Clearance of Vancomycin-Resistant *Enterococcus* Concomitant With Administration of a Microbiota-Based Drug Targeted at Recurrent *Clostridium difficile* Infection

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Background. Vancomycin-resistant *Enterococcus* (VRE) is a major healthcare-associated pathogen and a well known complication among transplant and immunocompromised patients. We report on stool VRE clearance in a post hoc analysis of the Phase 2 PUNCH CD study assessing a microbiota-based drug for recurrent *Clostridium difficile* infection (CDI).

Methods. A total of 34 patients enrolled in the PUNCH CD study received 1 or 2 doses of RBX2660 (microbiota suspension). Patients were requested to voluntarily submit stool samples at baseline and at 7, 30, and 60 days and 6 months after the last administration of RBX2660. Stool samples were tested for VRE using bile esculin azide agar with 6 μg/mL vancomycin and Gram staining. Vancomycin resistance was confirmed by Etest.

Results. VRE status (at least 1 test result) was available for 30 patients. All stool samples for 19 patients (63.3%, mean age 61.7 years, 68% female) tested VRE negative. Eleven patients (36.7%, mean age 75.5 years, 64% female) were VRE positive at the first test (baseline or 7-day follow-up). Of these patients, 72.7%, n = 8 converted to negative as of the last available follow-up (30 or 60 days or 6 months). Of the other 3: 1 died (follow-up data not available); 1 patient remained positive at all follow-ups; 1 patient retested positive at 6 months with negative tests during the interim.

Conclusions. Although based on a small sample size, this secondary analysis demonstrated the possibility of successfully converting a high percentage of VRE-positive patients to negative in a recurrent CDI population with RBX2660.

Keywords. *Clostridium difficile*; microbiota-based drug; RBX2660; vancomycin-resistant *Enterococcus*; VRE.

Vancomycin-resistant *Enterococcus* (VRE) is a major healthcare-associated pathogen. VRE infection is a well known complication among critically ill, transplant and immunocompromised patients [1]. VRE colonization precedes infection, and vancomycin resistance is an independent predictor of mortality in patients with enterococcal bacteremia [1]. Colonization and infection are also associated with increased hospital length of stay [2, 3] and costs [2, 3], and carriers are at increased risk for infection and a source of transmissions to others. Controlling transmission in a healthcare setting can be challenging [4]. *Clostridium difficile* infection (CDI), likewise, is a challenging healthcare-associated infection (HAI) and can result in severe morbidity and mortality. CDI is now the most common cause of HAI and the leading

cause of gastroenteritis-associated deaths in the United States. A recent study found that CDI was responsible for approximately 453 000 infections and 29 000 deaths in the United States in 2011 [5]. Recurrence is an especially challenging aspect of treating CDI, with up to 25% of patients experiencing disease recurrence, usually within 30 days of treatment [6].

Both VRE and CDI share similar risk factors, including contact with the healthcare system, antimicrobial exposures, acuity of underlying illness, and immunocompromised status [7]. Increased frequencies of VRE colonization and infection have been observed to occur in tandem with increases in CDI. In a series of hospital inpatients with CDI, VRE colonization was also found in 58.7% of cases. There was also a greater prevalence of coinfection with multidrug resistant organisms (MDRO) in the VRE-positive patients [8]. Antimicrobial-induced perturbation of the gut microbiota may contribute to both VRE and CDI, allowing acquisition and over growth, and then persistence of colonization. Controlling the spread of VRE in the healthcare environment is difficult. Patients can remain colonized with VRE for prolonged periods of time, serving as a reservoir for transmission and infection to others. Decolonization of VRE is extremely difficult if not impossible. Although nonabsorbed antimicrobials are effective in suppressing VRE, recurrence of

colonization is common [9, 10]. Antimicrobial treatment options can have rate-limiting toxicities, and resistance to antimicrobials with activity against VRE is increasing. VRE infection also significantly increases length of stay and hospitalization costs [2, 11].

There is growing recognition that commensal bacteria present in the intestinal microbiome play an important role in colonization resistance to pathogens, including C. difficile and VRE, and that antimicrobial use can disrupt this protection and enable a cycle of persistence/reinfection. In the case of CDI, studies suggest that restoration of the gut microbiota is necessary to prevent or mitigate recurrence [12]. Fecal microbiota transplantation (FMT) has been used to repopulate the intestines with normal microbiota and has been demonstrated as effective in the treatment of recurrent CDI with few adverse events [13, 14]. We report on clearance of VRE in stool in a secondary analysis of the PUNCH CD study, a Phase 2 open-label study assessing the safety and efficacy of RBX2660, a microbiota-based drug, in a population of patients with recurrent CDI.

METHODS

Forty patients with recurrent CDI at 11 centers in the United States were enrolled in the PUNCH CD study between August 15 and December 16, 2013 [15]. Major inclusion criteria were as follows: age ≥ 18 years old and at least 2 recurrences of CDI after a primary episode, or at least 2 episodes of severe CDI resulting in hospitalization. Completion of a 10- to 14-day course of oral antimicrobials for CDI, the last 7 days of which were standardized to oral vancomycin (125 mg 4 times daily), was required, followed by a 24- to 48-hour washout period before RBX2660 administration. A single dose of RBX2660 was administered via enema. A second dose was permitted if CDI recurrence was suspected within 8 weeks of the first dose. No antimicrobials for the treatment of CDI or bowel prep were given before the second dose. Major exclusion criteria were as follows: history of inflammatory bowel disease (ulcerative colitis, Crohn's disease, or microscopic colitis); irritable bowel syndrome; chronic diarrhea; celiac disease; colostomy; evidence of active, severe colitis; planned surgery requiring perioperative antibiotics within 6 months of study enrollment; compromised immune system and white blood cell count <1000 cells/μL.

RBX2660

RBX2660 is a microbiota-based drug sourced from live human-derived microbes. Donors underwent a comprehensive initial health and lifestyle questionnaire and then provided blood and stool samples that were tested for a wide variety of pathogens. RBX2660 is produced with Good Manufacturing Practices and a standardized chain of custody. Product is stored in a secure location at ≤−80°C before shipment. Each 150 mL dose (50 g of stool and 0.9% saline/polyethylene glycol 3350 vehicle)

contains ≥10^7 microbes/mL and is available in a single-dose, ready-to-use enema bag.

VRE Testing Protocol

Baseline stool testing of the study patients included culture for VRE. In addition, patients were requested to voluntarily submit stool samples at 7, 30, and 60 days and 6 months after the last administration of RBX2660. Stool samples were shipped on ice to Fairview Diagnostic Laboratories (Minneapolis, MN) via overnight delivery. Laboratory requirements for testing were fresh stool, within 72 hours of collection; refrigerated if not tested directly after collection. To determine the presence of VRE, stool was inoculated onto bile esculin azide agar with 6 μg/mL vancomycin (Remel, Lenexa, KS). Enterococcal isolates were identified based on colony morphology, Gram stain, and biochemical testing. Suspected enterococcal isolates were subcultured on blood agar with a vancomycin disk, and vancomycin resistance was confirmed by Etest.

Antimicrobial use Exposure Post-RBX2660 Administration

After RBX2660 administration, physicians could treat patients with antimicrobials as medically necessary. Medication use was collected on the case report form in free-form text for all patients enrolled in the PUNCH CD study. Data on post-RBX2660 antimicrobial administration were abstracted and placed on a timeline for the purposes of determining whether or not VRE was detectable in fecal specimens throughout the course of the study.

Definitions

For the PUNCH CD study, successful treatment of CDI was defined as the absence of C difficile-associated diarrhea at 56 days after the last dose of RBX2660. For the VRE analysis, patients were grouped into always negative and positive at least once. A baseline, ie, pre-RBX2660 administration, stool specimen was not collected for many patients; therefore, both the pre-RBX2660 and day 7 follow-up stool specimens were used to identify patients likely colonized with VRE at time of RBX2660 administration. VRE clearance was defined as no stool specimens positive for VRE after at least 1 positive stool test.

Statistical Methods

Descriptive statistics were used for data analysis. This secondary analysis was not powered to determine statistical significance.

RESULTS

Baseline Characteristics

A total of 34 patients received 1 or 2 doses of RBX2660. Of these, 30 patients had at least 1 stool sample available for VRE testing. Of these patients, the mean age was 66.7 years with a range of 26.7–89.5 years. Twenty (66.6%) patients were female and 29 (96.6%) were white (Table 1). Patients with at least 1 stool positive for VRE were older than patients without stool positive for VRE (75.5 vs 61.7 years old). Before study enrollment,

Table 1. Baseline Characteristics

Parameter	Stool Tested for VRE n = 30	Always VRE (−) n = 19	At Least 1 VRE (+) n = 11	Entire PUNCH CD Cohort n = 34
Mean age, range, y	66.7 (26.7–89.5)	61.7 (26.7–77.8)	75.5 (47.6–89.5)	66.8 (26.7–89.6)
Female sex, (%)	20 (66.6)	13 (68.4)	7 (63.6)	23 (67.6)
White, (%)	29 (96.6)	19 (100)	10 (90.9)	32 (94.2)
Mean BMI, range k/m²	24.4 (15–37)	23.9 (15–31)	25.3 (19–37)	24.4 (15–37)
History of cardiovascular disease, %	16 (53.3)	10 (52.6)	6 (54.5)	19 (55.9)
History of gastrointestinal comorbidity, %	18 (60)	11 (57.9)	7 (63.6)	21 (61.8)

Abbreviations: BMI, body mass index; VRE, vancomycin-resistant *Enterococcus*.

patients had been on a variety of CDI treatment regimens, primarily standard dose vancomycin but also vancomycin taper and standard-dose fidaxomicin; 1 patient had been on a fidaxomicin taper.

VRE Status

All stool samples submitted for testing were found acceptable by the laboratory performing VRE testing. A total of 30 of 34 (88%) of patients treated with RBX2660 submitted at least 1 stool for VRE testing (Table 2). All stool samples for 19 patients were negative for VRE; 11 patients were positive for VRE at the first test (baseline or 7-day follow-up). Of the patients who were positive for VRE at least once, 72.7% (n = 8) converted to negative as of the last available follow-up. The proportion of patients testing positive for VRE after the last dose of RBX2660 decreased over time (Figure 1). Three patients were classified as having failed to clear VRE: one patient died of respiratory failure unrelated to RBX2660 administration soon after FMT.

Therefore, follow-up VRE resolution data were not available. A second patient remained VRE positive at all follow-ups (prescribed a 14-day course of vancomycin at 16 days post-RBX2660 administration). The third patient retested positive at 6 months after having negative tests in the interim. This patient was VRE positive at 9 days post-RBX 2660 administration and then tested VRE negative at the 1- month and 2-month follow-ups. Subsequently, this patient developed several episodes of recurrent CDI and received 8 courses of antimicrobials between the last negative stool test for VRE and the 6-month specimen that was positive.

Antimicrobial use post-RBX2660 administration was analyzed for the 11 patients who were VRE positive on their first test. Patients received antimicrobials post-RBX2660 administration primarily for CDI or diarrhea but also for pneumonia, urinary tract infection, sinus infection, abscess, and nonspecified bacterial infection. Of these patients, 6 received antimicrobials post-RBX2660 administration; the mean duration of their

Table 2. VRE Culture Results for Patients With at Least 1 Positive Culture for VRE[a]

Patient Number	VRE Test Status						Antimicrobials Post-RBX2660	CDI Status	
	Baseline	7 d	30 d	60 d	6 mo	VRE Cleared	Prescriptions, n	RBX2660 Doses	CDI Outcome
1	+	−	−	−	+	No	Ciprofloxacin, 2 Amoxicillin, 2 Penicillin, 1 Vancomycin, 2	1	Success
2	+	+	+	+	−	Yes	Vancomycin, 1 Fidaxomicin, 1	2	Failure
3	+	−	−	−	−	Yes	None	1	Success
4	NA	+	NA	−	−	Yes	None	2	Success
5	NA	+	−	−	NA	Yes	None	2	Success
6[b]	NA	+	NA	NA	NA	NA	Cefuroxime, 1	2	Success
7	NA	+	+	+	+	No	Vancomycin, 1	2	Failure
8	NA	−	+	−	NA	Yes	None	2	Success
9	NA	+	−	−	−	Yes	Sulfamethoxazole, 1 Trimethoprim, 1	1	Success
10	+	+	−	−	−	Yes	None	1	Success
11	+	+	−	−	−	Yes	Doxycycline, 1 Metronidazole, 1 Macrobid, 1	2	Success

Abbreviations: CDI, *Clostridium difficile* infection; NA, not available; VRE, vancomycin resistant *Enterococcus*.

[a] VRE status reflects status after the last dose of RBX2660.

[b] Died 35 days after last dose of RBX2660 of causes unrelated to drug administration; follow-up data on VRE status was unavailable.

VRE STATUS AFTER RBX2660 ADMINISTRATION
VRE Positive Patients by Time Since Last Dose

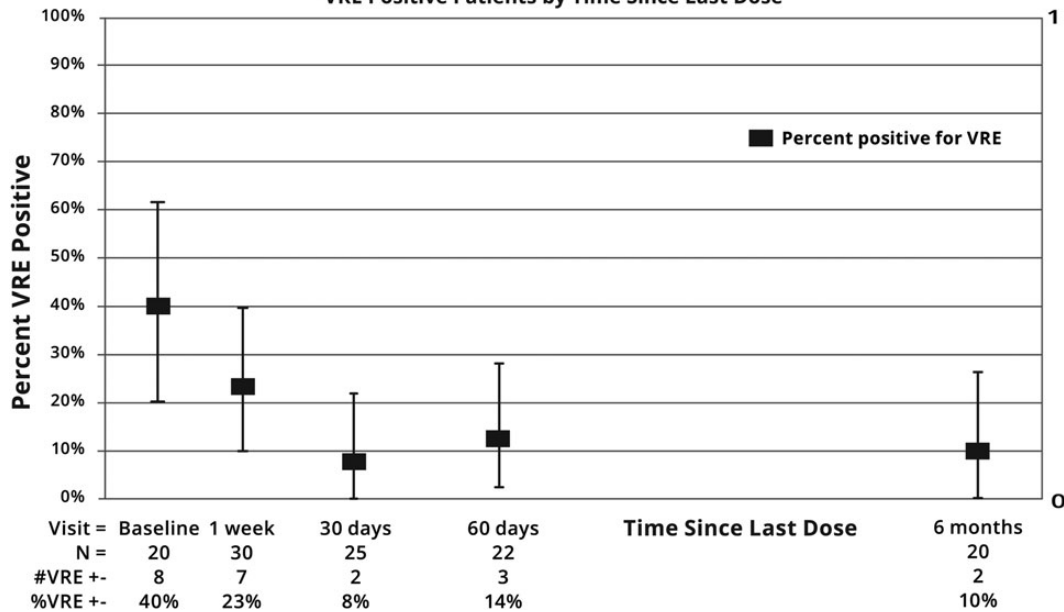| Visit =	Baseline	1 week	30 days	60 days		6 months
N =	20	30	25	22		20
#VRE +-	8	7	2	3		2
%VRE +-	40%	23%	8%	14%		10%

Figure 1. The percentage of patients testing vancomycin-resistant *Enterococcus* (VRE) positive after the last dose of RBX2660 decreased over time.

antimicrobial exposure post-RBX2660 administration was 6.2 (range, 1–14) days. Considering only the patients who were initially VRE positive and converted to VRE negative at last assessment, 4 received antimicrobials post-RBX2660 administration; mean duration was 7.0 (range, 2–13) days. In the 11 patients who tested VRE positive at least once, the antimicrobials prescribed post-RBX2660 administration were as follows: vancomycin (n = 5); fidaxomicin (n = 3); metronidazole (n = 1); ciprofloxacin (n = 2); amoxicillin (n = 2); doxycycline (n = 1); and other (n = 5). Analysis of variance shows that antimicrobial use was concentrated in 2 of the 11 patients.

DISCUSSION

VRE colonization and CDI share similar risk factors, and VRE infection and colonization have been observed to occur in tandem with CDI. Of 158 cases of CDI evaluated by Fujitani et al [8], 55.7% were colonized with VRE. In this subset of 30 patients with recurrent CDI who were enrolled PUNCH CD study, 36.7% had stool positive for VRE at baseline. The major risk factor for acquiring and developing infections from both VRE [16–18] and *C difficile* is antimicrobial exposure [19–21]. There is recognition that antimicrobials disturb the microbiome and facilitate selection and expansion of resistant bacteria [22]. Concurrent with increased understanding of the role of the commensal bacteria in preventing colonization and infection with CDI and VRE, as well as other MDROs, has prompted a look at use of microbiota-based approaches to prevent colonization and infection due to these organisms. Recent work has

demonstrated that commensal bacteria provide not only colonization resistance, but they are also involved in immune processes that stimulate the development of antimicrobial factors [23]. Antimicrobials, by killing the commensal bacteria, decrease the diversity of the intestinal microbiota, enabling pathogens such as VRE and *C difficile*, among others, to colonize and proliferate [24]. Therefore, a normal intestinal microbiota is necessary for colonization resistance. Fecal microbiota transplantation has been demonstrated to be effective against recurrent CDI [25, 26] and to restore diversity in the gut microbiota in successfully treated patients [27, 28].

Based on the positive experience with the use of FMT for recurrent CDI, FMT is now being considered for the treatment of many other conditions, and it has been suggested that it may be effective in clearing VRE and other MDROs by restoring colonization resistance [22, 23]. Case reports have described the use of FMT for MDRO decolonization [29, 30]. Jang et al [29] reported that a patient with severe refractory CDI who was also colonized with VRE was cured of CDI with FMT. However, VRE was cultured from the stool throughout the 3-month follow-up. Crum-Cianflone et al [30] reported one case where FMT successfully cured relapsing CDI and several MDROs including VRE. Stripling et al [31] reported that FMT cleared VRE and CDI in a woman with orthotopic cardiac and single cadaveric kidney transplants complicated by multiple episodes of VRE infection and CDI posttransplant. Between the time of organ transplants and FMT, the patient was hospitalized 18 times. The patient had no further CDI or VRE infections at

1-year after FMT. Singh et al [32] reported on eradication of extended spectrum β-lactamase (ESBL)-producing *Escherichia coli* in a man with a renal allotransplant with end-stage renal disease consequent to recurrent episodes of pyelonephritis post-transplant. After removal of the transplanted kidney, he remained colonized. After FMT, the ESBL cleared at 12-weeks follow-up and he was then placed on the waiting list for renal transplantation.

In this case series, RBX2660, a microbiota-based drug undergoing Phase 2 study for recurrent CDI, was associated with clearance of VRE in a high percentage of patients who were colonized at time of drug delivery (72.7%, 8 of 11). For 2 of the patients who failed to clear VRE, the treatment also failed to prevent recurrence of CDI. The recurrence of CDI in those patients may indicate that the gastrointestinal microbiota was not effectively reestablished after treatment with RBX2660. The proportion of patients with VRE detected in stool after the last dose of RBX2660 decreased over the course of 6-month follow-up. Of note, it is possible RBX2660 suppressed VRE below the threshold of the culture method used to detect VRE colonization, as demonstrated by the patient in whom VRE was detected again after exposure to multiple courses of antimicrobials. Repeat exposures to antimicrobials are associated with persistence of VRE detection in stool [16–18]. Although VRE may no longer be detected in the absence of additional antimicrobial exposures, Donskey et al [16] found that VRE can be detected again when a person is later exposed to antimicrobials. However, VRE was not detected again in 4 of 6 (67%) patients positive at first test who converted to negative after RBX2660 who received additional antimicrobials after receipt of RBX2660. This suggests that VRE was truly "cleared" from the colon of several patients. It should be noted, however, that in some cases, the absence of recurrence could potentially be related to antimicrobials with a low propensity to promote VRE colonization (eg, fidaxomicin, doxycycline). RBX2660 may represent a potentially promising microbiota-based treatment strategy in a population with a well documented risk of VRE infection.

LIMITATIONS

The findings in this analysis have a number of limitations. This was a small secondary analysis conducted in the context of a Phase 2 open-label assessment of RBX2660 for recurrent CDI, and there was no comparator arm. However, natural history observation estimates a median time to clearance of VRE carriage at 26 weeks [4], whereas the majority of evaluable patients appeared to clear in a shorter interval. Patient compliance with stool submission post-RBX2660 administration varied over the course of follow-up. The findings should be confirmed in a larger study with VRE decolonization as a primary outcome using a placebo arm for comparison.

CONCLUSIONS

This secondary analysis demonstrates the possibility of converting a high percentage of VRE-positive patients to negative with RBX2660. Based on an analysis of post-RBX2660 antimicrobial exposure, it appears that the VRE conversion results may be durable. Additional study in a larger prospective trial is needed to confirm these results.

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