a high-volume diabetic foot ulcer (DFU) center who were discharged on systemic antibiotics. Given that many medications are lifelong prescriptions for chronic conditions, we included only the first hospital admission with DFO to avoid overestimation of DDIs resulting from patients with multiple hospitalizations. Patients hospitalized with a DFO were identified using previously described methods [15]. Briefly, we queried hospital discharge billing records using International Classification of Diseases, revision 10, codes for DFU, DFO, and/or lower extremity amputation. If an International Classification of Diseases, revision 10, code of interest were present, we performed a manual chart review to confirm these diagnoses. DFO was defined based on a foot X-ray and/or magnetic resonance imaging obtained during or 3 months before the hospitalization, given poor documentation of probe-to-bone tests in our institution.

Among included patients, we reviewed the records to determine if a bacterial culture from soft tissue and/or bone was obtained and if *Staphylococcus aureus* was present because it is the most common DFO-associated bacteria and data suggest rifamycins are especially beneficial for *S aureus*–associated

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osteomyelitis [16]. We also reviewed the medical records for comorbidities that increase DFO-associated amputation risk (eg, peripheral artery disease [PAD]) and those that are likely to require use of medications associated with rifamycin DDIs (heart failure, PAD, cerebrovascular disease, atrial fibrillation, deep venous thrombosis, and pulmonary embolism). All chart reviews were performed by trained personnel using a standardized case report form and entered in a REDCap database [17].

To investigate if potential rifamycin DDIs were present, we used the electronic medical records to obtain the complete list of medications prescribed at hospital discharge. We then determined the predicted number of DDIs between rifampin and rifabutin with discharge medications if one of these rifamycins had been prescribed. DDIs were determined using the Lexicomp database with focus on categories D (consider therapy modification) and X (avoid combination) [18]. Last, we determined the number of predicted DDIs between rifampin and rifabutin with discharge medications if a discharge medication was substituted for a medication within the same class that has a better rifamycin DDI profile (eg, switch omeprazole, rifampin class X, to pantoprazole, no significant rifampin interaction).

RESULTS

We identified 190 unique patients diagnosed with DFO and discharged on antibiotics between 2017 and 2019. The median age was 55 years, most patients were male 137 (72%), and the median hemoglobin A1c was 9.2% (Table 1). The prevalence of comorbidities is described in Table 1. Notably, only 10 (5%) patients had a diagnosis of PAD. Cultures were obtained in 101 (53%) cases and *S aureus* was identified in 28% of those. No patients were discharged on rifampin for DFO.

Among the 190 patients, 38 (20%) were discharged on ≥1 medication with a rifampin class X DDI and these 38 patients were prescribed a total of 40 medications with a rifampin class X DDI (Table 2). Among these 40 medications, the most common were proton pump inhibitors (PPIs) (n = 28 [70%]) followed by directly acting oral anticoagulants (n = 8 [20%]). Conversely, 2 (1%) patients were discharged on ≥1 medication with a rifabutin class X DDI, and all were antiretrovirals.

Ninety-five (50%) patients were discharged on ≥1 medication with a rifampin class D DDI; these 95 patients were prescribed a total of 131 medications with a rifampin class D DDI. Among these 131 medications, the most common were atorvastatin (n = 69 [53%]) followed by clopidogrel (n = 20 [15%]). Five (3%) patients were prescribed antipsychotics,

Table 1. Baseline Characteristics

Characteristic	N = 190
Age, median (IQR), y	55 (46–60)
Male	137 (72)
Baseline HbA1c, median (IQR)	9.2 (7–12)
Comorbidities	
Heart failure	34 (18)
Peripheral artery disease	10 (5)
Cerebrovascular disease	19 (10)
Atrial fibrillation	3 (2)
Deep venous thrombosis/pulmonary embolism	9 (5)
Infection and treatment	
Culture obtained	101 (53)
Nonsurgical culture	42 (42)
Surgical culture	59 (58)
S aureus identified	28 (28)
Intravenous antibiotics on discharge	56 (30)
Total number of antibiotics on discharge, median (IQR)	2 (1–2)
Medications prescribed at hospital discharge	
Total number of medications, median (IQR)	8 (6–11)

All data are presented as n (%) unless stated otherwise.

Abbreviations: HbA1c, hemoglobin A1c; IQR, interquartile range.

Table 2. Rifamycin Drug–drug Interactions (n = 190)

	Rifampin	Rifabutin
Lexicomp class X drug–drug interactions		
Patients with ≥1 prescription with a class X DDI, n (%)	38 (20)	2 (1)
Total prescriptions with class a X DDI, n	40	2
Medication classes (% of prescriptions with a class X DDI)		
Directly acting oral anticoagulant	8 (20)	-
Proton pump inhibitors	28 (70)	-
Antiretrovirals	2 (5)	2 (100)
Ibrutinib	1 (3)	-
Naloxegol	1 (3)	-
Lexicomp class D drug–drug interactions		
Patients with ≥1 prescription with a class D DDI, n (%)	95 (50)	3 (2)
Total prescriptions with class a D DDI, n	131	3
Medication classes (% of total prescriptions with a class D DDI)		
Atorvastatin	69 (53)	…
Clopidogrel	20 (15)	…
Trazodone	5 (4)	…
Cefazolin	13 (10)	…
Warfarin	2 (2)	2 (67)
Antipsychotics	5 (4)	…
Levonorgestrel	…	1 (33)
Other	17 (13)	…
Rifamycin drug–drug interactions if within-class medications substituted[a]		
Lexicomp class X drug–drug interactions		
Patients with ≥1 prescription with a class X interaction, n (%)	12 (6)	2 (1)
Total prescriptions with class a X drug–drug interaction, n	12	2
Lexicomp class D drug–drug interactions		
Patients with ≥1 prescription with a class D interaction, n (%)	52 (27)	3 (2)
Total prescriptions with class a D drug–drug interaction, n	62	3

Abbreviation: DDI, drug–drug interaction.

[a]Proton pump inhibitors (esomeprazole n = 22, lansoprazole n = 1, and omeprazole n = 5) and atorvastatin n = 69.

and 2 (1%) patients were prescribed warfarin. Conversely, 3 (2%) patients were discharged on ≥1 medication with a rifabutin class D DDI; 2 were prescribed warfarin and 1 was prescribed levonorgestrel.

If the PPIs with a rifampin class X DDI esomeprazole, omeprazole, and lansoprazole were substituted for pantoprazole or the statin with a class D rifampin, DDI atorvastatin was substituted for rosuvastatin, pravastatin, or simvastatin and the number of patients discharged on ≥1 medication with a class X or class D rifampin DDI would be 12 (6%) and 52 (27%), respectively. These substitutions would not alter the number of patients with a class X or D rifabutin DDI.

DISCUSSION

We performed a retrospective study of patients with DFO who might benefit from rifampin adjunctive therapy, should this approach prove effective in the ongoing VA INTREPID trial [7]. We found that considerably more patients were prescribed medications with a Lexicomp class X (avoid combination) and/or class D (consider therapy modification) rifampin DDI compared to rifabutin. This suggests rifabutin may be easier than rifampin to implement in clinical practice and rifabutin should be considered for future clinical trials.

It is noteworthy that most of the class X rifampin interactions were due to PPIs, which, cost aside, may be substituted by a different PPI (eg, use pantoprazole instead of omeprazole) or H2 blockers that have minimal or no rifampin DDIs [9]. Indeed, when we excluded all PPI prescriptions, the number of patients with at least 1 medication with a class X rifampin interaction decreased from 20% to 6%. In contrast, class X rifampin DDIs that may be prohibitive such as directly acting oral anticoagulants and class D rifampin DDIs that are difficult to manage such as warfarin were infrequent, even though atrial fibrillation and venous thromboembolism had higher prevalence compared to the general population [19, 20]. Most class D rifampin DDIs were due to atorvastatin, which, cost aside, may be substituted for other statins with a better DDI profile such as rosuvastatin. When we excluded all atorvastatin prescriptions, the number of patients with at least 1 medication with a class D rifampin interaction decreased from 50% to 27%, which is still a significant proportion of our patient population. Conversely, antipsychotics and clopidogrel, which might be challenging to substitute, accounted for 4% and 11% of rifampin class D interactions, respectively. Clopidogrel is notable given the overlap of PAD and DFUs [21] and that rifampin coadministration increases clopidogrel active metabolites, possibly increasing bleeding risk [22]. Last, 13 (7%) of patients were prescribed cefazolin, which has a rifampin class D interaction because of increased bleeding risk [23]. This is relevant because methicillin-susceptible *S aureus* DFO is common, and cefazolin is a first-line antibiotic in that scenario [6, 16].

The prevalence of PAD in this cohort was remarkably low (5%). For example, in Eurodiale, a landmark European multisite study that systematically investigated for PAD among 1299 patients with a DFU, 49% had PAD [21]. Similarly, the PAD prevalence was 37% in the previously mentioned VA-based rifampin observational study [4]. We hypothesize that these differences could be due to PAD underdiagnosis in this cohort because of limited vascular testing during the study period [24] or from inaccurate clinical documentation. The high coprevalence of PAD and DFO may be a substantial barrier to using rifampin. The latest IWGDF PAD guidelines recommend an antiplatelet agent, preferably clopidogrel, for all persons with diabetes and symptomatic PAD [25]. These guidelines also state that aspirin and rivaroxaban, a direct oral anticoagulant, may be considered for those with diabetes and symptomatic PAD at low bleeding risk.

Our study limitations include the single site design and inclusion of hospitalized patients only, limiting generalizability. The Food and Drug Administration approved 225 drugs from 2019 to date, including 5 drugs for diabetes and/or heart failure (finerenone, Tzield, tirzepatide, sotagliflozin, and bexagliflozin) and none for PAD or anticoagulation [26, 27]. Among these 5 drugs, only finerenone has a significant DDI with rifampin and rifabutin (class X for both). The low PAD prevalence and low frequency of clopidogrel and direct oral anticoagulant use may have led to the underestimation of DDIs in the general population. Nonetheless, our findings suggest that, from a DDI standpoint, rifabutin would pose significantly fewer challenges in clinical practice compared to rifampin. Using the Lexicomp database to identify potentially clinically significant DDIs has limitations, rifampin significantly decreases clindamycin [28–30], linezolid [31, 32], and moxifloxacin [33] exposures. However, clindamycin and linezolid DDIs with rifampin are rated B (no action needed) and moxifloxacin with rifampin DDI is rated C (monitor therapy) because there were no known negative impact on outcomes. The lack of negative associations between decreased antibiotic concentrations and outcomes is based on small bone and joint infection studies that cannot properly control for confounders or studies of other types of infection (eg, tuberculosis).

The VA INTREPID trial aims to enroll 880 participants. If rifampin proves beneficial, a similar trial should investigate if rifabutin has a similar effect. However, it is exceedingly unlikely a well-powered trial investigating rifabutin instead of rifampin will be conducted. If rifampin proves beneficial, clinicians faced with significant rifampin DDIs will need to choose to (1) forgo use of a rifamycin, (2) use rifampin but adjust or substitute concomitant medications to avert DDIs, or (3) use rifabutin despite lower quality or indirect evidence. Clinicians caring for people with DFO may need to navigate rifamycin DDIs soon, a

problem tuberculosis clinicians are well-acquainted to. The "Rifamycin Drug-Drug Interactions: A Guide for Primary Care Providers Treating Latent Tuberculosis Infection" was created to clarify drug interactions between rifamycins and drugs commonly used in a primary care and can be a good source for DFO care [9]. Additionally, to use rifabutin for DFO, clinicians need to become familiar with its unique adverse effects, including neutropenia, uveitis, and polyarthralgia, despite their infrequency at usual doses (300 mg daily) [34].

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Potential conflicts of interest. All authors: No reported conflicts.

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