BRIEF REPORT

Interruption of Recurrent *Clostridium difficile*–Associated Diarrhea Episodes by Serial Therapy with Vancomycin and Rifaximin

Stuart Johnson,[1,2] Christopher Schriever,[1] Minerva Galang,[1] Ciarán P. Kelly,[3,4] and Dale N. Gerding[1,2]

[1]Loyola University Medical Center, Maywood, [2]Hines Veterans Affairs Hospital, Hines, Illinois; [3]Beth Israel Deaconess Hospital, and [4]Harvard University, Boston, Massachusetts

Eight women who each experienced 4–8 episodes of *Clostridium difficile*–associated diarrhea were given a 2-week course of rifaximin therapy when they were asymptomatic, immediately after completing their last course of vancomycin therapy. Seven of the 8 patients experienced no further diarrhea recurrence. The patient who had a recurrence responded to a second course of rifaximin therapy, but rifaximin-resistant *C. difficile* was recovered after treatment. A controlled trial for treating recurrent *Clostridium difficile*–associated diarrhea appears to be warranted.

The recurrence of diarrhea after the successful resolution of an episode of *Clostridium difficile*–associated diarrhea (CDAD) is a major problem that occurs in ~20%–25% of patients after the initial CDAD episode [1] and in ~45% of those who have had 1 recurrent CDAD episode [2]. Recent data from Quebec, Canada, in the context of a multihospital outbreak of a new epidemic *C. difficile* strain, documented a 47% recurrence rate of diarrhea after the first CDAD episode [3]. A subset of patients with CDAD have multiple CDAD recurrences. Although these patients predictably respond to treatment of each episode, they have recurrent symptoms shortly after discontinuation of treatment. A number of empirical approaches have been used to treat multiple CDAD recurrences, including tapering and/or pulsed-dosing regimens of vancomycin therapy, vancomycin therapy in combination with rifampin therapy, probiotic regimens that use *Saccharomyces boulardii* and *Lactobacillus* species, intentional colonization with nontoxigenic *C. difficile*, fecal transplantation, synthetic fecal bacterial replacement, intravenous immunoglobulin, and active vaccination with a *C. difficile* toxoid preparation [4]. All of these regimens have been effective in some patients, but the only controlled trial that showed a benefit was in a subgroup analysis that involved treatment with *S. boulardii* and high-dose vancomycin [5].

We report a new approach to this problem using treatment with rifaximin, a poorly absorbed rifamycin derivative that is highly active against *C. difficile* in vitro [6]. Rifaximin has a broad spectrum of antimicrobial activity against gram-negative and gram-positive organisms and is currently approved in the United States for the treatment of traveler's diarrhea caused by noninvasive *Escherichia coli*. Our approach was to use rifaximin as a follow-up therapy, or "chaser," immediately after vancomycin treatment for the most recent episode of CDAD in an unselected group of patients at our clinics who had multiple CDAD recurrences.

All patients were part of the clinical practices of the authors', and this regimen was the basis of an empirical trial by the authors, who used rifaximin therapy for an off-label indication. The patients each had experienced at least 4 episodes of CDAD, and multiple other approaches had been employed to treat the recurrent episodes. Patients were informed that rifaximin was an approved drug for another indication, and that although this drug was active against *C. difficile* in vitro and was usually well tolerated, there was no proof that rifaximin would be effective in this context. Rifaximin therapy was not initiated while the patients were symptomatic, but was begun immediately after completion of the last course of treatment for a CDAD episode and before the recurrence of symptoms. The following regimens were used: oral rifaximin at a dosage of 400–800 mg daily (in 2 or 3 divided doses) for 2 weeks; 6 patients received 400 mg of oral rifamixin twice daily, 1 patient received 200 mg of oral rifamixin 3 times daily, and 1 patient received 200 mg of oral rifamixin twice daily. The Institutional Review Board for Human Studies at Loyola University Medical Center (Maywood, IL) approved the patient chart review for the study.

The clinical diagnostic test used for identifying and continuing follow-up with the patients was a toxin A immunoassay for all cases except one, for which a toxin A/B assay was employed by the hospital [7]. Follow-up stool specimens were also obtained for culture 2–4 weeks after completion of the rifaximin regimen. The stool cultures were performed at the research

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Reprints or correspondence: Dr. Stuart Johnson, Hines Veterans Affairs Hospital/151, Fifth Ave. and Roosevelt Rd., Hines, IL 60141 (sjohnson@lumc.edu).

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laboratory of 2 of the author's (S.J. and D.N.G.), using pre-reduced, selective cycloserine cefoxitin fructose agar with taurocholate supplementation, as previously reported [8]. Follow-up culture results were negative for all patients except one, from whom 2 *C. difficile* isolates were available for further analysis. Restriction endonuclease analysis typing was performed, as previously described [8]. In vitro susceptibility testing was also performed on these isolates, using the Clinical and Laboratory Standards Institute (formerly, NCCLS)–recommended reference agar dilution method for anaerobes (M11-A6) [9].

The 8 patients who underwent the rifaximin regimen ranged in age from 43 to 88 years, and all were women (table 1). The patients each had experienced 4–8 CDAD episodes prior to use of rifaximin therapy, and each had received 79–372 total days of treatment for CDAD with the following regimens: metronidazole (8 patients), vancomycin (8 patients), vancomycin in combination with rifampin (3 patients) or *S. boulardii* (3 patients), and vancomycin in tapering or pulsed doses (6 patients). Although symptoms resolved or markedly improved during the various therapies, symptoms recurred 1–59 days after completion of the previous regimen (mean, 10.5 days). The recurrent episodes were not merely bothersome diarrheal episodes, but were severely debilitating, especially in the elderly patients. For example, patient 4 was an 81-year-old woman who was hospitalized for each of the first 3 episodes of *C. difficile* with multiple watery stools, abdominal pain, and leukocytosis.

Although diarrhea recurred predictably in patients following previous CDAD treatment prior to the rifaximin regimen, 7 of the 8 patients had no further recurrence of symptoms after rifaximin therapy was given. As of 1 July 2006, the duration of follow-up ranged from 51 to 431 days. Patients 2 and 5 died of unrelated illnesses 75 and 51 days after stopping rifaximin therapy, respectively, thus defining the minimum follow-up period for the group. The rifaximin regimen was well tolerated, and no adverse events or affects were described. One patient (patient 4) had a single episode of diarrhea and incontinence 10 days after completing the rifaximin regimen and was immediately given a second 2-week course of rifaximin therapy without further recurrence of symptoms (after 9 months of follow-up). Patients 1, 2, 3, 5, and 6 had follow-up stool specimens obtained 7–40 days after completing rifaximin therapy, and all had negative results for stool toxin and culture for *C. difficile.* A follow-up stool specimen was not obtained from patient 7, and patient 8 had a negative stool toxin assay result 50 days after completing rifaximin therapy.

The patient who was given the second course of rifaximin therapy (patient 4) had stool cultures performed before the first and after the second course of rifaximin therapy, and both showed positive results for *C. difficile.* Restriction endonuclease analysis typing of the strains showed identical restriction patterns, and in vitro rifaximin susceptibility testing demonstrated an MIC of 0.0078 μg/mL for the pretreatment isolate and >256 μg/mL for the posttreatment isolate. Again, the patient had no further episodes of diarrhea.

The use of rifaximin as a follow-up therapy, or "chaser," after vancomycin treatment was remarkably effective for interrupting recurrent CDAD episodes in this very challenging group of patients, all of whom had not responded to multiple, previous

Table 1. Summary of data on recurrent *Clostridium difficile*–associated diarrhea (CDAD) episodes and treatments.

Patient	Age, years	No. of episodes of CDAD	Total duration of CDAD treatment, days	Time between episodes,[a] days ± SD (range)	Regimens[b]	Duration of symptom-free follow-up[c]
1	69	6	146	12.6 ± 10.2 (1–28)	M, M, V, V/Rf, V_t and V/Sb, V	431
2	83	7	372	6.8 ± 6.6 (1–19)	M, V_t, V/Rf(x3), V_t, V_t	75
3	80	7	196	2.3 ± 2.2 (1–6)	M/V, M, V, M, V_t, V/Sb, V	410
4	81	4	79	13.3 ± 2.9 (10–15)	M, M, V, V_t	285
5	56	5	176	9.8 ± 6.7 (4–16)	V, V, M, V_t, V	51
6	43	5	92	12.8 ± 7.3 (3–20)	M, M, V, V/Rf, V	253
7	88	4	78	24.0 ± 30.8 (1–59)	M, M, V, V	85
8	76	8	323	11.3 ± 18.9 (1–54)	M, M, M/V, M_t, M_t, V_t, V/Lac, V[d]	277
Mean value ± SD	72 ± 15.3	5.8 ± 1.5	182.8 ± 111.5	10.5 ± 12.9	…	233.4 ± 149.1

NOTE. Lac, *Lactobacillus* GG; M, metronidazole; M_t, metronidazole taper; Rf, rifampin; Sb, *Saccharomyces boulardii;* V, vancomycin; V_t, vancomycin taper and/or pulse.

[a] Time between episodes was defined as number of days without treatment for CDAD.

[b] Regimens are listed in chronological order as given.

[c] No. of symptom-free days following receipt of rifaximin therapy. Follow-up as of 1 July 2006. Patients 2 and 5 died of unrelated illnesses 75 and 51 days after completing rifaximin therapy, respectively.

[d] Patient 8 was given Sb concurrently with her third through sixth regimens and with rifaximin therapy.

treatment regimens. Although this report is an uncontrolled observation, these patients had predictable symptom relapses a mean of 11 days after stopping treatment for their previous episodes, and all of the patients had at least 1.5 months of symptom-free follow-up after completion of rifaximin therapy. The patient who had a symptomatic relapse after completion of rifaximin therapy responded to a second course of rifaximin therapy without subsequent symptoms.

The mechanism by which rifaximin may be acting is unknown. However, rifaximin was one of the most active agents tested in vitro against a large group of diverse *C. difficile* strains with a MIC_{90} of 0.015 mg/mL [6]. Like vancomycin, rifaximin is not absorbed and leads to very high fecal drug concentrations [10]. However, rifaximin has been shown to cause minimal changes in fecal flora with respect to coliforms and enterococci [11]. It is possible that the differential effects on fecal flora may have prevented recrudescence of vegetative *C. difficile* growth after rifaximin therapy but not after vancomycin therapy.

Although all patients were ultimately cured, it is concerning that the 1 patient with a symptomatic recurrence had recovery of a *C. difficile* isolate with a high MIC following her second course of rifaximin therapy. It should be noted that this was the only deviation from the planned regimen of vancomycin treatment followed by rifaximin treatment. One study showed that *C. difficile* had a low incidence of developing spontaneous rifaximin-resistant mutants—in comparison with 45 other aerobic and anaerobic pathogens tested [12]—but our experience highlights this possibility. The design of this regimen (vancomycin therapy followed by rifaximin therapy) may be important for the prevention of resistance emergence by reducing any residual *C. difficile* organisms to a low level before giving rifaximin treatment. Because of this incident, it may be prudent not to deviate from the sequential administration of vancomycin therapy followed by rifaximin therapy, although our experience is obviously limited. In our previous in vitro study of 110 *C. difficile* strains, we found 3 strains that were also highly resistant de novo [6]. It is possible that a patient with a resistant strain of *C. difficile* present before receiving rifaximin therapy might not have the same positive response to this empirical approach, as we noted. It is noteworthy, however, that prior treatment with rifampin (in combination with vancomycin) in 3 of our patients did not predict failure of the rifaximin regimen.

In summary, using rifaximin as follow-up therapy after vancomycin treatment in patients with multiple CDAD recurrences was effective in breaking the cycle of predictable recurrences following other regimens used to treat CDAD. A prospective, placebo-controlled study of this approach seems clearly warranted and should include collection of *C. difficile* isolates to assess emergence of rifaximin resistance.

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