Rifaximin-Extended Intestinal Release Induces Remission in Patients With Moderately Active Crohn's Disease

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BACKGROUND & AIMS: Bacteria might be involved in the development and persistence of inflammation in patients with Crohn's disease (CD), and antibiotics could be used in therapy. We performed a clinical phase 2 trial to determine whether a gastroresistant formulation of rifaximin (extended intestinal release [EIR]) induced remission in patients with moderately active CD. **METHODS:** We performed a multicenter, randomized, double-blind trial of the efficacy and safety of 400, 800, and 1200 mg rifaximin-EIR, given twice daily to 402 patients with moderately active CD for 12 weeks. Data from patients given rifaximin-EIR were compared with those from individuals given placebo, and collected during a 12-week follow-up period. The primary end point was remission (Crohn's Disease Activity Index <150) at the end of the treatment period. **RESULTS:** At the end of the 12-week treatment period, 62% of patients who received the 800-mg dosage of rifaximin-EIR (61 of 98) were in remission, compared with 43% of patients who received placebo (43 of 101) ($P = .005$). A difference was maintained throughout the 12-week follow-up period (45% [40 of 89] vs 29% [28 of 98]; $P = .02$). Remission was achieved by 54% (56 of 104) and 47% (47 of 99) of the patients given the 400-mg and 1200-mg dosages of rifaximin-EIR, respectively; these rates did not differ from those of placebo. Patients given the 400-mg and 800-mg dosages of rifaximin-EIR had low rates of withdrawal from the study because of adverse events; rates were significantly higher among patients given the 1200-mg dosage (16% [16 of 99]). **CONCLUSIONS: Administration of 800 mg rifaximin-EIR twice daily for 12 weeks induced remission with few adverse events in patients with moderately active CD.**

Keywords: Nonabsorbed Antibiotic; IBD; Inflammation; Intestinal Microbiota.

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There is considerable experimental evidence supporting the hypothesis that an altered immune response to commensal intestinal flora in genetically susceptible individuals plays a key role in the development and maintenance of the intestinal inflammation in patients with Crohn's disease (CD). Some researchers also suggest that patients with CD harbor abnormal intestinal microbiota able to trigger the chronic intestinal inflammation that characterizes CD.[1–4] Mutations in microflora-sensing genes, such as NOD2/CARD15, could explain individual susceptibility to the resident flora, leading to up-regulation of mucosal cytokine production and delayed bacterial clearance, thereby promoting and perpetuating inflammation.[5] Although this opens up the possibility that antibiotics could interrupt the pathway of "bacterial exposure-plus-susceptibility genes," [6–8] the results obtained in previous trials with antibiotics for the treatment of CD have been controversial.[9–19] Guidelines, therefore, do not recommend the use of antibiotics except for the treatment of septic complications in patients with CD.[20] In addition, long-term use of systemic antibiotics such as metronidazole and ciprofloxacin is complicated by an elevated number of adverse events (AEs).[16,20,21]

Rifaximin is an oral, minimally absorbed (<0.4% of the dose), nonsystemic, antimicrobial agent that exerts its bactericidal activity in the intestinal lumen. Rifaximin has a broad-spectrum in vitro activity against gram-positive and gram-negative bacteria.[22–26] Safety and efficacy of rifaximin for the treatment of intestinal bacterial infections,[26] irritable bowel syndrome,[27] and hepatic encephalopathy[28] has been demonstrated in controlled trials. Recent experimental evidence has suggested that rifaximin's mechanism of action might not be limited to a direct bactericidal activity: rifaximin has been reported to decrease in vitro the adhesion of pathogenic bacteria to the intestinal mucosa[29,30] and to protect against experimental colitis in murine models, probably through down-regulation of the nuclear factor-κB-mediated expression of proinflammatory factors.[31]

Abbreviations used in this paper: AE, adverse event; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; EIR, extended intestinal release; FA, full analysis; OR, odds ratio.

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Rifaximin-EIR (Alfa Wassermann SpA, Bologna, Italy) is a new pharmaceutical formulation that contains microgranules of rifaximin (400 mg) coated with a gastric acid-resistant polymer. This formulation has been designed to bypass the stomach and to release the microgranules in the intestinal tract, thereby increasing the local concentration of rifaximin, to maximize the therapeutic efficacy of the drug. In an exploratory placebo-controlled trial, rifaximin-EIR 800 mg twice daily given for 3 months has shown itself to be significantly superior to placebo in a subgroup of patients with mild to moderately active CD and an elevated level of C-reactive protein (CRP).[32]

To confirm the safety and efficacy of rifaximin-EIR in patients with moderately active CD, we performed a dose-escalation trial to compare 3 different dosages of rifaximin-EIR (400, 800, and 1200 mg twice daily).

Materials and Methods

This multicenter, randomized, double-blind, placebo-controlled trial was conducted at 55 centers across France, Germany, Hungary, Israel, Italy, Poland, and Russia, between September 2007 and September 2009.

The protocol was approved by the Institutional Review Boards/Ethics Committees at each center, and all patients gave written informed consent. The study was conducted according to the European Clinical Trials Directive (EudraCT number: 2007-001014-17) and registered with ClinicalTrials.gov (number: NCT00528073).

Patients

Adults aged between 18 and 75 years with active CD localized in the ileum and/or colon, documented either radiologically or endoscopically more than 3 months before entry into the study were enrolled. At the screening visit, the inclusion criteria were moderately active disease, as defined by a Crohn's Disease Activity Index (CDAI) score of 220 to 400 points. Patients were excluded if they had short-bowel syndrome, an ostomy, obstructive symptoms with strictures, abscess, active perianal disease, positive stool culture for common pathogenic bacteria, a history of drug or alcohol abuse, mental illness, concomitant immunological, hematological or neoplastic disease, severe hepatic insufficiency (Child C), and severe cardiac insufficiency (III-IV New York Heart Association classes). Subjects who were treated with anti-tumor necrosis factor agents within the previous 6 months, systemic or local steroids in the preceding 30 days, and antibiotics less than 15 days before screening, were also excluded from the study. Patients could receive concomitant therapy with stable dosages for at least 12 weeks before screening of mesalamine, thiopurines, methotrexate, and probiotics. Dosages of concomitant medications had to be maintained constant throughout the full duration of the trial. Initiation of biologicals, steroids, or antibiotics during the study or any increases in the dosage of the permitted concurrent therapies was considered a treatment failure. Anti-diarrheals were allowed, provided their use was included in the calculation of a patient's CDAI.

Study Design and Procedures

Rifaximin-EIR (multiples of 400-mg tablets to give 400-, 800-, or 1200-mg dosages) or placebo was administered orally twice daily for 12 weeks. Patients in remission at the end of the treatment period were followed for an additional 12 weeks. Before baseline assessment, patients underwent a 2-week screening period. At the baseline visit, all eligible patients were centrally randomized to rifaximin-EIR 400 mg twice daily, rifaximin-EIR 800 mg twice daily, rifaximin-EIR 1200 mg twice daily, or placebo, using the Interactive Voice Response System, which assigned each patient to a treatment group and a unique 5-digit randomization number, based on the predefined randomization list and prepared using permuted blocks of size 8. Randomization was stratified by country. Interactive Voice Response System provided the Investigator with the number of the medication package to be administered to each patient.

Each patient was provided with a diary card to be completed the week before visits to the clinic with the items necessary to calculate the CDAI.

Patients were assessed in the clinic at weeks 0, 2, 4, 8, and 12 during the treatment period, and at weeks 14 and 24 during the follow-up period.

Standard laboratory tests, including hematology, biochemistry, and urinalysis, together with measurement of serum CRP protein, were performed at screening, randomization, and at weeks 4, 8, 12 and 24. Serum CRP levels were analyzed centrally by a turbidimetric high-sensitivity assay.

Efficacy End Points

The primary study end point was the remission rate, defined as percentage of patients with a CDAI score <150 points at week 12. Secondary end points were as follows: the proportion of patients in clinical response, defined as a reduction in CDAI score of 100 points at week 12; the proportion of patients who maintained clinical remission at week 14 and 24; "treatment failure," defined as failure to achieve a decrease of at least 70 points in CDAI score after 1 month of treatment, or an increase in CDAI score of >100 points from the baseline at any time during the study period, or rescue medication and/or surgery being necessary.

Safety Evaluations

AEs were monitored throughout the study. The duration and intensity of each event were recorded by the investigator, together with its relationship to the study drug, and its outcome and seriousness.

Statistical Analysis

The full analysis (FA) and safety sets of data included all patients randomized who received at least 1 dose of the placebo and/or rifaximin-EIR. The per-protocol dataset included all patients in the FA dataset with at least 1 post-baseline CDAI evaluation and without major protocol violations.

Baseline characteristics were compared using χ^2 test for categorical variables and analysis of variance for continuous variables. Clinical remission rate and response rate to the 3 dosages of rifaximin-EIR and placebo were compared using χ^2 test. For the primary end point, adjustment for multiplicity was performed using the Bonferroni-Holm procedure.[33] All comparisons were made at the 2-sided significance level of .05. In addition, the proportion of patients in remission in each study group (FA dataset) was compared with the use of a logistic regression with adjustment for country, age, sex, disease duration, smoking habit, baseline CRP, location of disease, and previous surgery.

For the primary end point, patients without any CDAI score after the baseline assessment were classified as nonresponders. CDAI values were analyzed by carrying forward the last available value in patients without a CDAI score at the end of treatment. CDAI values at each visit were compared using an analysis of variance with repeated measurements. The clinical response was

evaluated, considering withdrawals due to treatment failure as nonresponders, and excluding all other patients without a CDAI score at the end of treatment. For maintenance of clinical remission, no CDAI value was carried forward and patients without a CDAI score at week 14 and/or week 24 were excluded from the analysis.

A post-hoc explorative subgroup analysis was performed to examine the relationship between primary end point and disease location, CRP at baseline, and disease duration. The median duration of the disease was considered as a cutoff value for the analysis. The duration below the median was defined as early-stage disease. The cutoff value was 5 mg/L of CRP according to the upper reference normal range.

The percentage of patients affected by AEs was compared between the 4 study groups by means of the exact version of the 2-sided Cochran Armitage trend test, used the planned dosages (0, 400, 800, 1200 mg twice daily) as scores.[34]

For the primary end point of a remission rate at week 12, we estimated that 410 patients (including dropout rate of 20%) would need to provide a power of 90% to detect a difference of 24% between the most effective rifaximin dose and placebo, assuming a clinical remission rate of 50% in the patients who received the most effective dose of rifaximin-EIR and 26% in the placebo group.[35]

Results

Characteristics and Disposition of Patients

A total of 402 patients received at least 1 dose of study drug: 101 patients in the placebo group, 104 patients in the rifaximin-EIR 400 mg twice daily group, 98 patients in the rifaximin-EIR 800 mg twice daily group, and 99 patients in the rifaximin-EIR 1200 mg twice daily group. Eight patients were excluded from the analysis because they did not take the study drug.

Thirty-six patients (9%) were not included in the per-protocol population due to at least one major protocol violation: 7 (7%) patients in the placebo group, 6 (6%) in the rifaximin-EIR 400 mg twice daily group, 10 (10%) in the rifaximin-EIR 800 mg twice daily group, and 13 (13%) in the rifaximin-EIR 1200 mg twice daily group. Among these, 13 patients did not have any valid post-baseline CDAI evaluation, 13 patients had a compliance of <75%, 4 patients did not have eligibility criteria, and 2 patients received a wrong medication kit.

The distribution and progression of patients through the study is shown in Figure 1. The characteristics of patients at baseline were well balanced among the groups (Table 1). Mean CDAI was 278. The median duration of disease, considered as a cutoff value to differentiate early- from late-stage disease, was 3 years.

Overall, 73% of patients received concomitant CD-specific drugs maintained at stable dose throughout the study (23% of patients were on immunosuppressive agents and 61% on mesalamine). Treatments for CD during the year before screening are listed in Table 1.

Efficacy

Primary end point. Significantly more patients in the FA set who received 800 mg rifaximin-EIR twice daily

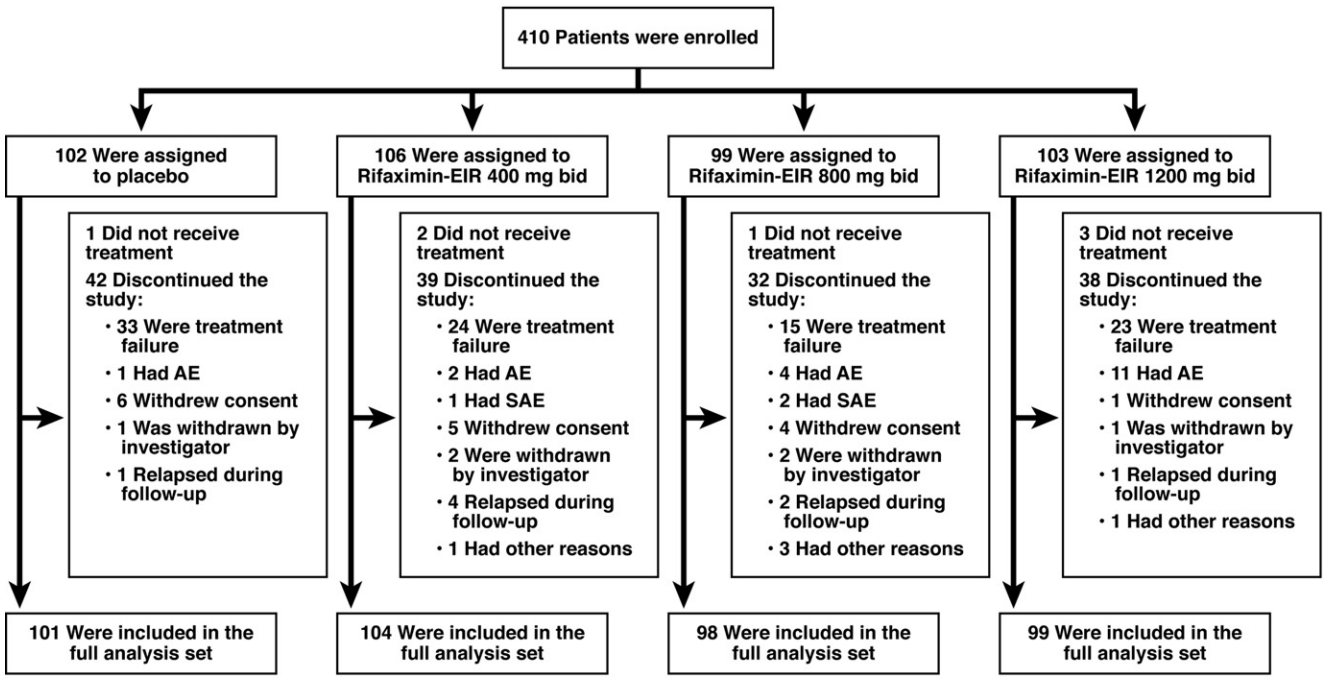

Figure 1. Patient disposition: randomization and follow-up of the FA set. A total of 410 patients were enrolled. Eight patients were excluded from the analysis because they did not take the study drug. Thus, 402 patients received at least 1 dose of the study drug and were included in the FA. Of these, 251 patients completed the study. Patients could have more than one reason for withdrawal after randomization. Major reasons for withdrawal during the treatment period were treatment failure (88 patients), AEs (18 patients), withdrawal of consent (14 patients), investigator's opinion (6 patients), and serious AEs (3 patients). Major reasons for withdrawal during the follow-up period were relapse of symptoms (16 patients) and withdrawal of consent (5 patients).

Table 1. Baseline Characteristics of Patients (Full Analysis Dataset)

		Rifaximin-EIR			
	Placebo (n = 101)	400 mg BID (n = 104)	800 mg BID (n = 98)	1200 mg BID (n = 99)	All patients (n = 402)
Sex, *n* (%)					
Male	41 (41)	40 (38)	45 (46)	41 (41)	167 (42)
Female	60 (59)	64 (62)	53 (54)	58 (59)	235 (58)
Age, *y*					
Median (Q1–Q3)	37 (29–49)	32 (26–49)	34 (28–48)	34 (28–48)	36 (28–50)
Range	18–72	18–66	18–74	18–73	18–74
Race, *n* (%)					
Caucasian	99 (98%)	103 (99)	97 (99)	99 (100)	398 (99)
Black	1 (1)	0 (0)	0 (0)	0 (0)	1 (0.2)
Others	1 (1)	1 (1)	1 (1)	0 (0)	3 (1)
Smoker, *n* (%)	26 (26)	20 (19)	30 (31)	17 (17)	93 (23)
Time since first diagnosis (*months*)					
Median (Q1–Q3)	39 (13–116)	37 (17–81)	40 (13–87)	43 (15–91)	40 (15–87)
Range	3–446	3–303	3–374	2–270	2–446
Location of CD, *n* (%)					
Ileum	25 (25)	37 (36)	34 (35)	40 (40)	136 (34)
Colon	29 (29)	25 (24)	20 (20)	21 (21)	95 (24)
Ileum + colon	47 (47)	42 (40)	44 (45)	38 (38)	171 (43)
CDAI					
Median (Q1–Q3)	268 (239–325)	275 (236–312)	270 (239–299)	263 (235–306)	270 (237–306)
Range	219–392	220–390	219–398	221–385	219–398
CRP, *mg/L*					
Median (Q1–Q3)	5 (1–20)	5 (1–19)	6 (2–20)	5 (1–16)	5 (1–17)
Range	<1–144	<1–183	<1–120	<1–162	<1–183
Previous surgery for CD, *n* (%)	32 (32)	34 (33)	27 (28)	27 (27)	120 (30)
No treatment for CD during the study, *n* (%)	28 (28)	24 (23)	28 (29)	29 (29)	109 (27)
Previous[a] and concomitant CD-specific drugs, *n* (%)					
Mesalamine[b]	72 (71)	68 (65)	63 (64)	72 (73)	275 (68)
Immunosuppressive agents[c,d]	27 (27)	33 (32)	24 (24)	19 (19)	103 (26)
Steroids[e]	48 (48)	45 (43)	51 (52)	51 (51)	195 (49)
Antibiotics[e]	30 (30)	28 (27)	26 (26)	26 (26)	110 (27)
Anti-TNF[e]	5 (5)	6 (6)	6 (6)	4 (4)	21 (5)

Q, quartile; TNF, tumor necrosis factor.
[a]CD-specific drug administered during the year before entering the study.
[b]Overall, 31 patients (8%) discontinued mesalamine before entering the trial.
[c]Immunosuppressive agents included azathioprine, mercaptopurine, and methotrexate.
[d]Overall, 12 patients (3%) discontinued immunosuppressive agents before entering the trial.
[e]Discontinued before entering the study, according to inclusion/exclusion criteria.

achieved the primary end point of clinical remission at week 12 than patients on placebo (62% [61 of 98] vs 43% [43 of 101]; $P = 0.005$; odds ratio [OR] = 2.22; 2-sided 95% confidence interval [CI]: 1.26–3.92). Higher remission rates compared with placebo, even if not statistically significant, were also observed in patients who received rifaximin-EIR 400 mg and 1200 mg twice daily (54% [56 of 104] and 47% [47 of 99], respectively) (Figure 2).

These results were confirmed by per-protocol dataset analysis, where remission was achieved in 66% (58 of 88) vs 45% (42 of 94) of patients treated by rifaximin-EIR 800 mg twice daily or placebo, respectively ($P = .004$), in 54% (53 of 98) of the patients who received rifaximin-EIR 400 mg twice daily, and in 53% (46 of 86) of those on rifaximin-EIR 1200 mg twice daily.

Secondary end points. Clinical remission was maintained in a higher number of patients treated by rifaximin-EIR 800 mg twice daily compared with those on placebo, at both the week 14 (51% [47 of 92] vs 35% [35 of 99]; $P = .03$) and 24 (45% [40 of 89] vs 29% [28 of 98]; $P = .02$) during the follow-up period. Maintenance of clinical remission in rifaximin-EIR 400 mg and 1200 mg groups was higher than placebo but did not reach a statistically significant difference (week 14: 45% [45 of 101] and 39% [37 of 95] for rifaximin-EIR 400 mg and 1200 mg, respectively; week 24: 38% [39 of 102] and 32% [30 of 94] for rifaximin-EIR 400 mg and 1200 mg, respectively).

At week 12, the clinical response rate was highest in patients on rifaximin-EIR 800 mg twice daily (72% [67 of 93]) compared with placebo (56% [52 of 93]; $P = .02$). Patients on either rifaximin-EIR 400 or 1200 mg twice daily showed a higher but not statistically significant rate of clinical response compared with placebo (63% [59 of 94] and 57% [50 of 87], respectively) (Figure 2). Administration of rifaximin-EIR 800 mg twice daily had a lower rate of treatment failure compared with placebo (26% [25

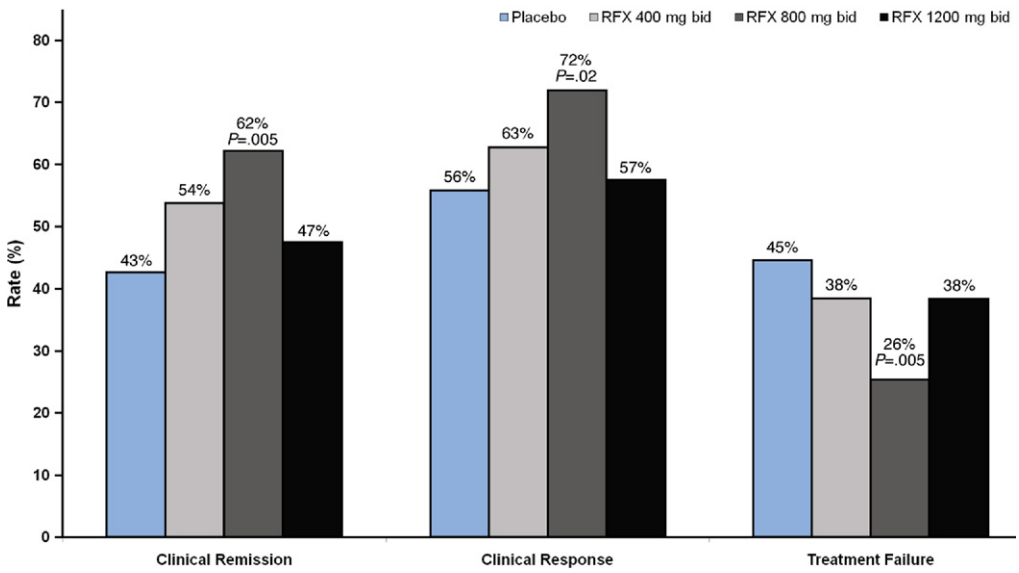

Figure 2. Efficacy of the 3 different doses of rifaximin-EIR 400 mg tablet, as compared with placebo (FA dataset). As evaluated on the CDAI, percentages of patients with a clinical remission (CDAI < 150 points), clinical response (reduction of at least 100 points) and treatment failure rates are shown. RFX, rifaximin-EIR.

of 98] vs 45% [45 of 101]; $P = .005$) (Figure 2). Thirty-eight percent of patients treated by rifaximin-EIR 400 mg (40 of 104) and 1200 mg (38 of 99) were considered treatment failures.

Mean CDAI over time for the 4 treatment groups are shown in Figure 3. The analysis of variance showed a difference in CDAI values between the treatment groups ($P < .05$). Median CRP values over time showed no statistically significant differences between treatment groups (Supplementary Material).

Exploratory subgroup analyses. The logistic regression analysis demonstrated that adjustment for country, age, sex, disease duration, smoking habit, baseline CRP, location of disease, and previous surgery did not affect the efficacy of rifaximin-EIR 800 mg twice daily. CD duration (early disease: first diagnosis ≤3 years before enrollment in the study) (OR = 1.7; 95% CI: 1.1–2.7; $P = .02$) and location (colonic involvement) (OR = 0.5; 95% CI: 0.3–0.8; $P = .004$) were indicated as prognostic factors. Russian patients had a higher response to treatment compared with other countries (OR = 1.8; 95% CI: 1.1–2.9; $P = .02$) (Supplementary Material).

Patients were divided into subgroups depending on disease location and stage. Subgroup analysis confirmed the logistic regression data on patients with early-stage disease and patients with colonic location.

To further characterize the patients who could potentially benefit from rifaximin-EIR treatment, an exploratory post-hoc analysis was also performed on patients with elevated CRP at baseline. Patients with a baseline CRP level >5 mg/L were significantly more likely to achieve remission when they received rifaximin-EIR 800 mg twice daily compared with placebo (Supplementary Material).

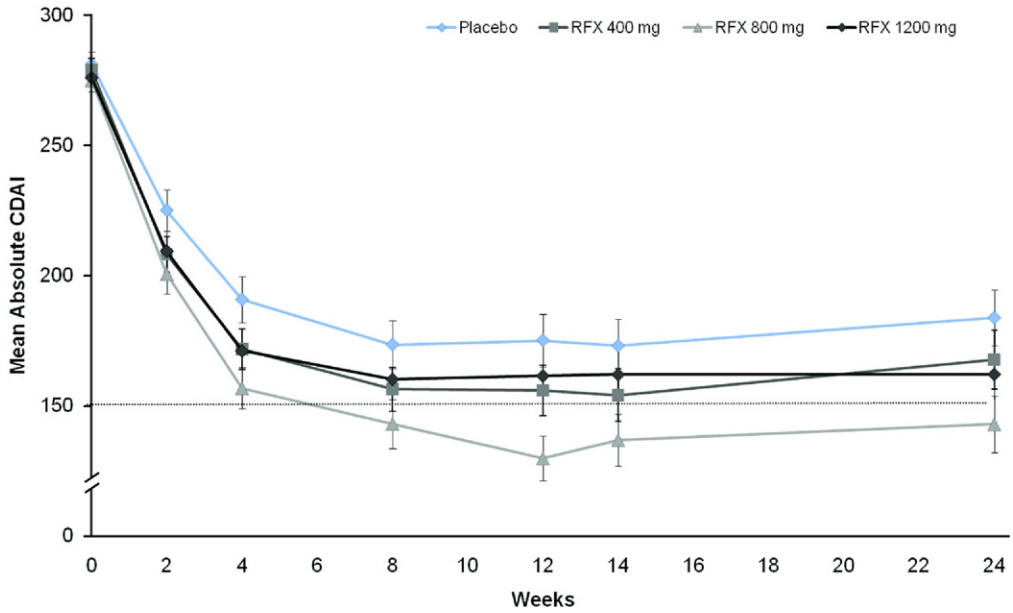

Figure 3. CDAI scores (mean value ± SE) over time per study group. The *horizontal dashed line* indicates the threshold for clinical remission (CDAI = 150 points). RFX, rifaximin-EIR.

Table 2. Summary of Safety Analyses (Safety Dataset)

Adverse event	Placebo (n = 102)[a]	Rifaximin-EIR 400 mg BID (n = 104)	Rifaximin-EIR 800 mg BID (n = 99)[a]	Rifaximin-EIR 1200 mg BID (n = 99)	All patients (n = 402)	CA trend test
Treatment period	102	104	99	99	402	
Any AE	45 (44)	35 (34)	38 (38)	45 (46)	163 (41)	0.72
AEs leading to discontinuation of study drug	6 (6)	5 (5)	5 (5)	16 (16)	32 (8)	0.01
Serious AE	1 (1)	2 (2)	1 (1)	2 (2)	6 (1)	0.72
AEs occurring in ≥2%						
Abdominal pain	2 (2)	2 (2)	1 (1)	3 (3)	8 (2)	
Vomiting	2 (2)	2 (2)	1 (1)	3 (3)	8 (2)	
Nausea	3 (3)	6 (6)	5 (5)	1 (1)	15 (4)	
CD-related symptoms	4 (4)	6 (6)	6 (6)	9 (9)	25 (6)	
Flatulence	5 (5)	0	2 (2)	2 (2)	9 (2)	
Headache	6 (6)	7 (7)	9 (9)	4 (4)	26 (6)	
Nasopharyngitis	1 (1)	2 (2)	4 (4)	2 (2)	9 (2)	
Fever	1 (1)	4 (4)	2 (2)	2 (2)	9 (2)	
Respiratory tract infection	2 (2)	0	4 (4)	2 (2)	8 (2)	
CRP increased	2 (2)	0	3 (3)	2 (2)	7 (2)	
Drug-related AE	13 (13)	9 (9)	8 (8)	18 (18)	48 (12)	0.30
Drug-related AE leading to discontinuation of study drug	2 (2)	2 (2)	1 (1)	10 (10)	15 (4)	0.006
Serious drug-related AE leading to discontinuation of study drug	0	0	0	1 (1)	1 (0.2)	0.25
Follow-up period	62	75	74	67	278	
Any TEAE	11 (18)	14 (19)	16 (22)	12 (18)	53 (19)	0.89
Drug-related AE	1 (2)	0	0	1 (2)	2 (1)	>0.99
Serious AE	0	1 (1)	3 (4)	2 (3)	6 (2)	0.19
Death due to AE[a]	0	0	1 (1)	0	0	>0.99

NOTE. Values are numbers of patients (%). Two patients received the wrong study drug at randomization and then received the correct treatment at the later dispensation visits. For the safety evaluation, the patients were counted for both treatment received, resulting in a number of 102 patients for the placebo group and 99 patients for rifaximin-EIR 800 mg BID group. With regard to AEs, both patients were counted for the treatments that they actually received.

CA, Cochran-Armitage; TEAE, treatment emergent adverse event.

[a]Two patients received the wrong study drug at randomization and then received the correct treatment at the later dispensing visits.

Safety

In total, 301 patients were exposed to rifaximin-EIR for a mean period of 70 ± 26 days. Treatment compliance was >96% in all 4 groups. Overall incidence of AEs reported during the treatment period and follow-up is summarized in Table 2. There were no significant differences between the study groups, except that a significantly higher proportion of patients in the rifaximin-EIR 1200 mg twice daily discontinued the treatment due to AEs ($P = .01$).

During the overall treatment period, 163 (41%) patients experienced at least 1 AE, with a total of 315 events recorded (85, 73, 76, and 81 in the placebo, and 400, 800, and 1200 mg twice daily groups, respectively), of which 77 were considered to be drug-related. Headache (6% of patients), CD symptoms (6% of patients), nausea (4% of patients), flatulence (2% of patients), nasopharyngitis (2% of patients), and fever (2% of patients) were the most common reported drug-related AEs. One case of *Clostridium difficile* infection was diagnosed 20 days after the end of the treatment period in a patient who received rifaximin-EIR 800 mg twice daily. A sudden death during the follow-up period, caused by an acute massive bilateral pulmonary edema, was reported in a patient with pre-existing concomitant arrhythmia. The death was assessed as unlikely related to the study drug. No clinically significant changes in the results of safety laboratory tests were observed in any study group.

Discussion

The results of this dose-range finding study suggest that rifaximin-EIR, at the dosage of 800 mg twice daily for 3 months, is safe and well tolerated, and effectively induces clinical remission of moderately active CD.

Abdominal pain was the CDAI parameter that was predominantly affected by the treatment, reaching a statistically significant difference from placebo in the rifaximin-EIR 800 mg twice daily (Supplementary Material).

Given that the primary end point of the study was clinical remission, evaluated by CDAI score, it cannot be excluded that some patients might not have had active inflammation during the study and the success of rifaximin was obtained by reduction of the bacterial flora, without interfering with the pathological process of CD. Some symptoms included in the CDAI could be caused by bacterial overgrowth on which rifaximin has been shown to be effective.[36,37] This mechanism of action is advocated to explain the successful use of

rifaximin in irritable bowel syndrome.[38] On the other hand, the reduction of the flora might lead to down-regulation of the immune system in genetically susceptible individuals who are intolerant toward commensal bacteria. At present, it is not possible to say which hypothesis is correct, although the latter seems by far more probable.

The patient population recruited in this trial could be described as having moderately active CD at the time of enrollment into the study, with a CD diagnosis confirmed either radiologically or endoscopically more than 3 months before study entry. We acknowledge that an initial and a final endoscopy would have better verified the efficacy of the drug, but at the time of the study design in all the CD trials, the primary aim of a treatment was judged by the CDAI response to the investigational drug.

This study showed a higher clinical remission rate in the other 2 rifaximin-EIR groups (400 and 1200 mg twice daily) vs placebo, but only the former showed a trend toward a clinical effect. The lack of a dose-response relationship was probably determined by the higher number of patients who withdrew from the study because of AEs in the group administered rifaximin-EIR 1200 mg twice daily. Most of the AEs reported by patients in this group were of gastrointestinal origin (ie, diarrhea, vomiting, abdominal pain), either attributable to symptoms of the underlying disease, with consequent increases of CDAI values and treatment failure or to common side effects observed on antibiotic treatment. However, seeing that the withdrawal was caused either by side effects or because of nonefficacy, the 1200 mg dosage has to be considered ineffective. In addition, the patients in the rifaximin-EIR 1200 mg twice daily group experienced a higher number of protocol deviations (13% vs 7%, 6%, and 10% in the placebo, 400 mg twice daily and the 800 mg twice daily groups, respectively).

Logistic regression analysis showed that early-stage disease and colonic location seem to be associated with a higher efficacy of rifaximin-EIR 800 mg twice daily.

In terms of the location of disease, patients with Crohn's colitis are considered to be more susceptible to treatment with antibiotics, probably because of the high bacterial content of the colon. To define the presence of early-stage CD, a cutoff point of 3 years, which was the median disease duration for our patient population, was used in this trial. This choice is supported by the definition of a recent diagnosis of CD used in previous clinical studies.[39] Early-stage CD is generally regarded as the more easily treatable form of the disease and this was reflected in this study, where rifaximin-EIR 800 mg twice daily produced clinical remission in 76% of the patients who had early-stage CD.

The logistic regression analysis showed that CRP was not a significant prognostic factor. However, a retrospective exploratory subgroup analysis of patients with elevated CRP showed that patients with baseline CRP level >5 mg/L achieved a high remission rate at the end of the treatment. The relationship between efficacy of treatment and elevated CRP in patients with CD has already been reported in other trials.[40,41]

Even when administration of the drug was stopped, the clinical remission achieved by patients on rifaximin-EIR 800 mg twice daily was maintained throughout a follow-up period of 12 weeks in 65% of the patients. This long-lasting effect of rifaximin has also been demonstrated in a recent study involving patients with irritable bowel syndrome,[27] and may reflect a long-term reduction or suppression of harmful bacterial flora or, alternatively, the natural course of remission in patients with CD.

A noteworthy result of this trial is the response of patients to placebo (overall rate of remission of 43%), which was even higher than that assumed for sample size calculation, although this did not impact the power of the comparison between rifaximin-EIR 800 mg twice daily and placebo for the primary end point. In particular, the patient population enrolled in Russia has shown a higher response compared with the other countries. Some clinical characteristics of the Russian patients (ie, more participants with "early disease," a higher use of concomitant CD-specific drugs in comparison with the other countries) can explain this higher placebo response. This difference might also reflect possible dissimilarity in practice between the health services in each study country.[42]

In a systematic review of placebo-controlled randomized clinical trials for active CD, remission rates for patients receiving placebo ranged from 0% to 50%. Study duration, number of study visits, and entry CDAI score were important predictors of the placebo remission rate, with study duration the most important.[35] In our study, placebo remission rates were 15%, 36%, and 43% at 4, 8, and 12 weeks, respectively. The positive correlation between study duration and the placebo remission rate is intuitively plausible because patients are more likely to enter spontaneous remission over time.

The high placebo response rate could be also linked to the fact that approximately 50% of patients had a low CRP value at baseline. Even in two placebo-controlled trials with biologicals, CD patients with a low baseline CRP concentration had placebo response rates of 47% and 60%.[43,44] The high placebo response in CD patients with low level of CRP is also discussed in a very recent study on Certolizumab Pegol.[45] In our study, patients with high mean baseline CRP had significantly lower placebo remission rates. This is consistent with the concept that patients with more severe disease are less likely to enter spontaneous remission.

It should be considered that the patients enrolled in the study were allowed to continue other active treatments for CD at stable dose. We cannot exclude that a more prolonged use of immunosuppressants could have had a clinical impact; however, the 4 groups were comparable with regard to their use.

The results from this study indicate that rifaximin-EIR has a good safety profile, as the incidences of AEs and serious AEs were similar between patients administered rifaximin-EIR and placebo (41% vs 44%). Among the most important AEs, one case of *C difficile* infection was reported after administration of 800 mg rifaximin twice

daily. It is important to note that *C difficile* is of particular concern in patients with CD, who are frequently treated by systemic antibiotics and often hospitalized. Although rifaximin has been successfully used for the treatment of *C difficile* in patients unresponsive to metronidazole,[46] it is probable that rare clones of rifaximin-resistant *Clostridium* can develop.[47] This possible side effect has to be taken into account, especially when long-term treatment with rifaximin is contemplated.

In conclusion, this was the first large-scale trial to demonstrate efficacy of rifaximin in inducing remission in patients with active CD; this effect was maintained during a 12-week follow-up period. The lack of a dose-response relationship and the higher than expected placebo response suggest that these findings need to be confirmed from pivotal studies.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2011.11.032.

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Conflicts of interest

The authors disclose the following: Dr Prantera has served as a consultant for and received research funding from Alfa Wassermann SpA and as advisory board member of Giuliani and Chiesi. Dr Lochs has served as a consultant and on Speakers Bureau for Alfa Wassermann SpA. Dr Gionchetti has served on the Advisory Board/ Speakers Bureau for Alfa Wassermann SpA. Dr Danese has served as a speaker and an advisory board member for Ferring, Astra Zeneca, and Cosmo Pharmaceuticals. Dr Grimaldi is an employee of Alfa Wassermann SpA. The remaining author discloses no conflicts.

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Appendix

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Supplementary Table 1. Efficacy Results: Primary and Secondary Outcomes (Full Analysis Dataset)

		Rifaximin-EIR			
	Placebo	400 mg BID	800 mg BID	1200 mg BID	Pooled doses
Clinical remission (CDAI <150 points), *n* (%)	43/101 (43)	56/104 (54)	61/98 (62)	47/99 (47)	164/301 (54)
P (vs placebo)		.11	.005	.49	.04
Clinical response (CDAI decreased by 100 points), *n* (%)	52/93 (56)	59/94 (63)	67/93 (72)	50/87 (57)	176/274 (64)
P (vs placebo)		.34	.02	.83	.15
Treatment failure rate, *n* (%)	45/101 (45)	40/104 (38)	25/98 (26)	38/99 (38)	103/301 (34)
P (vs placebo)		.38	.005	.38	.06
Maintenance of remission 2 weeks after last drug administration, *n* (%)	35/99 (35)	45/101 (45)	47/92 (51)	37/95 (39)	129/288 (45)
P (vs placebo)		.18	.03	.60	.10
Maintenance of remission 12 weeks after last drug administration, *n* (%)	28/98 (29)	39/102 (38)	40/89 (45)	30/94 (32)	109/285 (38)
P (vs placebo)		.15	.02	.61	.09

BID, twice daily.

Supplementary Table 2. Clinical Remission in the Subgroup of Patients with CRP >5 mg/L, Early Disease and Colonic Location of the Disease (Full Analysis Dataset)

		Rifaximin-EIR			
	Placebo	400 mg BID	800 mg BID	1200 mg BID	Pooled doses
Clinical remission in patients with CRP[a] >5 mg/L at baseline, *n* (%)	19/52 (37)	24/51 (47)	31/50 (62)	22/47 (47)	77/148 (52)
P (vs placebo)		.28	.01	.30	.054
Clinical remission in patients with early disease (≤3 y), *n* (%)	25/49 (51)	30/49 (61)	34/45 (76)	27/46 (59)	91/140 (65)
P (vs placebo)		.31	.01	.45	.08
Clinical remission in patients with disease localized in the colon, *n* (%)	28/76 (37)	35/67 (52)	36/64 (56)	25/59 (42)	96/190 (51)
P (vs placebo)		.06	.02	.51	.04

BID, twice daily.
[a]CRP normal range values: 0–5 mg/L.

Supplementary Table 3. Treatment Emergent AEs >2% by System Organ Class (Safety Dataset)

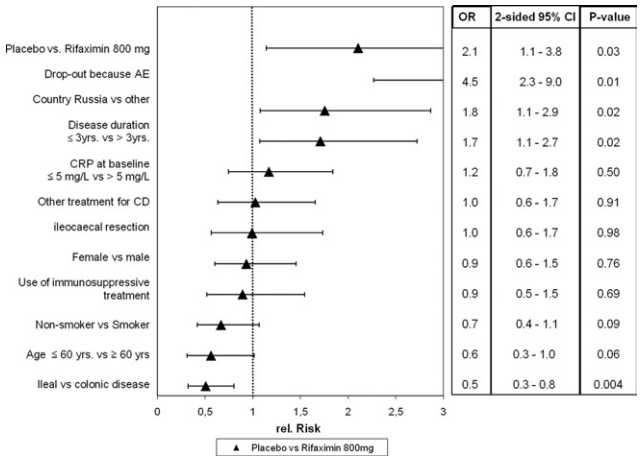
	Placebo (n = 102)		Rifaximin-EIR 400 mg BID (n = 104)		Rifaximin-EIR 800 mg BID (n = 99)		Rifaximin-EIR 1200 mg BID (n = 99)		All Patients (n = 402)	
	n[a] (%)	No. of events	*n* (%)	No. of events	*n* (%)	No. of events	*n* (%)	No. of events	*n* (%)	No. of events
Treatment period, n	102		104		99		99		402	
Any TEAE	45 (44)	85	35 (34)	73	38 (38)	76	45 (46)	81	163 (41)	315
Gastrointestinal disorders	24 (24)	29	22 (21)	36	21 (21)	29	21 (21)	29	88 (22)	123
Infections and infestations	12 (12)	14	7 (7)	7	17 (17)	18	10 (10)	11	46 (11)	50
Nervous system disorders	8 (8)	9	8 (8)	8	10 (10)	11	5 (5)	8	31 (8)	36
General disorders and administration site conditions	6 (6)	7	6 (6)	7	5 (5)	5	5 (5)	5	22 (6)	24
Investigations	4 (4)	4	1 (1)	1	6 (6)	6	4 (4)	4	15 (4)	15
Musculoskeletal and connective tissue disorders	2 (2)	3	2 (2)	3	0	0	6 (6)	6	10 (2)	12
Skin and subcutaneous tissue disorders	3 (3)	3	2 (2)	2	1 (1)	1	4 (4)	4	10 (2)	10
Respiratory, thoracic, and mediastinal disorders	2 (2)	2	4 (4)	6	1 (1)	1	0	0	7 (2)	9
Eye disorders	3 (3)	5	0	0	2 (2)	2	0	0	5 (1)	7
Follow-up period, n	62		75		74		67		278	
Any TEAE	11 (18)	13	14 (19)	20	16 (22)	18	12 (18)	15	53 (19)	66
Gastrointestinal disorders	7 (11)	8	10 (13)	14	4 (5)	4	2 (3)	2	23 (8)	28
Infections and infestations	1 (2)	1	2 (3)	2	5[b] (7)	5[b]	7 (10)	8	15 (5)	16

BID, twice daily; TEAE, treatment emergent adverse event.
[a]Number of patients.
[b]One case of *Clostridium difficile* infection is included.

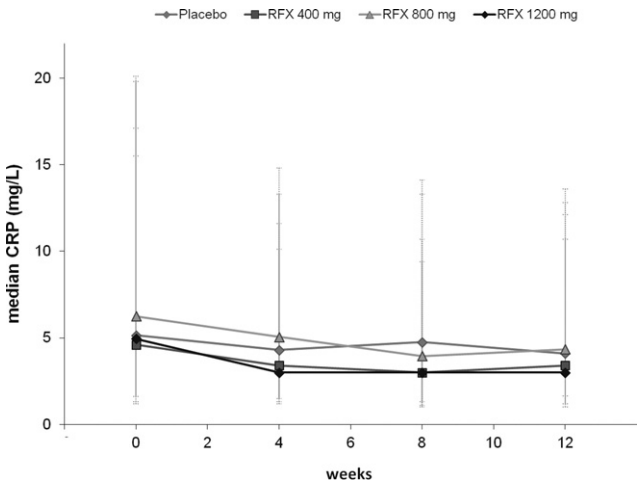
Supplementary Table 4. Single CDAI Parameters at Baseline and at End of Treatment

CDAI parameters	Placebo	Rifaximin-EIR 400 mg BID	Rifaximin-EIR 800 mg BID	Rifaximin-EIR 1200 mg BID	*P* value
Abdominal pain, mean score					
Baseline	1.8	1.9	1.8	1.8	.30
End of treatment	1.0	1.0	0.7	0.9	.04
Maximum abdominal pain, mean score					
Baseline	2.3	2.5	2.3	2.4	.28
End of treatment	1.5	1.6	1.1	1.3	.03
Mean no. of days with abdominal pain					
Baseline	6.7	6.8	6.6	6.7	.54
End of treatment	4.4	4.2	3.5	4.2	.11
Mean no. of soft or liquid stools per day					
Baseline	4.0	3.6	3.7	3.5	.46
End of treatment	2.4	2.1	1.9	1.9	.40
Mean no. of days with liquid stools					
Baseline	6.8	6.6	6.7	6.8	.14
End of treatment	6.0	5.0	5.4	5.1	.07
Mean loperamide intake, %					
Baseline	15.6	10.6	14.6	10.8	.44
End of treatment	4.2	1.9	4.2	6.5	.36

BID, twice daily.



Supplementary Figure 1. Logistic regression analysis: prognostic factors of the rifaximin-EIR 800 mg remission rate (Full Analysis Dataset).



Supplementary Figure 2. Median CRP values with confidence intervals over time during the treatment phase per study group. RFX, rifaximin-EIR.