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Therapeutic Success of Rifaximin for *Clostridium difficile* Infection Refractory to Metronidazole and Vancomycin

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Key Words

Recurrent *Clostridium difficile* infection · Rifaximin · Vancomycin · Metronidazole · *Saccharomyces boulardii*

Abstract

We report the case of a 46-year-old white male with confirmed *Clostridium difficile* infection for >4 weeks after fluoroquinolone therapy. The patient received two courses of metronidazole 500 mg three times daily (t.i.d.) during which time diarrhea resolved; however, symptoms recurred 14–15 days after treatment termination. He received a 2-week course of vancomycin 125 mg four times daily, with symptoms recurring 10 days after treatment conclusion. The patient then received a pulsed tapering schedule of vancomycin with adjunctive *Saccharomyces boulardii*. Diarrhea recurred 12 days after treatment completion. He received rifaximin 400 mg t.i.d. while hospitalized for diarrhea-associated complications. Symptoms resolved within 24 h. The patient received a 4-week regimen of rifaximin 400 mg orally t.i.d. after discharge. No further episodes of diarrhea were reported within 6 months after treatment termination. The present case supports the potential benefit of rifaximin for the treatment of recurrent *Clostridium difficile* infection.

Introduction

Clostridium difficile infection (CDI) is a frequent cause of morbidity and mortality among hospitalized patients [1]. This infection typically presents with watery diarrhea without blood in the stool accompanied by lower abdominal pain, fever, and leukocytosis [2]. Symptoms usually occur after antibiotic treatment for previous illness due to the propensity of antibiotics to cause disruption of the gastrointestinal flora, thereby permitting growth of toxigenic *C. difficile* strains [2]. CDI has been increasing in prevalence and severity in recent years, perhaps due to the emergence of uncommon,

hypervirulent strains [1, 2] and a reduction in efficacy of standard CDI treatments (i.e., metronidazole and vancomycin) [2, 3]. Indeed, failure rates with first-line therapies of metronidazole and vancomycin are reported to be 22–28% and 8–19%, respectively [3]. Even after initial resolution of symptoms with standard antibiotic therapy, relapses of CDI occur in approximately 12–24% of patients [4]. This number increases dramatically (up to 65%) in patients with multiple instances of CDI recurrence [4]. These data illustrate the need for additional therapeutic options for CDI, especially for patients with multiple recurrences of the disease.

Rifaximin is a nonsystemic, rifamycin-derived antibiotic that has in vitro bactericidal activity against *C. difficile* through inhibition of bacterial RNA synthesis [5]. Rifaximin is currently indicated for the treatment of travelers' diarrhea caused by noninvasive *Escherichia coli* and the reduction in risk of overt hepatic encephalopathy recurrence [6] and has been shown to elicit no clinically relevant bacterial antibiotic resistance [7]. As rifaximin demonstrates in vitro activity against *C. difficile* [5] and does not significantly alter the gastrointestinal flora [7], rifaximin has been used off label for CDI [5]. An initial study in a hamster model of CDI showed that rifaximin, alone or in combination with vancomycin, increased survival compared with vehicle treatment [8]. In addition, fewer hamsters who received rifaximin therapy (0%) had recurrence of CDI compared with animals who received vancomycin (75%, $p < 0.01$) [8]. A subsequent case series of rifaximin use in humans established that rifaximin effectively prevented CDI recurrence when used as a 'chaser' in patients who had symptom resolution induced by vancomycin [9]. Another small, uncontrolled pilot study by Garey et al. [10] demonstrated the efficacy of a tapered regimen of rifaximin in resolving CDI symptoms and preventing disease recurrence. It remains to be seen, however, whether a standard regimen of rifaximin may be effective in resolving CDI. The current case report expounds on the observations of Garey et al. [10] and demonstrates the effective resolution and prevention of recurrence of CDI refractory to standard therapies by rifaximin.

Case Report

The 46-year-old white male patient experienced symptoms of CDI for >4 weeks after completing a fluoroquinolone regimen for an episode of pneumonia. He had multiple previous gastrointestinal problems, including chronic constipation, chronic abdominal pain, and dysphagia. His medical history included coronary artery disease, hypertension, seizures, and bipolar disorder. The patient's surgical history included bilateral splanchnicectomy for chronic pancreatitis, 4-vessel coronary stent placement, and right inguinal hernia repair.

The patient developed CDI after receiving a 2-week course of moxifloxacin 400 mg orally every day for pneumonia and presented with symptoms of bloating, lower abdominal cramping, and ≥ 10 episodes of watery diarrhea. Stool toxin assay results showed the presence of *C. difficile*, and flexible sigmoidoscopy indicated the presence of confluent mild colitis with yellow-white pseudomembranes in the sigmoid and descending colon. Subsequent treatment regimens are provided in [table 1](#). The patient received metronidazole 500 mg orally 3 times daily (t.i.d.) for 2 weeks, and gastrointestinal symptoms abated. Fourteen days after the termination of metronidazole treatment, the patient's abdominal and diarrheal symptoms returned. He again received metronidazole 500 mg t.i.d. for 2 weeks, which resolved the gastrointestinal symptoms, but they returned 14–15 days after treatment termination. After the patient's symptoms returned a second time, he received oral vancomycin 125 mg four times daily (q.i.d.). His symptoms subsided during vancomycin treatment, but 10 days after treatment termination, he called his outpatient gastroenterologist with symptoms of recurrent diarrhea and lower abdominal cramping. He then received a pulsed tapering schedule of vancomycin with adjunctive probiotic therapy of *Saccharomyces boulardii* 250 mg twice daily. The schedule consisted of vancomycin 125 mg q.i.d. for 1 week, then t.i.d. for 1 week, then every day for 1 week, then every other day for 2 weeks, and then

every third day for 2 weeks. Diarrheal and abdominal cramping symptoms were alleviated but returned 12 days after the termination of vancomycin treatment. The patient experienced these symptoms for 10 days before he was admitted to the hospital for dehydration and acute renal failure.

On admission, the patient had a white blood cell count of 10,500 cells, which were composed of the following: 76% neutrophils, 16.8% lymphocytes, and 5.8% monocytes. He had elevated hemoglobin and hematocrit values (16.2 g/dl and 45.5%, respectively), most likely due to low total body water volume. Upon physical examination, the patient appeared dehydrated but had normal levels of blood urea nitrogen (38 mg/dl) and blood creatinine (1.4 mg/dl). Stool samples were obtained and tested positive for *C. difficile*. The patient received intravenous fluid replacement, and his abdominal and diarrheal symptoms were treated with oral rifaximin (XIFAXAN®; Salix Pharmaceuticals, Inc., Morrisville, N.C., USA) 400 mg t.i.d. The diarrhea and associated gastrointestinal symptoms resolved within 24 h, and stool samples taken 14 days after rifaximin treatment initiation tested negative for *C. difficile*. The patient was discharged from the hospital and received a 4-week regimen of rifaximin 400 mg t.i.d. No adverse events were reported. During the 6-month follow-up period, he experienced no episodes of diarrhea. Repeat stool samples from 180 days after termination of rifaximin treatment tested negative for *C. difficile*, and flexible sigmoidoscopy revealed absence of pseudomembranes.

Discussion

The current standard of treatment for initial CDI includes discontinuing the inciting antibiotic and prescribing a regimen of either oral metronidazole or vancomycin [1]; however, recurrence of infection after symptoms have abated completely while on appropriate therapy has been reported [3]. Several studies have described various pharmacotherapeutic regimens to treat recurrent CDI [11–14], but there has not yet been one designated as standard treatment.

Current treatment strategies for recurrent CDI include the use of metronidazole 500 mg t.i.d. for 10 days for initially recurrent cases of CDI [2]. If symptoms recur, pharmacotherapy is usually switched, most often to oral vancomycin 125 mg q.i.d. for 10 days [2]; however, other treatment regimens have been proposed, including treatment with high-dose vancomycin (2 g/day) [13], tapered-dose vancomycin [14], and vancomycin in combination with rifampin (a rifamycin derivative) [15]. Despite the small sample size of these studies (n = 6–22), an available treatment algorithm for multirecurrent CDI (≥3 episodes) suggests that patients unresponsive to vancomycin 500 mg/day be given a high dose of vancomycin (2 g/day) or have rifampin 600 mg/day added to their current vancomycin regimen [2]. If the diarrheal symptoms continue, colectomy may be advisable [2].

In the case presented, CDI recurred despite several different regimens of metronidazole and vancomycin, including 2 treatments with metronidazole 1,500 mg/day followed by low-dose vancomycin (500 mg/day) and a tapering vancomycin schedule combined with probiotics. Despite this therapy, diarrhea recurred, and the patient developed acute renal failure that required hospitalization for volume and electrolyte repletion. This hospitalization might have been prevented had there been another safe therapeutic option for recurrent CDI after metronidazole and vancomycin treatment. These observations support the necessity of an alternative antibiotic, such as rifaximin (a rifamycin derivative similar to rifampin), for the treatment of recurrent CDI.

Rifaximin is a nonsystemic, gut-selective antibiotic that, unlike rifampin, has an excellent safety profile, with adverse drug interactions and overall adverse events comparable to those associated with placebo [5]. A previous study of 8 patients with

multiple CDI recurrences who received rifaximin 400–800 mg/day for 2 weeks immediately after vancomycin therapy demonstrated that only 1 of 8 patients (12%) experienced CDI recurrence [9], suggesting that rifaximin effectively prevents CDI after symptom resolution induced by other antibiotics (i.e., vancomycin). Further, a study by Garey et al. [10] showed that 5 of 6 patients (83%) had complete resolution of CDI after receiving rifaximin. These 5 patients received a tapered rifaximin regimen consisting of rifaximin 1,200 mg/day for 14 days followed by rifaximin 600 mg/day for 14 days. Symptom resolution occurred in an average of 8 ± 5 days with no recurrence of symptoms during a mean follow-up period of 310 ± 145 days. The sixth patient in this study received rifaximin 400 mg t.i.d. for 36 days and had recurrence of *C. difficile*-negative diarrhea, suggesting that rifaximin was effective for CDI resolution; however, long-term follow-up of this patient was not possible due to the patient's death.

The present case report expounds on the findings of Garey et al. [10] by demonstrating that rifaximin 1,200 mg/day effectively resolved CDI symptoms and achieved bacterial cure in a patient with recurrent CDI refractory to standard therapies. In addition, this case report demonstrates that rifaximin 1,200 mg/day effectively prevented recurrence of CDI for up to 6 months posttreatment. The rapidity of the patient's symptom relief after rifaximin therapy was remarkable, given his history of recurrent diarrhea. The findings from the present case, along with other previously published works [9, 10], suggest that rifaximin may offer a promising solution to the frustrating clinical problem of recurrent CDI that faces many clinicians today.

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Table 1. Treatment regimens and outcomes for a patient with recurrent CDI

Drug	Dose	Duration	Outcome
Metronidazole	500 mg t.i.d.	2 weeks	initial resolution of diarrhea followed by recurrence of symptoms 14 days posttreatment
Metronidazole	500 mg t.i.d.	2 weeks	initial resolution of diarrhea followed by recurrence of symptoms 14–15 days posttreatment
Vancomycin	125 mg q.i.d.	2 weeks	initial resolution of diarrhea followed by recurrence of symptoms 10 days posttreatment
Tapered vancomycin with <i>Saccharomyces boulardii</i> therapy (250 mg b.i.d.)	125 mg q.i.d.	1 week	initial resolution of diarrhea followed by recurrence of symptoms 12 days posttreatment
	125 mg t.i.d.	1 week	
	125 mg q.d.	1 week	
	125 mg q.o.d.	2 weeks	
	125 mg dieb. tert.	2 weeks	
Rifaximin	400 mg t.i.d.	4 weeks	initial resolution of diarrhea with sustained response up to 6 months posttreatment

CDI = *Clostridium difficile* infection; b.i.d. = twice daily; dieb. tert. = every third day; q.d. = every day; q.i.d. = 4 times daily; q.o.d. = every other day; t.i.d. = 3 times daily.

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