Newer Concepts

Digestive Diseases

Dig Dis 2014;32:378–383
DOI: 10.1159/000358141

Is Rifaximin Effective in Maintaining Remission in Crohn's Disease?

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Key Words
Antibiotics · Crohn's disease · Intestinal microbiota · Rifaximin

Abstract
Background: Recent studies indicate that persistent intestinal inflammation in patients with Crohn's disease (CD) might be caused by abnormal intestinal microbiota. This hypothesis may suggest a beneficial effect of antibiotics in CD therapy. So far, guidelines do not recommend antibiotics except in the treatment of complicated CD, and there are few studies on the effects of rifaximin in these patients. ***Methods:*** Between December 2011 and December 2012, we performed a blinded randomized trial in 168 patients with a previous history of moderately active CD concerning the efficacy of rifaximin. All the patients had previously achieved remission with standard therapy (prednisone/budesonide). Data from patients receiving 800 mg of rifaximin (83 patients) twice a day for 12 weeks were compared with those from patients who received placebo (83 patients). The primary endpoint was maintaining remission during the follow-up. ***Results:*** All the patients (100%; 83/83) on 800 mg of rifaximin were in remission after 12 weeks of treatment in comparison with 84% (70/83) of the placebo group. This significant difference was also persistent at the 24-week follow-up [78% (65/83) vs. 41% (34/83), respectively]. The last evaluation performed at 48 weeks revealed disease activity in 45% (38/83) of the patients of the rifaximin group, i.e. a significant decrease compared with the placebo group [75% (63 of 83)]. ***Conclusions:*** Remission previously obtained with standard treatment can be sustained in patients with moderately active CD after the administration of 800 mg of rifaximin.

Introduction

Crohn's disease (CD) is a chronic idiopathic inflammatory bowel disorder characterized by transmural inflammation that could affect any part of the gastrointestinal tract with relapses and remissions throughout its course [1]. Even though the etiology of CD remains unknown, several factors were proven to be involved in its pathophysiology (immunological, genetic, environmental, and psychological factors). The hypothesis that the intestinal microbiota has a leading role in chronic inflammation that characterizes CD was confirmed in several

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studies [2]. This susceptibility to the resident flora could be explained by mutations in the NOD2/CARD15 microflora sensing genes leading to the upregulation of mucosal cytokine production, which delays bacterial clearance [3]. Two cytokines, interferon-γ and tumor necrosis factor (TNF-α), have been found at high levels in the intestinal mucosa of patients with intestinal bowel disease (IBD) [4]. Via various mechanisms, interferon-γ and TNF-α induce an increased uptake of proteins from the intestinal lumen and reduce the efflux of foreign substances from the cells, thus increasing the permeability of macromolecules to the lamina propria [5, 6].

Another factor correlated with an increased susceptibility to IBD is pregnane X receptor (PXR). PXR is a ligand-activated transcription factor involved in the induction of drug transport and metabolism, in particular the induction of cytochrome P_{450} [7]. Studies have shown a significant inhibition of PXR and its target genes in patients with CD [8]. Its major importance for clinical practice is represented by the fact that an agonist for the specific human PXR is rifaximin, a nonsystemic rifamycin-derived antibiotic [9].

Probably secondary to these alterations, the concentration of intestinal bacteria is higher in patients with CD than in the normal population and increases with the severity of the disease [2]. There was also a loss of anaerobic anti-inflammatory commensal bacteria *(Eubacterium, Faecaelibacterium prausnitzii,* and *Lactobacillus)* and an increase in *Escherichia coli, Clostridium, Peptostreptococcus* or *Campylobacter concisus* [10–13].

All the data presented above could be sufficient motive for the use of antibiotics in CD. However, guidelines recommend the use of antibiotics only for the treatment of CD complications, especially due to the high number of systemic adverse events in long-term treatment (mostly for metronidazole and ciprofloxacin) [14, 15].

Rifaximin is a minimally absorbed, nonsystemic antimicrobial agent with important antibacterial activity. It is used for many gastrointestinal disorders, e.g. irritable bowel syndrome, intestinal bacterial infections, hepatic encephalopathy, or chronic diverticular disease [16]. The efficacy of this agent is probably due to its inflammatory activity, which is derived from increased PXR expression and its antagonistic effect to TNF-α on intestinal epithelial cells [11]. Rifaximin also increases the concentration of bifidobacteria and *F. prausnitzii* in the colonic microbiota of CD patients [17].

During the last years, the role of rifaximin as a therapeutic agent for patients with IBD has been evaluated in several studies.

Patients and Methods

We performed a randomized study in which the effectiveness of complementary therapy with 800 mg of rifaximin was compared with placebo for maintaining remission in CD patients treated with standard therapy (azathioprine, infliximab/adalimumab, and 5-aminosalicylate agents), which was conducted in several Romanian centers between December 2011 and December 2012.

Patients

The study included 168 adult patients aged between 21 and 73 years; active CD was noted in the ileum, colon, or ileocolon, and was radiologically, endoscopically, or histologically confirmed. The main inclusion criteria were a previous history of moderately active disease, defined by a CD Activity Index (CDAI) score between 220 and 400. Exclusion criteria were obstructive symptoms, abscesses, infections, mental illness, severe cardiac disease or neoplasia, or potential need for immediate surgery.

Study Design

Rifaximin (800 mg) was administered orally twice a day (400 mg ×2) for 12 weeks. In patients who achieved remission following this 12-week treatment, treatment was continued for a further 12 weeks (total treatment time: 24 weeks). Patients were evaluated before treatment initiation (week 0) and after 12 weeks of rifaximin treatment, and at 24 and 48 weeks during the follow-up period, and serum C-reactive protein (CRP) levels were analyzed and the CDAI score was calculated.

The primary endpoints were maintaining remission (CDAI score <150) at the 12-week follow-up and maintaining clinical remission (a reduction in the CDAI score of 100 points in comparison with the initial evaluation).

Statistical Analysis

The database was elaborated with Excel 2010 for Windows 7 and the statistical evaluation was performed using SPSS (version 17.0; Statistical Package for the Social Sciences) for Windows. To establish statistical differences between the categories included in the study and rifaximin, the χ^2 test was employed. Correlations between several parameters and CDAI scores were assessed using analysis of variance.

Results

A total of 168 patients were included: 84 in the placebo group and 84 in the rifaximin group. Two patients were excluded due to lack of compliance during the follow-up, 1 patient in the placebo group and 1 in the rifaximin group (fig. 1). At baseline, the mean CDAI was 285 ± 49.34 (SD). All the patients were Caucasians and their medium age was 41 ± 11.5 (SD) years, with a mode of 34 years (fig. 2). Further patient characteristics are listed in table 1.

At the 12-week evaluation, 100% (83/83) of the patients from the group who received rifaximin combined with standard therapy maintained remission compared to 84% (70/83; $p < 0.001$; fig. 3) in the placebo group. Clin-

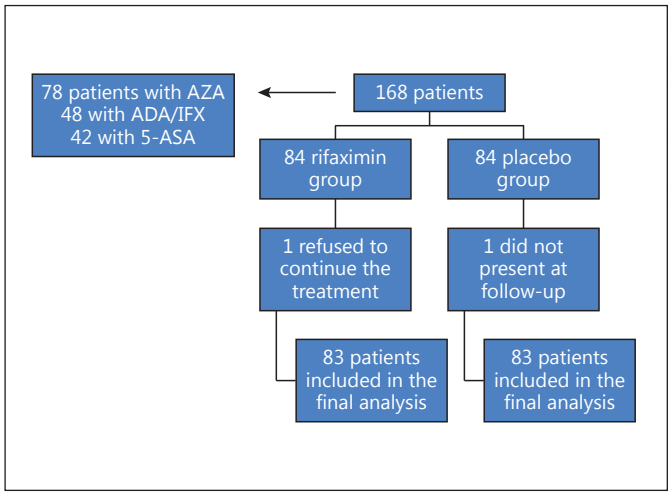

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Fig. 1. Patient distribution. AZA = Azathioprine; IFX = infliximab; ADA = adalimumab; 5-ASA = 5-aminosalicylate agents.

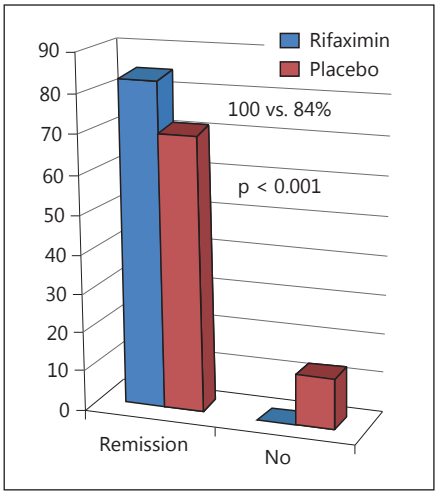

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Fig. 3. Twelve-week efficacy of rifaximin versus placebo according to the CDAI score.

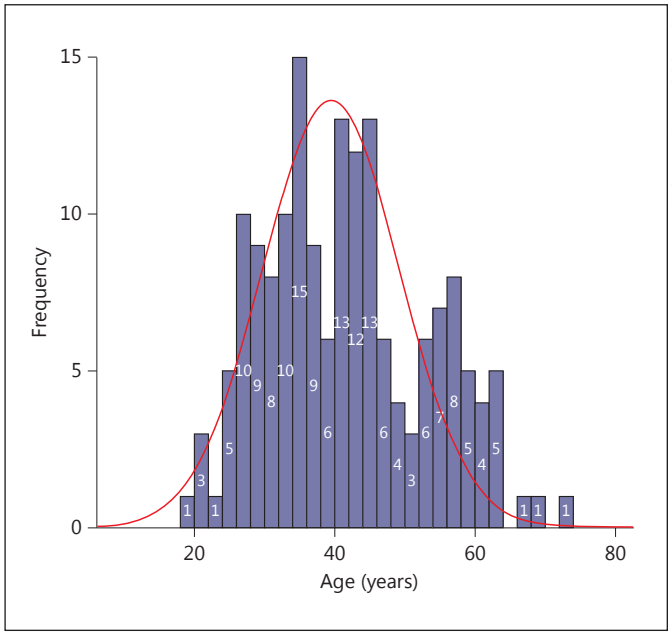

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Fig. 2. Age distribution. Mean = 41.22, SD = 11.51, n = 166.

Table 1. Baseline characteristics of the study patients

	Rifaximin (n = 83)	Placebo (n = 83)	Total (n = 166)
Gender			
Male	38 (45.7)	59 (71)	97 (58.4)
Female	45 (54.3)	24 (29)	69 (41.6)
Area			
Urban	75 (90.3)	58 (69.8)	133 (80.1)
Rural	8 (9.7)	25 (31.2)	33 (19.9)
Smokers	54 (65)	32 (38.5)	86 (51.8)
Mean CRP, mg/dl	4.3	4.18	4.25
Azathioprine	30 (36.1)	48 (57.8)	78 (46.9)
Infliximab/adalimumab	30 (36.1)	18 (21.6)	48 (28.9)
5-Aminosalicylate	23 (27.7)	17 (20.4)	40 (24)

Values are presented as n (%) unless indicated otherwise.

ical remission (100-point decrease in the baseline CDAI score) was obtained in 96% of the patients at this time point. In addition, the CDAI score was markedly decreased in all the patients at the 12-week evaluation in comparison with the initial CDAI (mean ± SD: 102 ± 47.9 vs. 285 ± 49.3; fig. 4). The significant difference was still present at the 24-week follow-up when 78% of the patients receiving rifaximin treatment were in remission in comparison with 41% from the placebo group [78% (65/83) vs. 41% (34/83); p < 0.001; fig. 5], with a medium (SD) CDAI for both groups of 135 ± 57.2 (fig. 6).

The last evaluation performed at 48 weeks revealed significantly decreased disease activity [45% (38/83)] in the patients in the rifaximin group compared with the placebo group [75% (63/83); p < 0.001; fig. 7], with a medium (SD) overall CDAI of 158 ± 59.5 (fig. 8). There was also a statistically significant difference in clinical remission between the two groups at the study end (71 vs. 53%; p < 0.05; fig. 9).

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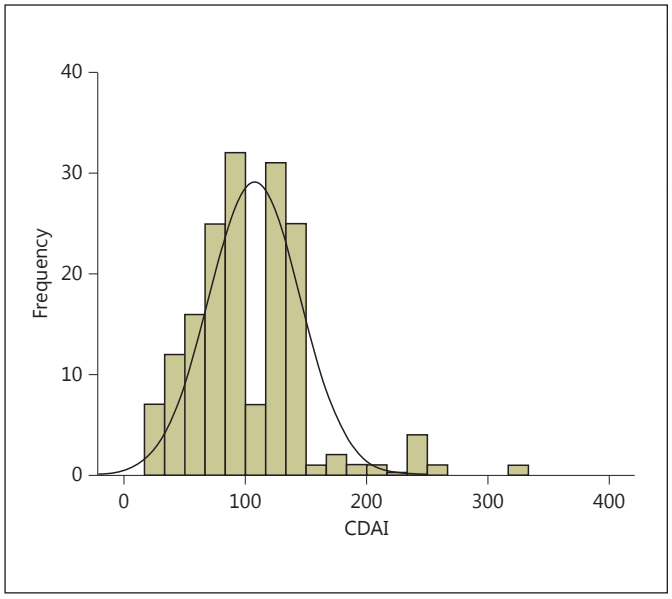

Fig. 4. 12-week medium CDAI. Mean = 102.62, SD = 47.91, n = 166.

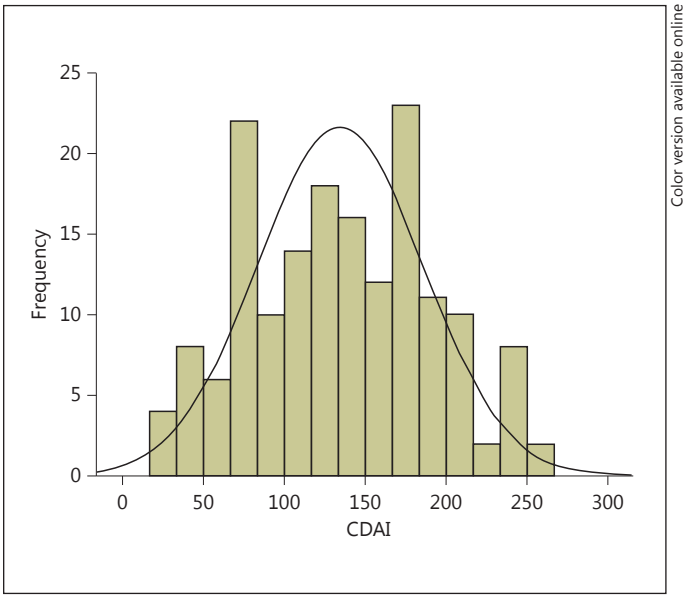

Fig. 6. 24-week medium CDAI. Mean = 135.24, SD = 57.20, n = 166.

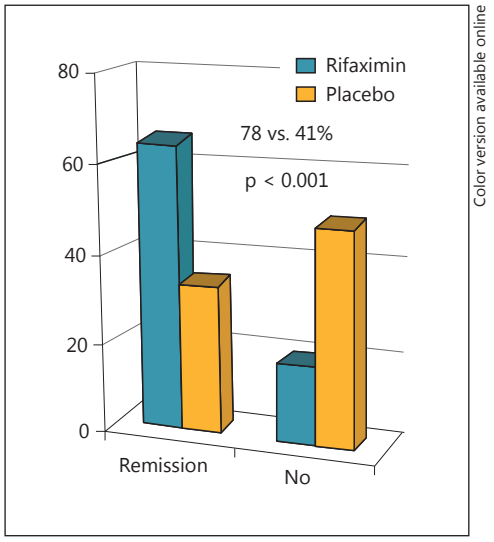

Fig. 5. 24-week efficacy of rifaximin versus placebo according to the CDAI score.

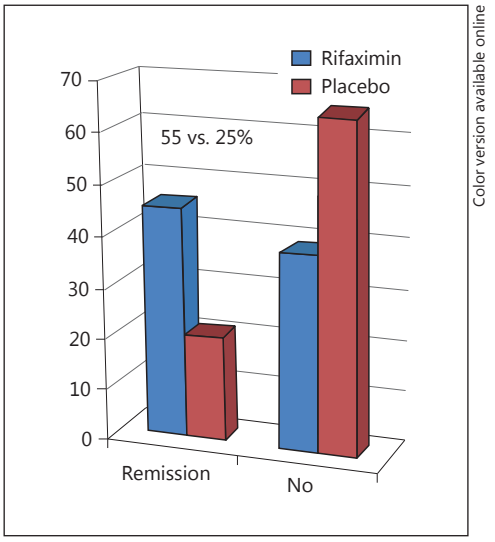

Fig. 7. 48-week efficacy of rifaximin versus placebo according to the CDAI score.

During all the stages of the follow-up, no statistically significant differences were observed concerning the medium CRP values. There was only a slight difference during the 48-week evaluation, when the mean CRP value was higher in the placebo group compared with the rifaximin group (table 2).

Discussion

The main findings of this study indicate that 800 mg of rifaximin per day can be an important adjuvant to standard therapy in order to maintain remission in CD patients.

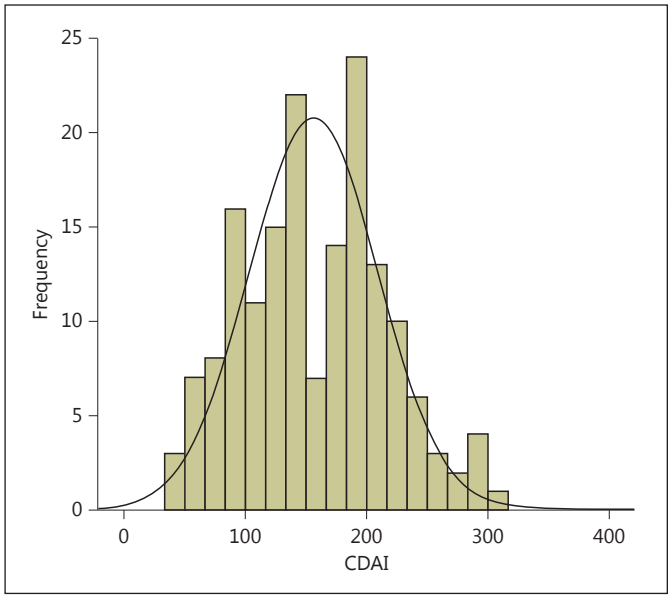

Fig. 8. 48-week medium CDAI. Mean = 158.15, SD = 59.56, n = 166.

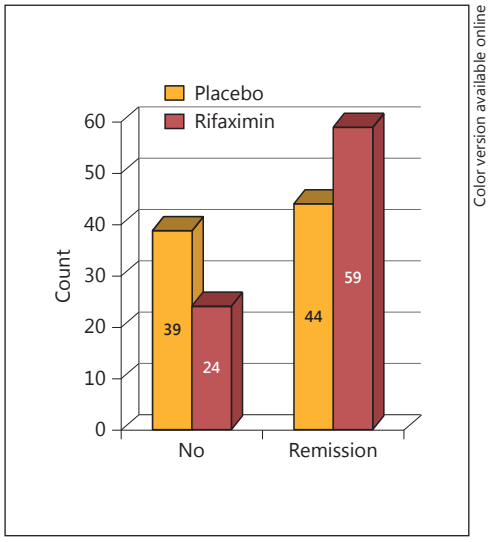

Fig. 9. 48-week clinical remission.

Table 2. CRP levels (mg/dl)

Follow-up	Rifaximin group	Placebo group	Mean
12 weeks	2.14	2.02	2.07
24 weeks	1.2	1.6	1.41
48 weeks	1.18	1.68	1.43

Given the heterogeneity of the standard therapy (azathioprine, infliximab/adalimumab, or 5-aminosalicylate derivatives) between the two groups, it is difficult to determine the exact role of rifaximin in the pathophysiology of CD in these patients. Since the main criterion of evaluation was the CDAI score, the decrease in its value could have been due to the effects of rifaximin on bacterial overgrowth, which is also responsible for the decrease in symptoms when given in irritable bowel syndrome [18]. This aspect was mentioned by Prantera et al. [19] when interpreting the results of the so far largest trial (402 patients) concerning the efficacy of rifaximin in inducing remission in patients with CD. The results of our study are in support of the results of their study, in which the clinical remission rate at 12 weeks was 72 versus 56% (for placebo); of note, all our patients received standard therapy and rifaximin was only given as adjuvant therapy. In a similar retrospective analysis performed in 68 patients, adjunctive rifaximin given for 16 weeks at a mean dose of 600 mg induced remission in up to 70% of the patients [20].

In our study, adverse effects were not a parameter in the statistical analysis especially due to the fact that it would have been difficult to differentiate adverse effects of rifaximin from those of the standard therapy. CRP was not a factor that could be considered as a prognostic indicator of remission in our patients, which was in contrast to previous studies, particularly in patients with high baseline levels [21–23]. No correlation between the CRP value and disease activity could be performed mostly due to the fact that few of our patients had increased baseline levels and any analysis could not have statistical significance.

The main limitation of our study consists in the absence of an endoscopic evaluation at least at the end of the treatment to be able to correlate eventual clinical remission with endoscopic activity. Due to financial limitations, it was also impossible to evaluate all hematological and biochemical parameters in all the patients during the study.

In conclusion, remission previously obtained with standard treatment can be sustained for at least 48 weeks in patients with moderately active CD following the administration of 800 mg of rifaximin.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the article.

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