

Does rifaximin offer any promise in Crohn's disease in remission and concurrent irritable bowel syndrome-like symptoms?

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Abstract

Microbiota plays an important role in many diseases including inflammatory bowel diseases. Inflammatory bowel disease patients can have concurrent irritable bowel syndrome symptoms similar to those associated with a flare. The potential role of gut dysbiosis in the pathogenesis of inflammatory bowel disease provides a rationale for treating such patients with rifaximin. This study aimed to assess the efficacy of rifaximin in the management of irritable bowel syndrome-like symptoms (bloating, abdominal pain, stool consistency) and quality of life in patients with Crohn's disease in remission.

The present study included 86 patients with Crohn's disease in remission (fecal calprotectin $<50 \mu\text{g/g}$, C-reactive protein $<0.5 \text{ mg/dL}$, simple endoscopic score for Crohn's disease <2) and associated irritable bowel syndrome-like symptoms (bloating, abdominal pain, diarrhea). These patients were randomly assigned to rifaximin treatment group (44 patients) and the control group (42 patients). Besides the baseline inflammatory bowel disease treatment and antispasmodics (as needed), patients in the rifaximin treatment group received 3 repeated courses of treatment, each course being represented by 1200 mg/d of rifaximin for 10 days and 20 days free of treatment (3 months consecutively); patients in the control group also received antispasmodics as needed and were observed for 3 months.

Monthly analyses of bloating score, abdominal pain score, stool consistency score, and quality of life score showed significant improvement after treatment in the rifaximin group in contrast with control group. Significantly more patients in the rifaximin group than in the control group met the criteria for adequate improvement of bloating score after 3 months of treatment (59.09% vs 19.04%, $P=.01$), adequate improvement of abdominal pain score (54.5% vs 21.4%, $P=.04$), stool consistency score (34.09% vs 14.2%, $P=.03$), and quality of life score (70.4% vs 21.4%, $P<.001$).

Rifaximin in a dose of 1200mg/d, 10d/mo, 3 months consecutively is an effective medication for concurrent irritable bowel syndrome-like symptoms in patients with Crohn's disease in remission.

Abbreviations: BSF = Bristol stool form, CD = Crohn's disease, CDAI = Crohn's disease activity index, CRP = C reactive protein, fC = fecal calprotectin, GI = gastrointestinal, IBD = inflammatory bowel diseases, IBS = irritable bowel syndrome, IBS-D = irritable bowel syndrome predominant diarrhea, QoL = quality of life, SES-CD = simple endoscopic score for Crohn's disease, SIBDQ = short inflammatory bowel disease questionnaire, VAS = visual analog scale.

Keywords: inflammatory bowel disease, irritable bowel syndrome, quality of life, rifaximin

1. Introduction

Microbiota plays an important role in many diseases including inflammatory bowel diseases (IBD).^[1] IBD patients can have concurrent irritable bowel syndrome (IBS) symptoms, similar to

those associated with a flare. The potential role of gut dysbiosis in the pathogenesis of IBD provides a rationale for treating such patients with rifaximin which has already proved its effectiveness in diarrhea-predominant IBS (IBS-D).^[2] Distinguishing IBS-like

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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symptoms from those driven by pathological changes like inflammation or fibrosis which are characteristic of IBD can be difficult. Persistent gastrointestinal (GI) symptoms may be present despite successful IBD therapy resulting in disease remission. Unfortunately, evidence for diagnosis and treatment in this category of patients is scarce. Moreover, treatment strategies mostly include empirical approaches based on lessons learned from patients with IBS. The severity of symptoms does not always correlate to the degree of inflammatory activity.^[3] It is important to identify this category of patients with IBS-like symptoms and disease in remission because over-treating intestinal inflammation negatively affects the clinical benefits as well as the health-care system.

The pool prevalence of functional GI symptoms in IBD is 39%. Symptoms are more frequent in Crohn's disease (CD)^[4] and besides increased health-care utilization, these symptoms are also associated with anxiety, depression, and lower quality of life (QoL).^[5,6]

The potential role of rifaximin in IBS-D has been already proved,^[2] but its role in treatment of CD in remission and associated functional GI symptoms has not been much explored. This study aimed to assess the efficacy of rifaximin in the management of IBS-like symptoms in patients with CD in remission. The end-points measured were improvement in bloating, abdominal pain, stool consistency, and QoL.

2. Methods

2.1. Study patients, inclusion, and exclusion criteria

The present study enrolled 134 patients with CD who visited to Department of Gastroenterology, Constanta County Clinical Emergency Hospital, between January 01, 2017, and December 31, 2018.

Inclusion criteria were: CD in remission, fecal calprotectin (fC) <50 µg/g, C-reactive protein (CRP) <0.5 mg/dL, and documented endoscopic remission with Simple Endoscopic Score for Crohn's disease <2 (colonoscopies performed no later than 3 months were agreed), presence of IBS-like symptoms (recurrent abdominal pain at least 1 d/wk in the last 3 months, associated with at least 2 of the following: related to defecation, a change in the frequency of stool, or a change in the appearance of stool), age >16 years. All the patients were informed about the study and written consent was taken from them.

Exclusion criteria for the study included infectious etiology of diarrhea (stool cultures, ova, and parasites stool test were

performed. *Clostridium difficile* infection, Cytomegalovirus, and Epstein Barr virus were also tested), and short bowel syndrome (surgical history of CD).

Based on these exclusion criteria, 48 patients were excluded (32 had active disease with fC >50 µg/g, 11 had normal fC but their symptoms did not fit the criteria for IBS-like, and 5 had associated bowel infections). Of the total enrolled patients, 86 patients met all the inclusion and exclusion criteria and, therefore, were included in the study. These patients were randomly assigned to rifaximin treatment group (44 patients) and the control group (42 patients). Because placebo could not be provided, patients knew the group to which they were assigned. Randomization was carried out using a list of codes prepared by an independent advisor with a random number generator. Sequential patients were enrolled, and their group allocation was decided by referring to the code list.

2.2. Study design

The study design is illustrated in Table 1. Besides the baseline IBD treatment (immunosuppressants or biologic therapy, see Table 2), and antispasmodics (trimebutine 300mg, per os) as needed (according to local protocols), the patients in the rifaximin group received 3 repeated courses of rifaximin treatment. Each course of treatment included rifaximin 1200 mg/d for 10 days and next 20 days free of treatment (3 months consecutively). The patients in the control group received only antispasmodics (trimebutine 300 mg, per os) as needed (according to local protocols). All patients were observed for 3 months as described below.

The activity of CD was assessed by endoscopy (Simple Endoscopic Score for Crohn's disease score), fC, and CRP. The severity of bloating and abdominal pain was assessed by visual analog scale (VAS) (0–100 mm, where 0 means no pain/bloating and 100 means the worst possible pain/bloating). Stool consistency was assessed by Bristol stool form (BSF) (1–7, where 1 means solid stool and 7 means watery stools). QoL was assessed by the short inflammatory bowel disease questionnaire (SIBDQ) (10–70, where 10 means lowest QoL and 70 best QoL). At baseline, patients rated the average daily amount of abdominal pain and bloating according to VAS scores, along with average daily QoL according to SIBDQ and the average daily consistency of the stools according to BSF score over the course of at least 7 days. For the follow-up, they were provided a journal where they noted the average daily scores for abdominal pain, bloating, and BSF, and SIBDQ score was calculated by completing the questionnaire at each visit. Monthly analyses for abdominal

Table 1

The study design. All variables were measured in both rifaximin and control groups.

	Study visits			
	Day 1 (m0)	Day 30 (m1)	Day 60 (m2)	Day 90 (m3)
Bloating	X	X	X	X
Abdominal pain	X	X	X	X
QoL	X	X	X	X
Stool consistency	X	X	X	X
Adverse events	—	X	X	X
CDAI	X	—	—	X
CRP	X	—	—	X
fC	X	—	—	X

Screening period was up to 30 d.

BSF=Bristol stool form, CDAI=Crohn's disease activity index, CRP=C reactive protein, fC=fecal calprotectin, m0=baseline, m1=month 1, m2=month 2, m3=month 3, QoL=quality of life.

Table 2**Demographic and baseline characteristics of the patients enrolled in the 2 groups.**

Baseline data	Rifaximin group (n = 44)	Control group (n = 42)	P-value
Age (yr)*	39.5 +/- 11.5	35 +/- 9.8	.34
Male/female, n (%)	23 (53.3%)/21 (46.7%)	22 (52.4%)/20 (47.6%)	.44
Location (L1/L2/L3), n (%)	8 (18.1%)/20 (45.5%)/16 (36.4%)	8 (19%)/20 (47.6%)/14 (33.4%)	.21
Phenotype (B1/B2/B3), n (%)	38 (86.3%)/1 (2.3%)/5 (11.1%)	38 (90.4%)/1 (2.4%)/3 (7.2%)	.30
Treatment, n (%)			
AZA	24 (54.5%)	23 (54.7%)	.37
Anti - TNF	7 (16%)	6 (14.2%)	.40
Combo therapy	13 (29.5%)	13 (31.1%)	.39
Disease duration (yr)*	6 +/- 3.5	8 +/- 5	.17
CRP (<0.5 mg/dL)*	0.3 +/- 0.1	0.4 +/- 0.1	.35
fC (<50 mg/kg)*	29.2 +/- 10	30.4 +/- 10	.38
Abdominal pain (0–100 mm)*	72.4 +/- 11.9	69.1 +/- 10.7	.21
Bloating (0–100 mm)*	68.8 +/- 10.9	65.1 +/- 10.3	.19
BSF (1–7)†	6 (4–7)	6 (3–7)	.22
SIBDQ (13–70)*	32.4 +/- 18.9	35.4 +/- 14.2	.20

Anti - TNF = anti tumor necrosis alpha, AZA = azathioprine, BSF = Bristol stool form, CRP = C reactive protein, fC = fecal calprotectin, SIBDQ = the short inflammatory bowel disease questionnaire.

* Mean +/- SD.

† Median (interquartile range).

Table 3**Analyses of endpoints in the rifaximin and control group in the 4 moments of the study.**

		m0	m1	m2	m3	P-value
Abdominal pain	Rifaximin	72.43 +/- 7.57	51.87 +/- 8.93	40.09 +/- 7.49	36.76 +/- 6.82	<.001
	Control	69.12 +/- 8.40	61.42 +/- 7.31	54.42 +/- 7.31	59.98 +/- 10.24	<.001
Bloating	Rifaximin	68.89 +/- 9.73	37.48 +/- 9.31	40.89 +/- 7.80	34.39 +/- 6.47	<.001
	Control	65.19 +/- 7.70	54.35 +/- 7.58	49.72 +/- 7.84	46.14 +/- 8.43	<.001
SIBDQ	Rifaximin	32.46 +/- 7.23	45.11 +/- 6.33	53.67 +/- 6.81	59.67 +/- 5.36	<.001
	Control	35.47 +/- 7.22	38.51 +/- 6.81	41.33 +/- 6.60	39.67 +/- 6.30	.02
BSF	Rifaximin	6 (4–7)	4 (2–6)	3 (2–5)	3 (2–4)	<.001
	Control	6 (3–7)	5 (4–6)	5 (3–6)	5 (3–6)	<.001

Abdominal pain, bloating, and SIBDQ are expressed as mean +/- standard deviation, and BSF is expressed as median and interquartile range; P-value represent the result after comparing mean scores from the baseline (m0) with mean scores from the end of the study (third month = m3); see detailed analysis in Supplementary Content 5 and 6, <http://links.lww.com/MD/F514>.

BSF = Bristol stool form, m0 = baseline, m1 = month 1, m2 = month 2, m3 = month 3, SIBDQ = the short inflammatory bowel disease questionnaire.

pain, bloating and stool consistency were calculated based on daily assessments noted in the journal in the last 30 days before the study visit. QoL was assessed at the time of each monthly visit for QoL. Except for fC, CRP, and CDAI which were assessed only at baseline and the end of the study period, the rest of the variables were assessed monthly. Safety assessment included the close monitoring of adverse events during the 3 months of the study.

At the end of the study, the adequate improvement was defined by at least 30% decrease in the mean scores of bloating and abdominal pain, an increase of at least 30% in the mean scores of SIBDQ, and a decrease of at least 1 point in median BSF score, compared with baseline mean scores.

2.3. Ethics approval and consent to participate

The study was conducted according to good laboratory practice and in concordance with the Declaration of Helsinki and national and institutional standards. Informed written consent was obtained from all patients, and the study was approved by the Local Ethics Commission for the Approval of Clinical and Research Developmental Studies (approval no. 16/20.12.2016).

2.4. Statistics

Statistical analysis was performed using SPSS Version 23 statistic software package (IBM, Chicago, IL). Data were expressed as mean ± standard deviation for continuous variables (bloating, abdominal pain, QoL) and as the absolute frequency for categorical variables (BSF) at each time-point of the study viz. baseline (m0), month 1 (m1), month 2 (m2), and month 3 (m3). The normality of distribution was analyzed using the Shapiro–Wilk test ($P > \alpha = .05$ shows a normal distribution of the population). For continuous variables, parametric tests like ANOVA and nonparametric tests like Kruskal–Wallis were performed. For categorical variables, the nonparametric Chi-square test was used. The Bonferroni test was performed for multiple comparisons between continuous variables at the different time-points of the study. A P-value < .05 was considered statistically significant.

3. Results

Baseline data of the patients enrolled in the study has been illustrated in Table 2. Overall, there were no significant

differences between the baseline data of both study groups. The mean age of the enrolled patients was 39.5 ± 11.5 years in the rifaximin group and 35 ± 9.8 years in the control group and approximately half of the patients were male. Regarding the location of the disease, 46% patients in the rifaximin group and 49% patients in the control group had colonic involvement, followed by ileocolonic and ileal involvement. Significant number of patients in both the groups had an inflammatory phenotype. Most of the patients had azathioprine in their treatment protocol with or without addition of anti-TNF. The mean duration of the disease was 6 ± 3.5 years in the rifaximin group and 8 ± 5 in the control group. As for activity was concerned, both the groups had CRP and fC between the normal range. VAS scores of abdominal pain and bloating were high and similar in both the groups. Stool consistency was also similar with a median value of 6 (4–7) in the rifaximin group and 6 (3–7) in the control group. Patients in both groups had a similar lower QoL.

The results of the tests performed for abdominal pain, bloating, QoL, and stool consistency in all 4 time-points of the study (baseline, month 1, month 2, and month 3) are illustrated in Table 3. Detailed analysis (*P*-values of the multiple comparisons between monthly mean scores) is available as Supplementary Content 1 to 7, <http://links.lww.com/MD/F514>.

4. Bloating

Mean bloating scores in the rifaximin group and control group are illustrated in Figure 1 (see Supplementary Content 1 and 2, <http://links.lww.com/MD/F514> for detailed analysis of bloating scores and multiple comparisons).

Monthly analyses of bloating score in the rifaximin group showed significant improvement after the first month of treatment ($P < .001$). Therapeutic effects achieved were maintained after the second and third administration of treatment. Analysis performed in the control group also showed statistically significant improvement in bloating score after the first month of treatment ($P < .001$), and therapeutic effect was maintained after second and third administration of treatment. However, the decrease of mean score in the rifaximin group was significantly greater than in the control group ($P = .03$).

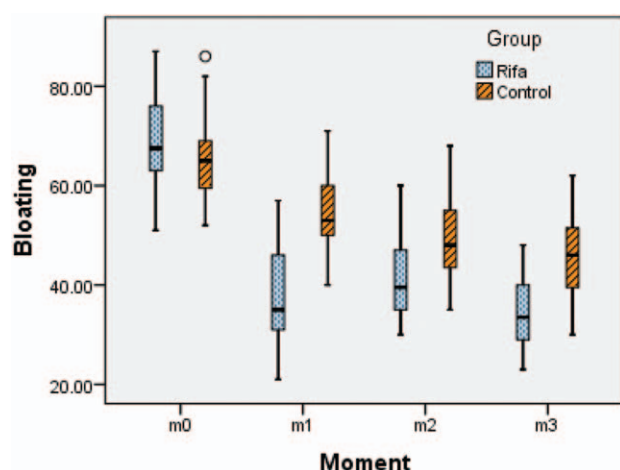


Figure 1. Graphic representation for bloating score in the rifaximin and control group. (m0=baseline, m1=month 1, m2=month 2, m3=month 3).

Table 4

Patients with adequate improvement of IBS-like symptoms from the rifaximin group compared with patients from the control group.

Variable, n (%)	Rifaximin group (n=44)	Control group (n=42)	<i>P</i> -value
Abdominal pain	24 (54.5%)	9 (21.4%)	.04
Bloating	26 (59%)	8 (19%)	.01
SIBDQ	31 (70.4%)	9 (21.4%)	<.001
BSF	15 (34%)	6 (14.2%)	.03

BSF=Bristol stool form, SIBDQ=the short inflammatory bowel disease questionnaire.

Significantly more patients in the rifaximin group than in the control group met the criteria for adequate improvement of bloating after 3 months of treatment (59.09% vs 19.04%, $P = .01$) (Table 4).

5. Abdominal pain

The values of mean abdominal pain scores in the rifaximin group and control group is illustrated in Figure 2 (see Supplementary Content 3 and 4, <http://links.lww.com/MD/F514> for a detailed analysis of abdominal pain scores and multiple comparisons).

Monthly analyses of abdominal pain score in the rifaximin group showed continuously significant improvement after the first 2 administrations of treatment ($P < .001$). This therapeutic effect was maintained after the third administration of rifaximin. In the control group, abdominal pain score was also improved during the first 2 months, but the loss of therapeutic effect (increased mean score) was noted in the last month ($P < .001$). Also, the decrease in mean scores in the rifaximin group was significantly higher than in the control group ($P < .001$).

Significantly more patients in the rifaximin group in comparison to the control group met the criteria for adequate improvement of abdominal pain after 3 months of treatment (54.5% vs 21.4%, $P = .04$) (Table 4).

6. QoL

Monthly analyses of the QoL score (Fig. 3) showed significant improvement during all the 3 months of treatment with QoL

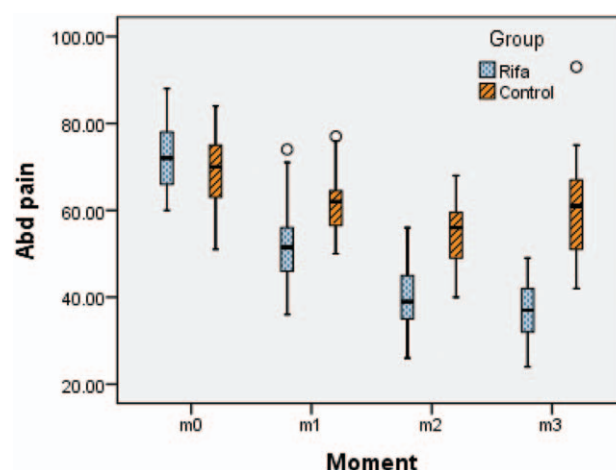


Figure 2. Graphic representation for abdominal pain score in the rifaximin and control group. (m0=baseline, m1=month 1, m2=month 2, m3=month 3).

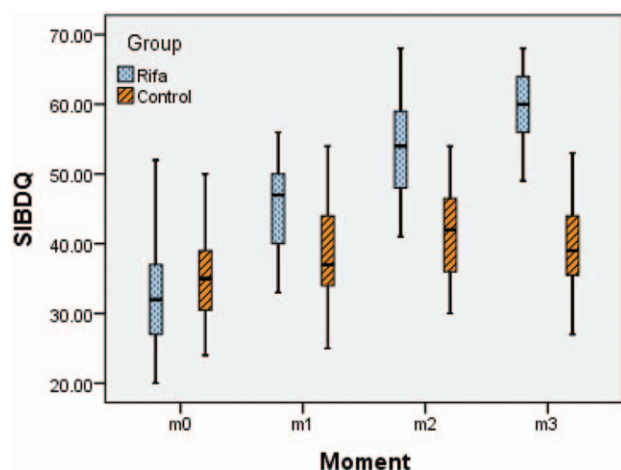


Figure 3. Graphic representation for quality of life scores in the rifaximin and control group. (m0=baseline, m1=month 1, m2=month 2, m3=month 3).

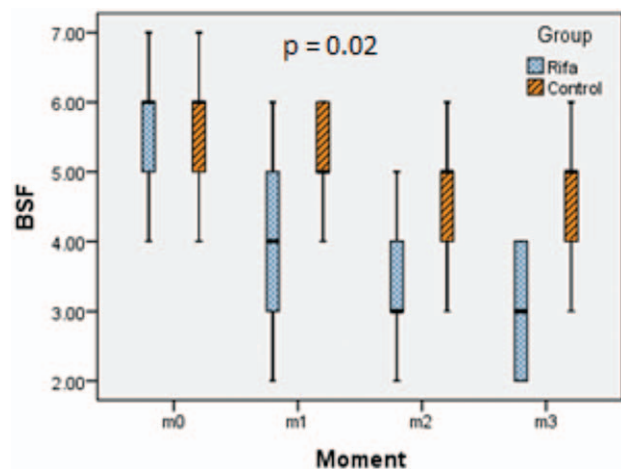


Figure 4. Graphic representation for stool consistency score in the rifaximin and control group. (m0=baseline, m1=month 1, m2=month 2, m3=month 3).

gradually improved in the rifaximin group ($P < .001$). On the contrary, monthly analysis performed in the control group showed no significant improvement in the QoL during the observation period ($P = .08$) (see Supplementary Content 5 and 6, <http://links.lww.com/MD/F514> for detailed analysis of QoL scores and multiple comparisons).

Significantly more patients in the rifaximin group than in the control group met the criteria for adequate improvement of QoL

after 3 months of treatment (70.4% vs 21.4%, $P < .001$) (Table 4).

7. Stool consistency

Median scores of stool consistency during various time points of the study are illustrated in Figure 4 (see Supplementary Content 7, <http://links.lww.com/MD/F514> for detailed analysis of stool consistency scores and multiple comparisons).

Monthly analyses in the rifaximin group showed that the stool consistency score improved gradually during all the 3 months ($P = .02$). In contrast, in the control group, the stool consistency score improved slightly, and that too only in the second month ($P = .04$). Significant difference was observed in patients who met the criteria for adequate improvement of stool consistency after 3 months of treatment in the rifaximin group and the control group (34.09% vs 14.2%, $P = .03$) (Table 4).

Overall, data indicates that most of the patients in the rifaximin group achieved an adequate improvement in all the studied IBS-like symptoms, whereas only a small number of the patients from the control group achieved an adequate improvement (Table 4).

Improvement of IBS-like symptoms and QoL of the patients in the rifaximin group was separately analyzed based on the patients' baseline treatment (patients receiving only azathioprine were compared with patients receiving combo therapy: azathioprine and anti-TNF). No significant difference was observed between patients receiving azathioprine and patients receiving combination therapy with reference to symptoms like improvement of bloating (54.1% vs 53.8%, $P = .98$), abdominal pain (50% vs 53.8%, $P = .82$), QoL (62.5% vs 69.2%, $P = .68$) and stool consistency (29.1% vs 23%, $P = .69$).

7.1. Disease activity assessed by fC, CRP, and CDAI score

The values of mean fC, CRP, and CDAI scores at different study time-points have been illustrated in Table 5. There were no statistically significant differences between the mean values of these variables at baseline compared to values observed at the end of the study. Of note, CDAI had a high score despite CD confirmed remission.

7.2. Adverse events

No adverse effects were observed in any of the 2 patient groups during the study period.

8. Discussion

Bowel symptoms vary widely among patients with IBS. No single endpoint has been found appropriate for the accurate assessment,

Table 5

Evolution of mean fecal calprotectin, C reactive protein, and CDAI scores during the study period.

	RIFAXIMIN GROUP			CONTROL GROUP		
	m0	m3	P-value	m0	m3	P-value
fC	29.2 +/- 10	31.5 +/- 9.5	$P = 0.45$	30.4 +/- 10	30.5 +/- 8	$P = .55$
CRP	0.3 +/- 0.1	0.42 +/- 1	$P = 0.36$	0.4 +/- 0.2	0.38 +/- 0.9	$P = .53$
CDAI	220 +/- 75	165 +/- 55	$P = 0.11$	210 +/- 70	225 +/- 60	$P = .24$

CDAI = Crohn's disease activity index, CRP = C reactive protein, fC = fecal calprotectin, m0 = baseline, m1 = month 1, m3 = month 3.

therefore several relevant endpoints (like abdominal pain, bloating, and stool consistency) must be considered for the study. Values obtained from the well-accepted instruments like VAS and BSF to measure these endpoints have been used to obtain valid and reproducible results.^[7]

A recent clinical update on the functional GI symptoms in patients with IBD was published by the American Gastroenterology Association.^[3] It mentioned that diagnostic algorithm for the evaluation of such symptoms in these patients is based on the assessment of inflammatory biomarkers for IBD activity such as fC and CRP, besides clinical assessment. When these biomarkers show no evidence of inflammatory activity and after further exclusion of other pathophysiological mechanisms, we could classify these symptoms as functional and treat the patients as having functional GI symptoms, as we did in this study. There is another category of patients who can have borderline inflammation and the recommendation is to perform endoscopy, histopathology, and/or imagistic tests before initiating any treatment. After these tests, options could be optimizing therapy when the cause of symptoms is the inflammation. Another scenario is when symptoms are less consistent with the degree of inflammation and for these patients also the treatment option could be similar to the patients having functional GI symptoms. To exclude this bias in our study, we excluded patients with borderline inflammation.

Functional GI symptoms have a major impact on a patient's QoL and also have an impact on health-care utilization. A recent study published by Zargar et al^[8] compared QoL of patients with IBD and associated functional GI symptoms with QoL of patients with only IBD. They observed a poor QoL in the first category of patients with the lowest mean scores of IBDQ in CD patients with functional GI symptoms. Similar to this study, patients in our study had poor QoL at baseline; moreover, QoL was significantly improved after treatment with rifaximin. Another study showed that patients with IBD and functional GI symptoms had more mean number of investigations and clinic appointments in comparison to patients with occult inflammation or quiescent disease and use almost the same resources as an active IBD.^[5] The same study also showed that, on long-term follow-up, even though this kind of patient requires a lot of resources, their survival rate is similar to that of patients with occult inflammation or quiescent disease.^[5] Therefore, recognizing and properly treating functional symptoms in IBD patients is of paramount importance.

Rifaximin was the treatment of choice in this study because it has proven efficacy in positively modulating the gut microbial composition,^[9,10] in particular in patients with IBS-D as demonstrated in TARGET studies.^[2] Jolley et al^[11] demonstrated that rifaximin at the dose of 1200mg/d for 10 days improved functional GI symptoms. Furthermore, patients who did not respond to the initial dose were administered a higher dose of 2400 mg/d for 10 days. Improvement, in this case, was similar to the percentage improvement achieved in the patients responsive to the initial dose of 1200mg/d. A prospective, randomized, placebo-controlled trial^[12] demonstrated the efficacy of repeated treatments with rifaximin by a significant improvement in abdominal pain, prevention of recurrence, durable response, and bowel movement urgency. Based on these data, dose of rifaximin was considered to be 1200mg/d, 10 d/mo, 3 months for this study. Moreover, there are studies which supported the hypothesis that rifaximin is also effective in inducing and

maintaining remission in patients with IBDs^[13,14] as well as improving the QoL of such patients.^[15]

In our study, all the 4 endpoints were achieved in the rifaximin group: adequate improvement in bloating, abdominal pain, stool consistency, and QoL, and improvement sustained during all the 3 months of the study period. The monthly analyses showed a consistent response to rifaximin in patients with CD in remission over the course of 3 months. Regarding bloating, it was significantly improved after the first month of treatment with rifaximin, and improvement sustained in the next months. In case of abdominal pain, a decrease in the mean scores was noted after the first month of treatment and a constant decrease was observed till the end of the study, suggesting a gradual improvement. The same significant improvement was also noted in the QoL of treated patients with rifaximin. Regarding diarrhea, stool consistency had a trend similar to bloating showing significant improvement after the first month of treatment and sustained improvement until the end of the study period. Even though patients in the control group also achieved an improvement in IBS-like symptoms, the improvement was significantly high in the rifaximin group. Moreover the percentage of patients with adequate improvement (defined as a decrease of at least 30% in the mean scores of bloating and abdominal pain, an increase of at least 30% in the mean scores of SIBDQ and a decrease of at least 1 point in the monthly median BSF score) was higher in the rifaximin group. The subanalysis performed in the rifaximin group between patients receiving azathioprine and those receiving combination therapy showed that the results of the study were not influenced by the baseline treatment of the patients with the help of which remission of CD was achieved.

Diagnostic and treatment strategies of IBS-like symptoms in IBD in remission have been explored less. A small randomized study^[16] of 14 CD patients with the inactive ileal disease and breath-test diagnosed SIBO had a similar study design as this study but the end-points considered were different. They assessed negative breath-test after treatment with rifaximin which was achieved in all the patients.^[16]

We calculated the CDAI at baseline and the end of the study period, as recommended by Colombel et al.^[3] However, we did not include it as an end-point because this index might be as high in IBS as in IBD patients since it is based only on the points received by the number of watery stools and severity of abdominal pain of functional cause. Evidence regarding this aspect came from the SONIC trial^[17] where 1 treatment arm had high CDAI and a lack of objective inflammation.

Manipulation of the gut microbiota through fecal transplantation has gained interest among the researchers worldwide.^[18,19] Several attempts were made to target the microbiome for the clinical benefit in active IBD, like fecal microbiota transplant in mild to moderate UC,^[20] the use of probiotic VSL#3 in chronic pouchitis which was effective at preventing flares^[21] or studies on the role of diet in IBD.^[22] Based on these hypotheses, we also tried to target the microbiome in inactive IBD with rifaximin which showed promising results.

A possible limitation of our study, besides the small number of patients included, was that the control group did not use a placebo medication, so investigators could not be blinded and this could have in some way altered the results. However, the significant improvement achieved in the IBS-like symptoms in majority of the patients suggests therapeutic potential of rifaximin in this category of patients.

In conclusion, rifaximin in a dose of 1200mg/d, 10d/mo, 3 months consecutively is an effective medication for concurrent IBS-like symptoms in patients with CD in remission. Further extensive and detailed investigated in larger study groups are needed to strengthen this finding.

Author contributions

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