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ORIGINAL ARTICLE

Adjunctive Antibiotic Therapy with Rifaximin May Help Reduce Crohn's Disease Activity

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Abstract
Aims Enteric bacteria are thought to contribute to the pathogenesis of Crohn's disease, and antibiotics may be an effective therapy. This study examines the efficacy of the nonsystemic (<0.4% absorbed) antibiotic rifaximin for inducing remission in patients with Crohn's disease.
Methods Data from charts of patients with Crohn's disease who received rifaximin between 2001 and 2005 and had a Crohn's disease activity index score ≥220 at the time of rifaximin initiation were analyzed. The use of concomitant medications (e.g., steroids, anti-inflammatory agents) was allowed.
Results In the 68 patient charts analyzed, the median duration of rifaximin treatment was 16.6 weeks, and the majority of patients (94%) received rifaximin 600 mg/day. Eighteen patients (26%) received rifaximin monotherapy, and 31 patients (46%) received concomitant steroids. The median baseline Crohn's disease activity index score at the time of rifaximin initiation was 265 (range, 220–460), and the mean duration of Crohn's disease was 17 years (range, 1–50 years). Crohn's disease remission occurred in 65% of patients. A 70% remission rate was achieved in patients who did not receive steroids, versus 58% in patients who received steroids. Clinical improvements continued 4 months after rifaximin initiation. Remission was achieved in 67% of patients who received rifaximin monotherapy.
Conclusions Rifaximin therapy was associated with clinical improvement in patients with Crohn's disease and may be a useful treatment option to consider for inducing and maintaining remission.

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Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) characterized by discontinuous lesions of the gastrointestinal (GI) tract. Increasing evidence indicates that enteric bacteria may play a role in the pathogenesis of IBD, particularly CD [1–4]. The prevailing hypothesis for the etiology of CD involves chronic activation of the mucosal immune system caused by decreased immunologic tolerance to commensal luminal bacteria in genetically susceptible individuals [2, 4, 5]. In addition to normal intestinal flora, bacterial pathogens may also contribute to the pathogenesis of CD. In a clinical study of 303 patients with CD, individuals with the highest levels of immune reactivity to bacterial antigens experienced the greatest severity of disease complications, including strictures, internal perforations, and requirement for small-bowel surgery [6].

The suggested role of enteric bacteria in CD pathogenesis provides a solid rationale for investigating antibiotic therapy as treatment for this illness. However, there is a paucity of data demonstrating that systemic antibiotics are effective as primary therapy for CD. A small number of clinical studies have demonstrated the efficacy of systemic antibiotics in the treatment of CD with conflicting results [7–15]. Furthermore, systemic antibiotics have a poor tolerability profile, and long-term exposure to metronidazole is associated with serious adverse effects such as nausea and peripheral neuropathy [16].

The oral, nonsystemic, gut-selective antibiotic rifaximin has favorable characteristics that make it a suitable choice for the treatment of CD. Rifaximin is a minimally absorbed (<0.4%) antibiotic that concentrates in the GI tract and is primarily excreted in the feces [17]. In addition, rifaximin has broad-spectrum in vitro activity against enteric bacteria, a tolerability profile comparable with placebo in studies of infectious diarrhea [18, 19], no known drug–drug interactions, and a lack of clinically relevant antibiotic resistance [20]. In an animal model of IBD, rifaximin prevented translocation of intestinal bacteria to mesenteric lymph nodes, reduced the development of colitis, and accelerated disease healing [21]. In an open-label preliminary assessment ($n = 29$), rifaximin 600 mg daily for 4 months reduced the Crohn's disease activity index (CDAI) score [22] by 43% compared with pretreatment (i.e., baseline) and resulted in a ≥70-point improvement in CDAI score in 78% of patients, and induced clinical remission (CDAI score <150) in 59% of patients [23]. Furthermore, a double-blind, randomized, placebo-controlled trial of patients with mild-to-moderate CD ($n = 79$) demonstrated that rifaximin 1,600 mg/day achieved clinical remission (CDAI score ≤150) in 52% of patients and a clinical response (≥70-point reduction in baseline CDAI score) in 67% of patients [24]. The purpose of this retrospective analysis was to assess the efficacy of rifaximin (monotherapy or in combination with other therapies) in inducing remission in patients with CD, as measured by improvement in CDAI score from baseline.

Methods

Chart Selection

This retrospective analysis evaluated adults with CD treated with rifaximin (Xifaxan, Salix Pharmaceuticals, Inc., Morrisville, NC) between 2001 and 2005 at the Shafran Gastroenterology Center in Winter Park, Florida. Patients received rifaximin because of patient opposition to treatment with immunosuppressants or biologic therapies or because of failure of other treatment regimens. In some cases, rifaximin was administered as therapy in patients with short durations of CD (≤1 year), based on the results of a previous study that showed rifaximin to be effective in this patient population [23]. All patients with CD were routinely assessed for CDAI upon initial administration of rifaximin at the center and during subsequent follow-ups; therefore, CDAI score was used to select patients with similar CD severity. Medical records of all patients with CDAI scores ≥220 at the time of initiation of rifaximin therapy were abstracted for demographic data, history of disease, medications used to treat CD, primary disease location, severity of disease complications, and surgical events related to CD. Concomitant medications were permitted.

Primary and Secondary Endpoints

The primary endpoint of this analysis was successful remission in patients with CD treated with rifaximin (monotherapy or in combination with other therapies), with remission defined as a CDAI score <150. Secondary endpoints included overall improvement in CDAI score, as determined by ≥70-point and by ≥100-point reductions from baseline. Patients were categorized as achieving remission or improvement if their CDAI scores satisfied criteria for these endpoints at any time during treatment.

Statistical Analyses

Data for all variables collected for this review were summarized using descriptive statistics. Continuous variables (e.g., age, CDAI scores) were summarized using n, mean, standard deviation, minimum, median, and maximum values. Categorical variables (e.g., sex, remission) were summarized using the number and percentage of patients in each category. Patients' CDAI scores were summarized at baseline and by treatment month for up to 6 months and were calculated as the last observation recorded in each 1-month interval starting from baseline. Subgroup analyses included patients taking steroids or other concomitant medications, disease location (e.g., small intestine, large intestine, rectum/anus, small intestine only, large intestine only, multiple locations), and patients taking rifaximin only. Additionally, data from the subgroup of patients with disease in the small intestine only and taking rifaximin only were summarized.

Results

Patient Population

A total of 68 patients with CD were identified (Table 1), and the mean duration of disease was 17 years. The majority of patients had disease localized to the small or large intestine, and 56% of patients had undergone previous surgery. The median baseline CDAI score was 265 (range, 220–460), and 50% of patients were characterized as having fistulizing disease. All 68 patients were treated with rifaximin, with treatment lasting a median of 16.6 weeks (range, 0.4–134.9 weeks). Most patients (94%) received rifaximin at a dose of 600 mg/day (range, 200 mg three times weekly to 200 mg three times daily). Thirty-one patients (46%) were also treated with steroids at least

Table 1 Patient demographics and baseline characteristics

Characteristic	Patients ($n = 68$)
Age, mean (range), year	48 (22–82)
Male:female, %	44:56
Duration of CD, mean (range), year	17 (1–50)
Baseline CDAI score, median (range)	265 (220–460)
≥1 prior GI surgical event, *n* (%)	38 (56)
Primary disease location, *n* (%)	
Small intestine	51 (75)
Small intestine only	17 (25)
Large intestine	45 (66)
Large intestine only	11 (16)
Rectum/anus	15 (22)
>1 disease location	38 (56)
Disease complication, *n* (%)	
Fistula	34 (50)
Ulceration	33 (49)
Liver/biliary disease	0
Other	29 (43)
Rifaximin	
Any dose, *n* (%)	68 (100)
Duration of therapy, median (range), week	16.6 (0.4–134.9)
Monotherapy, *n* (%)	18 (26)
Duration of therapy, median (range), week	12.9 (2.1–75.4)
Concomitant medication, *n* (%)	
Steroid	31 (46)
Anti-inflammatory agent	19 (28)
Antibiotic (other than rifaximin)	8 (12)
Biologic	11 (16)
Antidiarrheal agent	13 (19)
Immunomodulator	7 (10)
Other	4 (6)

CD Crohn's disease; *CDAI* Crohn's disease activity index; *GI* gastrointestinal; *t.i.d.* three times daily

once during rifaximin therapy (2–40 mg for median treatment time of once daily). Other concomitant medications administered included antibiotics, anti-inflammatory agents, biologics (e.g., infliximab), antidiarrheal agents, and immunomodulators. If prescribed, infliximab intravenous infusions of 5–10 mg/kg were administered every 8 weeks, and oral immunomodulators were administered 75–300 mg once daily. Eighteen patients received rifaximin monotherapy for a median of 12.9 weeks (range, 2.1–75.4 weeks) without any concomitant therapy.

Induction of Clinical Remission

During rifaximin treatment, clinical remission was achieved in the majority of patients. Overall, induction of CD remission was reported in 44 patients (65%; Fig. 1). Analyses indicated that a similar remission rate was achieved in patients with CD primarily in the small intestine only (11 of 17 patients [65%]) and in patients with CD in multiple locations (25 of 38 patients [66%]). A slightly lower remission rate was observed in patients with CD primarily in the large intestine only (6 of 11 patients [55%]; Fig. 1). Furthermore, a slightly higher rate of remission was achieved in patients who did not receive steroids (26 of 37 patients [70%]) and in patients who received concomitant medications other than steroids (24 of 37 patients [65%]) compared with the remission rate for patients who received steroids (18 of 31 patients [58%]; Fig. 1). Clinical remission was also observed in 12 of 18 patients (67%) who received rifaximin without concomitant therapies.

Secondary Endpoints

In addition, substantial reductions from baseline CDAI scores were noted during rifaximin treatment. A ≥70-point reduction from baseline CDAI score was observed in 34 of 68 patients (50%) treated with rifaximin, and a ≥100-point reduction was observed in 29 of 68 patients (43%) treated with rifaximin (Table 2). Similar frequencies of patients with ≥70-point and ≥100-point reductions from baseline CDAI scores were observed among patients with CD localized primarily to the small or large intestine only and among patients who received rifaximin monotherapy (Table 2). Furthermore, consistently greater monthly improvements from baseline CDAI scores occurred through at least 4 months after initiation of rifaximin therapy, suggesting that rifaximin may be beneficial in maintaining remission of CD (Fig. 2). Improvements in CDAI scores were observed in all patients regardless of disease location or concomitant administration of steroids or other medications.

Discussion

The rationale for administering antibiotic therapy for the treatment of CD is based on increasing evidence implicating intestinal bacteria in the pathogenesis of this disease. Findings from animal models of IBD support this rationale [21, 25]. Additionally, a case-crossover study ($n = 1,205$) conducted from 1989 to 1997 found that previous antibiotic exposure within 60 days significantly reduced the risk of flare of CD ($p = 0.019$) [26]. Although systemic antibiotics are often prescribed for short-term treatment of CD in clinical practice, clinical studies demonstrating favorable efficacy are limited and conflicting [7–15]. One double-blind crossover study reported no difference in the overall clinical condition between metronidazole 1 g daily

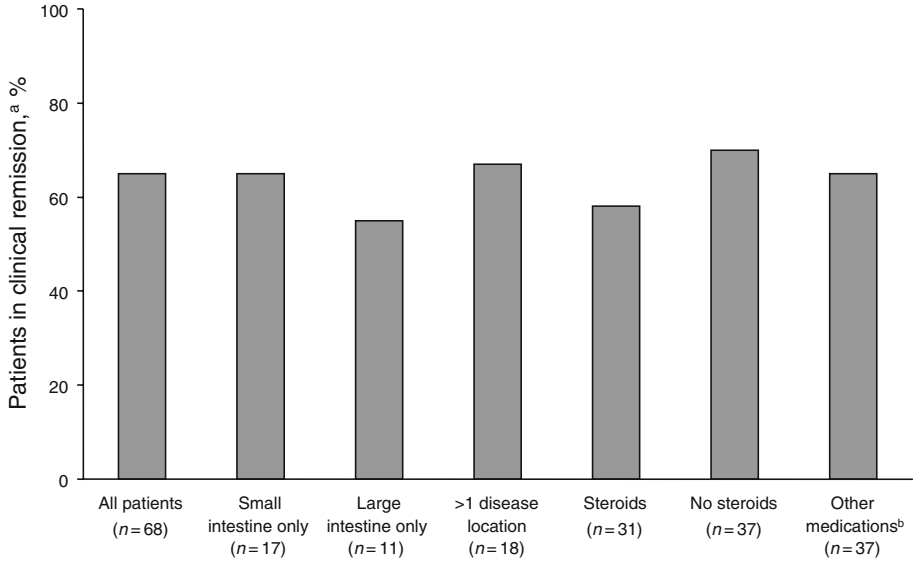

Fig. 1 Induction of clinical remission in patients with Crohn's disease taking rifaximin, stratified by disease location and concomitant medication. [a] Clinical remission defined as Crohn's disease activity index score <150. [b] Concomitant medications other than steroids

Table 2 Clinical improvement in Crohn's disease stratified by disease location and concomitant medication

Patient group	*n*	Patients, *n* (%)	
		CDAI score reduction by ≥70 points	CDAI score reduction by ≥100 points
All patients	68	34 (50)	29 (43)
Steroid therapy	31	15 (48)	13 (42)
No steroid therapy	37	19 (51)	16 (43)
Concomitant medication other than steroid therapy	37	20 (54)	17 (46)
Rifaximin monotherapy	18	9 (50)	7 (39)
Small intestine only	17	8 (47)	7 (41)
Large intestine only	11	6 (55)	4 (36)
>1 disease location	38	19 (50)	17 (45)

CDAI Crohn's disease activity index

and placebo treatments in 20 patients with active CD [9]. In a later, randomized, placebo-controlled study ($n = 105$), daily doses of metronidazole 10 or 20 mg/kg reduced CDAI scores in 56 patients with CD after 16 weeks of treatment but failed to induce clinical remission (CDAI score <150) [14]. In that study, metronidazole was effective in the treatment of colonic or ileocolonic disease but was not beneficial in patients with CD localized to the small bowel. In contrast, a prospective, randomized, placebo-controlled study ($n = 72$) that evaluated the efficacy of metronidazole 800 mg daily in CD demonstrated no significant benefit regardless of disease location [7]. Ciprofloxacin and metronidazole combination therapy is also commonly administered for the management of CD, despite clinical findings from two randomized, controlled trials that showed a lack of significant benefit versus corticosteroid therapy or budesonide monotherapy for induction of remission in patients with CD [12, 13].

Studies of antibiotic efficacy in the maintenance of CD remission are also limited. Results of a double-blind study ($n = 51$) showed that oral metronidazole 20 mg/kg daily for 3 months significantly reduced clinical recurrence versus placebo ($p = 0.044$) at 1 year in patients who had prior resection of all inflamed bowel sections [27]. However, metronidazole is not widely prescribed for long-term treatment due to its poor tolerability profile and risk of serious adverse effects, including nausea and peripheral neuropathy [16, 25]. In an additional randomized, double-blind study of patients with CD ($n = 78$), the oral antibiotic ornidazole 1 g daily significantly reduced the clinical recurrence rate of CD at 1 year versus placebo ($p = 0.0046$) [28]. However, significantly more patients in the ornidazole group discontinued the study because of adverse effects compared with the placebo group ($p = 0.041$). To date, ciprofloxacin has not been evaluated in a randomized controlled trial for prevention of recurrence of postoperative CD [16].

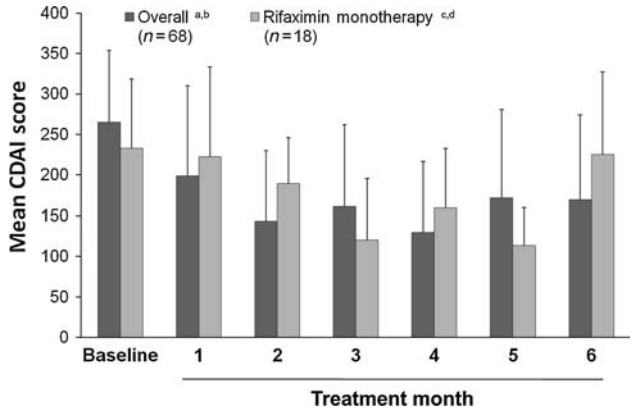

Fig. 2 Crohn's disease activity index scores stratified by month. Data represent the duration of time after initiation of rifaximin therapy and were calculated for each month as the last observation recorded in each 1-month interval starting from baseline. *Error bars* represent standard deviation. [a] Patients who received rifaximin and other concomitant medications. [b] Duration of therapy ranged from 0.4 to 134.9 weeks (median, 16.6 weeks). [c] Patients who received rifaximin without concomitant therapies. [d] Duration of therapy ranged from 2.1 to 75.4 weeks (median, 12.9 weeks). *CDAI* Crohn's disease activity index

Rifaximin, a nonsystemic antibiotic with broad-spectrum antimicrobial activity, might offer a better alternative for induction and maintenance of CD remission because of its favorable tolerability profile [18, 19]. Rifaximin is indicated for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* and is also being investigated in several other GI conditions, including pouchitis, *Clostridium difficile* infection, and ulcerative colitis. Findings from two previous clinical studies indicate that rifaximin might prove beneficial in reducing the severity of symptoms and inducing clinical remission in patients with CD [23, 24]. In addition, rifaximin monotherapy improved both GI symptom severity and small-intestinal mucosa healing in three patients with CD [29].

In the current retrospective review, clinical remission was achieved in 65% of all patients with CD, with a slightly greater percentage of patients who did not receive steroids (70%) achieving remission than patients who received steroids (58%). The reason for this slight discrepancy is unknown but may be due to factors such as increased disease severity, age, or disease duration in patients who received concomitant steroids. The results of the current study also demonstrated that 67% of patients who received rifaximin without concomitant therapy achieved remission, suggesting that rifaximin therapy alone is capable of inducing remission of CD.

The retrospective nature of this study did not allow the evaluation of the direct contribution of rifaximin because concomitant medications were allowed; however, the results of this study suggest that treatment with rifaximin, with or without steroids, may be beneficial in patients with CD who receive a variety of medications. This study also permitted the inclusion of patients receiving different dosing regimens of rifaximin, which may affect the overall efficacy reported, but the majority of patients (94%) in this study received rifaximin 600 mg/day, suggesting that this dose is beneficial in patients with CD.

Selection bias for study inclusion may be a concern, because of the retrospective nature of the study, but inclusion of only patients with CDAI score $\geq$220 should have prevented such bias. Of greater concern may be bias in the initial selection of patients to receive rifaximin therapy. This selection was based on several factors, including patient preference (i.e., opposition to other therapies), nonresponse to other treatments, and published results of rifaximin use in patients [23], which may be representative of a typical clinical process for assigning appropriate therapies. Finally, the open-label nature of this study may have elicited bias in assessing patient improvement; however, this is difficult to determine because data on patient improvement after placebo or other antibiotic therapy were not available for comparison. Because of these limitations, we recommend that additional studies examine the efficacy of rifaximin in treating CD.

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