Rifaximin for the Treatment of Active Pouchitis: A Randomized, Double-blind, Placebo-controlled Pilot Study

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Background: The efficacy of the nonabsorbable antibiotic rifaximin in patients with active acute or chronic pouchitis is unknown.

Methods: We performed a placebo-controlled pilot trial to evaluate the efficacy and safety of rifaximin in patients with active pouchitis. Eighteen patients with active pouchitis were randomized to receive oral rifaximin 400 mg or placebo 3 times daily for 4 weeks. Active pouchitis was defined as a total Pouchitis Disease Activity Index (PDAI) score = 7 points. Clinical remission was defined as a PDAI score <7 points and a decrease in the baseline PDAI score = 3 points. The primary analysis was clinical remission at week 4.

Results: Eight patients were randomized to rifaximin and 10 patients were randomized to placebo. One patient in the placebo group did not have a post-baseline efficacy evaluation and was excluded from the efficacy analysis. Two of 8 patients (25%) treated with rifaximin were in clinical remission at week 4 compared to 0 of 9 patients (0%) treated with placebo ($P = 0.2059$). None of 8 patients in the rifaximin group withdrew from the trial prior to week 4. Two of 9 patients in the placebo group withdrew prior to week 4 due to lack of efficacy and were categorized as treatment failures.

Conclusions: Clinical remission occurred more frequently in patients treated with rifaximin 400 mg 3 times daily but the difference was not significant in this pilot study. A larger trial would be required to determine if rifaximin is effective for the treatment of active pouchitis. Rifaximin was well tolerated.

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Key Words: pouchitis, antibiotics, ulcerative colitis, inflammatory bowel disease

Pouchitis is an idiopathic inflammatory disease of the ileal pouch that occurs in 15%–53% of patients who undergo total abdominal colectomy with ileal pouch–anal anastomosis (IPAA) for ulcerative colitis (UC).[1–3] This condition is the most common complication of this procedure and is characterized by increased stool frequency with variable symptoms of urgency, rectal bleeding, incontinence, malaise, fever, and lower abdominal pain.[4] The etiology of pouchitis is not well understood but indirect evidence suggests a role for fecal bacteria. The goal of creating a pouch is to create a reservoir for stool that will allow continence. The end result of pouch formation is fecal stasis in the terminal ileum. Bacteriologic studies on the fecal contents of patients with pouches and patients with end ileostomies have demonstrated that patients with pouches have higher concentrations of stool anaerobes and *Bacteroides* as compared to patients with ileostomies.[5] Small randomized trials have suggested that antibiotic therapy with metronidazole and ciprofloxacin may be effective for the treatment of active pouchitis.[6–8] However, metronidazole is poorly tolerated and treatment with systemically active antibiotics is not ideal from the perspective of the development of antibiotic resistance.

Rifaximin (Salix Pharmaceuticals, Morrisville, NC) is a poorly absorbed, non-aminoglycoside, semisynthetic antibiotic derived from rifamycin O.[9] Rifaximin exerts its antibacterial effect by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase. The antimicrobial spectrum is broad and includes coverage for both aerobic and anaerobic Gram-positive and -negative organisms. Rifaximin is approved to treat traveler's diarrhea at a dose of 600 mg per day

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and is effective for the treatment of traveler's diarrhea.[10] Because rifaximin is poorly absorbed from the gastrointestinal tract, it is theoretically an ideal antibiotic for treating the bacterial overgrowth in the lumen of the ileoanal pouch, believed to be important in the pathogenesis of pouchitis. There are several case reports and case series suggesting that rifaximin 2000 mg per day (in divided doses) in combination with ciprofloxacin 1000 mg per day is effective for the treatment of active, treatment-resistant, chronic pouchitis.[11,12]

This study was a 4-week placebo-controlled trial of rifaximin 1200 mg per day in patients with active pouchitis.

MATERIALS AND METHODS

Patients

This multicenter, randomized, double-blind, placebo-controlled study was conducted in the US at 10 sites between May 2003 and April 2004. The Institutional Review Board at each site approved the protocol. All patients gave written informed consent.

The criteria for eligibility for the trial included men and women (18 years of age or older) with a history of a total abdominal colectomy with ileal pouch anal anastomosis for UC and at the time of study enrollment had active pouchitis with a pouchitis disease activity index (PDAI) score of 7–18 points.[13] Two subgroups of patients with active pouchitis were enrolled: acute pouchitis was defined as active symptoms of pouchitis not treated with antibiotics or other medical therapy within the last 30 days; chronic pouchitis was defined as active symptoms of pouchitis treated with antibiotics or other medical therapy within the last 30 days. Women of childbearing potential consented to the use of contraception for the duration of the study. Patients were excluded if they had: infectious, ischemic, or immunologic diseases with gastrointestinal involvement; if they had clinically significant hepatic or renal disease; if they had unstable cardiovascular or pulmonary disease; if they had any condition that would prevent completion of the study including history of drug or alcohol abuse, history of mental illness, or history of noncompliance with treatments or visits; if they had participated in an investigational drug or device study within the 30 days prior to study screening; if they had an active malignancy within the last 5 years, except basal cell carcinoma of the skin, or if female, in situ cervical carcinoma that had been surgically excised; if they had evidence of Crohn's disease (clinical, endoscopic, histologic, radiographic); if they had endoscopic evidence of ileal inflammation proximal to the ileal pouch; if they had perianal disease (perianal abscess, anal fistulae, anal fissure, anal sphincter incontinence or tight anal stricture) on physical exam; if they were pregnant or breastfeeding; or if they were $<80\%$ compliant with respect to diary completion during the screening period. Concomitant therapy with antibiotics (including metronidazole, ciprofloxacin, amoxicillin/clavulanic acid, erythromycin, and tetracycline); probiotics (VSL#3, lactobacillus, etc.); sulfasalazine; olsalazine, balsalazide; rectal or oral mesalamine; rectal short chain fatty acids; rectal glutamine; loperamide; and diphenoxylate was not permitted after the patient enrolled in the study and began screening. Concomitant therapy with rectal or oral corticosteroids (including rectal or oral budesonide) was not permitted within 2 weeks of enrollment in the study. Concomitant therapy with immune-modifier therapy (azathioprine, 6-mercaptopurine, cyclosporine, methotrexate, infliximab) was not permitted within 3 months of enrollment in the study.

Study Design

Eligible patients were randomly assigned in a 1:1 ratio to receive either rifaximin (Xifaxan; Salix Pharmaceuticals) 400 mg orally 3 times daily or placebo orally 3 times daily for 4 weeks. Randomization was performed within each center according to a computer-generated randomization schedule with permuted blocks. Neither the patients nor the study investigators were aware of the treatment assignment.

Patient Schedule and Efficacy and Safety Evaluations

Patients were assessed at a screening visit (day -14 to day -7) and at weeks 0 (baseline) and 4. Flexible endoscopy of the ileoanal pouch with biopsy for histologic assessment was conducted at the baseline and week 4 visits. Disease activity was assessed with the PDAI scoring algorithm.[13] The components of the PDAI scoring system are: stool frequency, rectal bleeding, fecal urgency/abdominal cramps, fever, endoscopic findings, and histologic findings (Table 1).[13] The biopsy slides were scored in a blinded fashion by a single pathologist for all patients enrolled in the study. Complete remission was defined as a PDAI score $= 0$. Clinical remission was defined as a PDAI score <7 points and a decrease in the baseline PDAI score $= 3$ points. Symptomatic improvement was defined as a decrease from baseline in the PDAI clinical subscore $= 2$ points. Endoscopic improvement is defined as a decrease from baseline in the PDAI endoscopic subscore $= 2$ points. Disease-specific health-related quality of life was assessed with the Inflammatory Bowel Disease Questionnaire (IBDQ) scoring system at weeks 0 and 4 (total scores range from 32–224, with higher scores indicating better patient function and quality of life).[14]

The data for all 18 randomized patients were included in the safety analysis. At each visit, adverse events and medications were recorded and samples were collected for laboratory evaluations. Safety evaluations included vital signs, physical examination, hematology, and serum biochemistry.

Statistical Analysis

The primary efficacy endpoint was clinical remission at week 4. Secondary endpoints included complete remission,

TABLE 1. Pouchitis Disease Activity Index

Clinical Criteria	Score
Stool frequency	
<1.0 stools/day > than post-op usual	0
>1.0 to <3.0 stools/day > post-op usual	1
>3.0 stools/day > post-op usual	2
Rectal bleeding	
None or rare	0
Present daily	1
Fecal urgency / abdominal cramps	
None	0
Occasional	1
Frequent	2
Fever (temperature >100°F)	
Absent	0
Present	1
Endoscopic criteria	
Edema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucus exudates	1
Ulceration	1
Acute histologic criteria	
Polymorph infiltration	
None	0
Mild	1
Moderate + crypt abscess	2
Severe + crypt abscess	3
Ulceration per low power field (average)	
<25%	1
≥25% ≤50%	2
>50%	3

Pouchitis is defined as a total PDAI score ≥ 7 points. Adapted with permission from Sandborn WJ, Tremaine WJ, Batts KP, et al. Pouchitis following ileal pouch-anal anastomosis: a pouchitis disease activity index. Mayo Clin Proc 1994;69:409-415.

symptomatic improvement, endoscopic improvement at week 4, PDAI scores at weeks 0 and 4, and IBDQ scores at weeks 0 and 4. The intent-to-treat (ITT) population included all randomized patients who had a baseline efficacy evaluation, took at least 1 dose of the study medication, and had at least 1 post-baseline efficacy evaluation, either during therapy or within 3 days of the last day of treatment. Patients who prematurely withdrew from the study were included in the analyses using "last observation carried forward" methods.

To compare the proportion of patients achieving a specified endpoint, i.e., clinical remission, complete remission, symptomatic improvement, and endoscopic improvement between treatment groups, a 2-sided Fisher's exact test was used. Continuous response parameters were compared using the Wilcoxon rank sum test.

We estimated that 30 patients were needed in the rifaximin group and 30 patients in the placebo group in order to have 80% power to detect a true difference in the proportion of patients with active acute or chronic pouchitis who achieved clinical remission at week 4, assuming the proportion in the active group was 60% and that placebo was 25%. We planned to recruit a total of 66 patients.

Role of Funding Source

This study was designed by Salix Pharmaceuticals and 3 of the investigators who are authors of this article (K.L.I., R.S.S., W.J.S.). The investigators and Salix Pharmaceuticals analyzed and interpreted the data, wrote the article, and agreed to submit the article for publication. The principal investigator (K.L.I.) approved the content prior to submission.

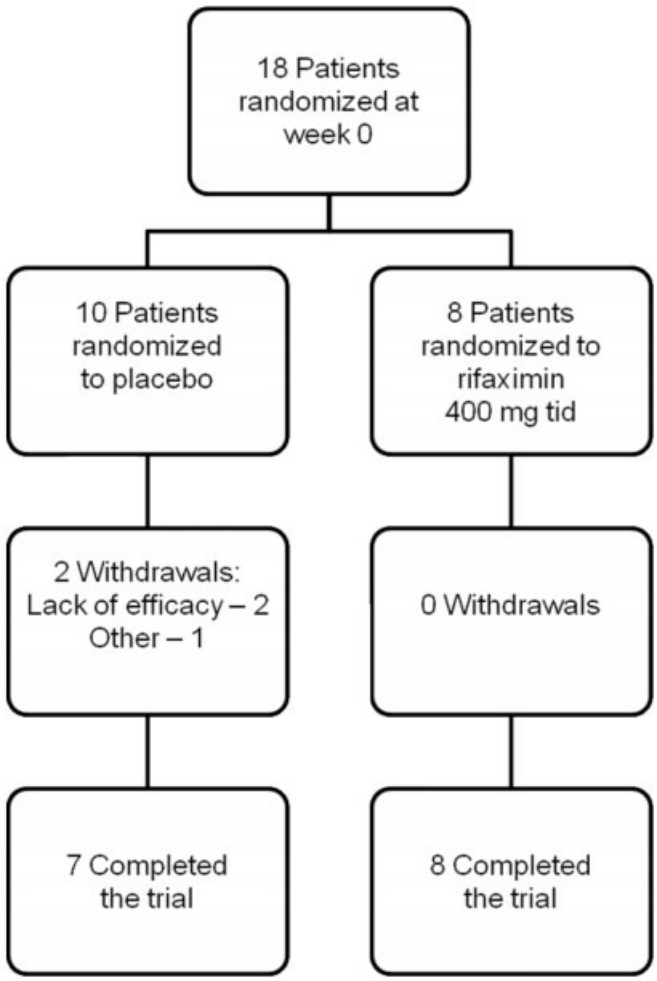

FIGURE 1. Enrollment and treatment of patients.

TABLE 2. Baseline Characteristics of All the Intent-to-Treat Population of Randomized Patients

	Placebo	Rifaximin 400 mg tid	*P*-value[a]
Number of patients randomized	9	8	
Male sex, no. (%)	8/9 (88.9)	6/8 (75)	0.58
White race, no. (%)	9/9 (100)	8/8 (100)	1.00
Age, years			
Mean (SD)	39.7 (9.5)	43.6 (12.3)	0.41
Time since colectomy with IPAA, years			
Mean (SD)	10 ± 7.63	5.75 ± 4.98	0.1891
Pouchitis subtype, no. (%)			
Acute pouchitis	3/9 (33.3)	2/8 (25)	1.00
Chronic pouchitis	6/9 (66.7)	6/8 (75)	
PDAI score (0-12)[b]Mean (SD)	9.2 (1.20)	10.6 (2.83)	0.286
IBDQ score (32-224) Mean (95% CI)	140 (121-160)	132 (110-154)	0.574
Previous medical therapies, no. (%) Antibiotics	8 (89)	8 (100)	0.53
Short chain fatty acid Enemas	1 (11)	1 (13)	0.53
5-Aminosalicylates[c]	7 (78)	7 (88)	0.41
Probiotics	1 (13)	2 (25)	0.37
NSAIDs[d]	1 (13)	4 (50)	0.10

[a] *P*-values for all categorical variables are based on Fisher's Exact test. *P*-values for continuous variables are based on the Wilcoxon rank sum test.
[b] The components of the Pouchitis Disease Activity Index (PDAI) are: stool frequency, rectal bleeding, fecal urgency/abdominal cramps, fever, endoscopic findings, and histologic findings. Values range from 0-18, with scores <7 points and a decrease ≥3 points from baseline indicating clinical remission.
[c] 5-Aminosalicylates: includes sulfasalazine, balsalazide, mesalamine.
[d] NSAIDs indicates patients who took at least 1 dose of nonsteroidal antiinflammatory medications during the trial. One patient in the placebo group took 81 mg per day of aspirin. Four patients in the rifaximin group took single doses of an NSAID for the following reasons: headaches (2 patients), menstrual cramps (1 patient); and arthralgias (1 patient).

RESULTS

Disposition and Characteristics of the Patients

Eighteen patients with active pouchitis were randomized to treatment (8 to rifaximin and 10 to placebo, respectively). One patient randomized to placebo did not have a post-baseline efficacy evaluation and was excluded from the ITT analysis. Thus, the efficacy population was comprised of 17 patients and the safety population was comprised of 18 patients. None of 8 patients in the rifaximin group withdrew from the trial prior to week 4. Two of 9 patients (22%) in the placebo group withdrew prior to week 4 (1 at day 9 and 1 at day 10) due to lack of efficacy. These 2 patients were categorized as treatment failures at week 4 (using the last observation carried forward analysis) and received rescue therapy with alternative antibiotics. A summary of patient disposition is provided in Figure 1. Enrollment in the study was terminated by the sponsor for administrative reasons before the target enrollment of 66 randomized patients was reached. The baseline characteristics were similar in the 2 treatment groups (Table 2).

Efficacy

Seventeen of 18 randomized patients were included in the efficacy analyses. At week 4, 25% (2 of 8) of patients in the rifaximin group achieved clinical remission, compared to 0% (0 of 9) of patients in the placebo group ($P = 0.211$, Fig. 2). Descriptive subgroup analyses were conducted in patients with acute pouchitis and chronic pouchitis. The clinical remission rates in the patients with acute pouchitis were 100% (2 of 2) in the rifaximin group and 0% (0 of 3) in the placebo group. The clinical remission rates in the patients with chronic pouchitis were 0% (0 of 7) of patients in the rifaximin group and 0% (0 of 6) in the placebo group. There were no

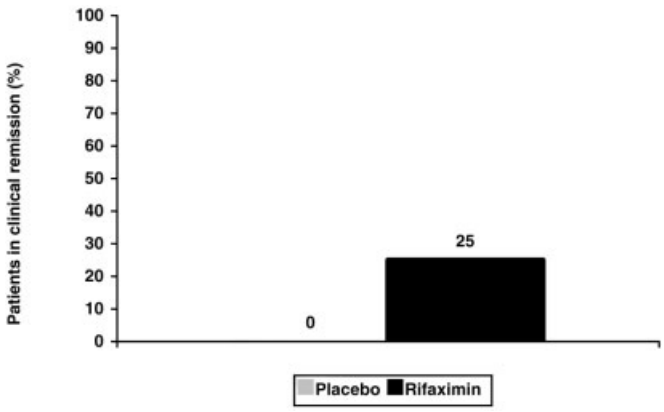

FIGURE 2. The proportions of patients at week 4 with clinical remission.

TABLE 3. Secondary Efficacy Measures in the Intent-to-Treat Population of Randomized Patients

	Placebo	Rifaximin 400 mg tid	*P*-value[a]
Number of patients randomized	9	8	
Complete remission, no. (%)	0/9 (0)	0/8 (0)	—
Symptomatic improvement, no. (%)	3/9 (33)	3/8 (38)	1.00
Endoscopic improvement, no. (%)	2/9 (22)	1/8 (13)	1.00
Change from baseline in PDAI scores (0-12)[b] Mean (SD)	0.9 (2.37)	–1.6 (2.67)	0.057

[a] *P*-values for all categorical variables are based on Fisher's Exact test. *P*-values for continuous variables are based on the Wilcoxon rank sum test.
[b] The components of the Pouchitis Disease Activity Index (PDAI) are: stool frequency, rectal bleeding, fecal urgency/abdominal cramps, fever, endoscopic findings, and histologic findings. Values range from 0-18, with scores <7 points and a change ≥3 points from baseline indicating clinical remission.

significant differences in the rates of complete remission, symptomatic improvement, or endoscopic improvement between the 2 treatment groups (Table 3). However, the mean change from baseline in PDAI scores was greater in the rifaximin treatment group (−1.67 points) than in the placebo treatment group (+0.9 points), and this difference approached statistical significance (0.057) (Table 3). In the rifaximin group the median IBDQ score (95% CI) was 132 (110–154) at week 0 and 136 (112–160) at week 4 ($P = 0.80$). In the placebo group the median IBDQ score was 140 (121–160) at week 4 and 140 (124–155) at week 4 ($P = 0.96$).

Safety

All 18 randomized patients received at least 1 dose of study agent and were included in the safety analyses. The proportions of patients with treatment emergent adverse events were generally similar in the placebo and rifaximin groups (Table 4). The incidence of any treatment emergent adverse event was similar in the placebo (5 patients) and rifaximin (6 patients) groups. No patients in either group discontinued treatment because of an adverse event. No patients in either group experienced a serious adverse event.

DISCUSSION

The results of this randomized, placebo-controlled pilot study failed to demonstrate a statistically significant clinical benefit of monotherapy with rifaximin 1200 mg per day to treat active acute or chronic pouchitis. However, clinical remission occurred in 25% of the rifaximin-treated patients and none of the placebo-treated patients; the mean change from baseline in the PDAI was greater in the rifaximin-treated patients than in the placebo-treated patients, and this difference approached statistical significance. Descriptive subgroup analyses showed that the clinical remission rates in the patients with acute pouchitis were 100% (2 of 2) in the rifaximin group and 0% (0 of 3) in the placebo group; the clinical remission rates in the patients with chronic pouchitis were 0% (0 of 7) of patients in the rifaximin group and 0% (0 of 6) in the placebo group. There was no difference in disease-specific health-related quality of life between week 0 and week 4 in either the rifaximin or placebo groups. Rifaximin was generally well tolerated in a patient population with active pouchitis.

There are several potential reasons for the negative

TABLE 4. Summary of Safety Analyses for All Randomized Patients Through Week 4

	Placebo	Rifaximin
No. of patients randomized	10	8
Adverse events, no. of patients (%)	5 (50)	6 (75)
Adverse events occurring at frequency of at least 10% in any treatment group, no. of patients (%)		
Ear pain		
Eye irritation	1 (10)	0 (0)
Abdominal pain	1 (10)	0 (0)
Defecation urgency	3 (30)	0 (0)
Diarrhea	1 (10)	0 (0)
Flatulence	1 (0)	1 (12.5)
Frequent bowel movements	0 (0)	1 (12.5)
Nausea	1 (10)	0 (0)
Proctalgia	1 (0)	1 (12.5)
Rectal hemorrhage	0 (0)	1 (12.5)
Vomiting	1 (10)	0 (0)
Thirst	1 (10)	1 (12.5)
Candida	0 (0)	1 (12.5)
Upper respiratory tract infection	0 (0)	1 (12.5)
Arthropod bite	0 (0)	1 (12.5)
Hepatic enzyme increased	1 (10)	0 (0)
Cluster headache	0 (0)	1 (12.5)
Headache	0 (0)	1 (12.5)
Pharyngeolaryngeal pain	1 (10)	0 (0)
Acne	0 (10)	0 (0)
Rash	1 (10)	0 (0)
Mole excision	1 (10)	0 (0)
	1 (0)	0 (0)

outcome of this study. First, the number of patients in this study was small. A total of 18 patients were randomized into the study, which was only 27% of the planned enrollment. Differences in clinical remission rates may not have been detected due to type 2 statistical error. Second, the study population phenotype was mixed, including patients with both acute and chronic pouchitis (based on treatment within the past 30 days). In the descriptive subgroup analyses, 2 of 2 patients with active acute pouchitis treated with rifaximin entered clinical remission. It is possible that patients with chronic pouchitis may be more difficult to treat. Third, the dose of rifaximin may have been too low to treat pouchitis. In previous open-label pilot studies combination therapy with high dose rifaximin (2000 mg per day) and ciprofloxacin (1000 mg per day) appeared to be of clinical benefit.[11,12] Finally, there is the possibility that rifaximin is not effective for the treatment of active pouchitis.

Rifaximin was well tolerated. There were few adverse events and most were related to pouchitis disease activity including abdominal pain and diarrhea. There were no apparent differences in the frequency of adverse events between the rifaximin and placebo groups.

In conclusion, in this small, placebo-controlled pilot study, clinical remission occurred more frequently in patients treated with rifaximin 400 mg 3 times daily but the difference did not reach statistical significance. In addition, the absolute change in PDAI from baseline was greater in the rifaximin-treated group (−1.6 vs. 0.9) and was trending toward a significant difference ($P = 0.057$). A larger trial would be required to determine if rifaximin is effective for the treatment of active pouchitis. Rifaximin was well tolerated.

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