Inflammatory Intestinal Diseases

Research Article

Inflamm Intest Dis 2024;9:22–28
DOI: 10.1159/000536124

Received: May 24, 2023
Accepted: December 31, 2023
Published online: January 24, 2024

Rifaximin Treatment of Collagenous Colitis: A Randomised, Double-Blind, Placebo-Controlled Trial

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Keywords
Collagenous colitis · Rifaximin treatment · Microbiota

Abstract
Introduction: Collagenous colitis (CC) is a disabling disease primarily affecting elderly women. Sparse, well-documented treatment modalities exist, except for budesonide. Long-term and repetitive treatment with budesonide is often necessary. Rifaximin is a poorly absorbed antibiotic with a positive modulatory effect on gut microbiota. In this randomised, double-blind, placebo-controlled single-centre trial, we test the effect of adding rifaximin in continuation to budesonide on relapse rates in CC. ***Methods:*** Eligible patients with active, biopsy-verified CC received oral budesonide during a 6-week open-label induction phase. Patients in clinical remission after 4 weeks of treatment were randomised to receive either rifaximin or placebo for 4 weeks. ***Results:*** Fifteen patients were randomised to receive either rifaximin (n = 7) or placebo (n = 8). At 12-week follow-up, 2 patients in the rifaximin group were still in remission and none in the placebo group (p = 0.2). The median number of days in remission in the rifaximin group was 42 (interquartile range [IQR] 33–126) compared to 18.5 (IQR 10.5–51.5) in the placebo group (p = 0.189). At 12-week follow-up, the relapse rate per 100 person-days in the placebo group was higher (3.25 [1.40–6.41]) than in the rifaximin group (1.33 [0.43–3.10]). ***Conclusion:*** Although not statistically significant (p = 0.0996), the study suggests a potential improvement in relapse rates within the rifaximin group compared to the placebo group. A major limitation in the study is the small sample size.

Introduction

Collagenous colitis (CC) is a chronic inflammatory bowel disease primarily affecting elderly women. In a nationwide cohort study, the annual incidence of CC in Denmark was found to be among the highest in Europe ($14.9/10^5$ inhabitants in 2011) [1]. The diagnosis is based on a combination of symptoms and characteristic histological findings with a thickened subepithelial collagenous band ≥10 μm and infiltration with lymphocytes in the lamina propria of the colon [1, 2].

Clinically, the condition is characterised by chronic watery diarrhoea, urgency, and episodic faecal incontinence, which can be socially disabling and compromise quality of life [3]. Despite a good prognosis, the disease is often protracted with relapsing symptoms [3–5].

The aetiology and pathogenesis of CC are largely unknown. Environmental factors as smoking and exposure to certain drugs such as proton pump inhibitors,

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non-steroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors have been reported to be associated with CC [6]. An aberrant immune response to luminal agents in genetically predisposed individuals has been proposed [7, 8], and altered gut microbiota in patients with active CC compared to healthy individuals has been documented [9]. The role of the gut microbiota is supported by reports of successful treatment of refractory CC with faecal stream diversion [10] and faecal transplantation [11].

The most well-documented treatment of CC is budesonide [12], a locally acting corticosteroid with low systemic exposure. As 10–20% of patients are non-responders to budesonide and relapse rates are high (61–88% even after long-term treatment), repetitive and long-lasting treatment courses are often necessary [5, 13–15]. Well-documented additional treatment options are needed.

Rifaximin is a poorly absorbed antibiotic with bactericidal and bacteriostatic activity. It is approved for the treatment of traveller's diarrhoea, small intestinal bacterial overgrowth [16], and irritable bowel syndrome [17, 18]. Rifaximin has showed promising results in inflammatory bowel disease by inducing a positive modulation of gut microbiota composition and downregulation of endotoxin levels [19, 20].

Assuming that an altered gut microbiota is a contributory factor for initiating an inflammatory process in CC, we suggest that treatment with budesonide reduces the inflammation without treating the underlying cause. Our hypothesis is that treatment with rifaximin in the continuation of a budesonide course can induce a positive modulation of the gut microbiota, resulting in delay of relapse of symptoms in CC patients. Therefore, this trial is set out to investigate the effect of treatment with rifaximin in addition to budesonide on remission and relapse rates in patients with CC.

Methods

Patients and Study Design

The XiCoCo trial (Xifaxan for Collagenous Colitis) was a randomised, double-blind, placebo-controlled, single-centre study (ClinicalTrials.gov identifier: NCT03658993). Eligible participants were aged 18 years or older with histologically confirmed CC. Patients were required to have active disease defined by Hjortswang activity index [21] as ≥3 stools per day or ≥1 watery stool per day measured as a mean during a week prior to baseline. Other causes of diarrhoea such as infectious disease, coeliac disease, or lactose intolerance were excluded by faecal cultures and blood tests at baseline. Patients treated with salazopyrine, 5-aminosalicylic acid, budesonide, or systemic glucocorticoid during the last 3 months were excluded. Other chronic gastrointestinal diseases, clinically relevant severe comorbidity, and previous intestinal resection or stoma were also defined as exclusion criteria.

During a 6-week open-label induction phase, eligible patients received oral budesonide 9 mg once daily (3 capsules of 3 mg). Patients with clinical remission after 4 weeks of budesonide treatment were randomised to receive either oral rifaximin 550 mg TID or oral placebo TID for 4 weeks. Study drugs were commenced during budesonide treatment and continued 2 weeks after cessation of budesonide treatment. The study design is shown in Figure 1. Computer-generated block randomisation (http://www.randomization.com/) was performed by the local pharmacy in blocks of eight. Study drug and placebo were packed and provided by Norgine and blinded to participants and researchers.

Histology

The CC diagnosis was validated from the Institute of Pathology's PatoWeb with ensurance of histopathological criteria, i.e., evidence of a collagenous band >10 μm and infiltration with lymphocytes upon colorectal mucosal biopsy. Diagnostic biopsies performed within the last 2 years were accepted, but all patients with biopsies older than 90 days were requested a new sigmoidoscopy with biopsies to verify the diagnosis. Biopsies were processed and analysed according to the local pathological guidelines.

Efficacy Assessments

The symptom burden was assessed using a 1-week symptom diary and the Short Health Scale (SHS) [22] completed by the patient prior to each visit. SHS is a four-part 100-mm visual analogue scale designed to assess the impact of inflammatory bowel disease on quality of life (symptom burden, activities of daily living, disease-related worry, and sense of general well-being). Scores range from 0.0 to 40.0 with higher scores reflecting high impact on quality of life. The mean number of stools and watery stools per day were calculated at each visit. The primary endpoint was the number of patients still in clinical remission 12 weeks after cessation of budesonide in the rifaximin group compared to the placebo group.

Clinical remission was defined by Hjortswang activity index as a mean of <3 stools per day and a mean of <1 watery stool per day. Active disease/relapse was defined as a mean of ≥3 stools per day or a mean of ≥1 watery stool per day.

Safety Assessments

Adverse events were recorded at each visit by the investigator and evaluated in terms of severity and causality. Laboratory tests were performed at baseline and after end of treatment.

Statistical Analysis

Sample size estimate was based on a minimum relevant difference of 50%, corresponding to an anticipated remission rate of 70% after 4 weeks of active therapy with budesonide and a historical placebo effect of 20% [23]. With a type 1 error risk of 5% and a statistical power of 80%, a total of 36 patients was needed. Given an anticipated remission rate of 90% after 6 weeks of open-label treatment with budesonide and a drop-out of 10% during the same period, we planned to include 25 patients in each treatment group corresponding to a total of 50 patients.

We tested whether participants randomised to receive rifaximin stayed in remission for a longer time compared to participants

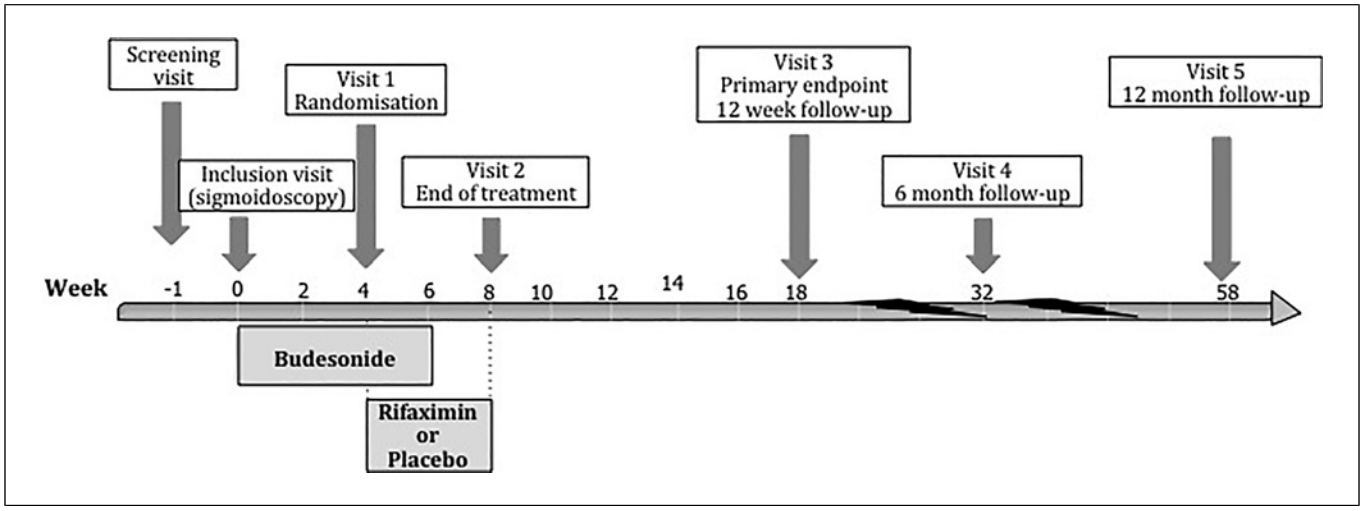

Fig. 1. Study design.

randomised to placebo. We used a modified intention-to-treat analysis excluding participants who did not fulfil the inclusion criteria (discovered after randomisation) and did not initiate the study treatment.

Baseline characteristics are reported as means ± standard deviation (SD) or medians with interquartile range (IQR) for continuous variables and percent (%) for categorical variables. Categorical outcome variables were analysed using the Fisher's exact test, and continuous variables were analysed using Wilcoxon rank-sum.

Kaplan-Meier Curves were used to analyse time to event of relapse. The equality of the two "remission functions" was tested using the log-rank test.

Follow-up started at date of budesonide cessation and ended at date of relapse of symptoms or after 52 weeks of follow-up. We used relapse rate per person-days at risk to standardise the rate and make it comparable across the two treatment groups at different follow-up frames. The relapse rate was calculated as the cumulated number of patients with relapse divided by the number of person-days at risk in each treatment group at the time points of 12-week and 52-week follow-up. All statistical tests were two-sided with the level of statistical significance set at p value <0.05.

The blinding of the trial was maintained until all data sets were locked, and all data analyses were performed. All log files were saved and time-marked. All analyses were performed using STATA 17 (Stata Corp, College Station, TX, USA).

Results

A total of 25 patients commenced open-label induction therapy with budesonide between September 2018 and December 2021. Five patients did not achieve clinical remission after 2 weeks of budesonide treatment, two no longer had CC in their biopsies after a new sigmoidoscopy, one did not achieve clinical remission nor fulfil histological criteria, and one was admitted to hospital for another reason. A total of 16 participants were randomised. One patient assigned to rifaximin treatment had delayed biopsy answers and did not fulfil the histological criteria after inclusion and was excluded from the analysis before study treatment was initiated. This leaves 8 patients randomised to placebo and seven to rifaximin. Patient enrolment is shown in Figure 2.

Baseline data in the two groups were comparable, although more patients in the placebo group had a longer disease duration and higher cumulated budesonide exposure. Three patients were included on biopsies older 90 days. The use of drugs reported to be associated with microscopic colitis is equal in the two groups. Proton pump inhibitor was used as needed in the placebo group for 2 patients. NSAIDs were used as needed in 1 patient in the rifaximin group. None used serotonin reuptake inhibitor. Clinical characteristics of the patients at baseline are presented in Table 1. The study was prematurely terminated as the COVID-19 pandemic reduced the numbers of patients eligible for inclusion.

At the primary endpoint at 12-week follow-up after cessation of budesonide, 2 patients in the rifaximin group were still in remission and none in the placebo group (p = 0.2) (Table 2). Only 1 patient was still in remission at week 52.

The median number of days in remission in the rifaximin group was 42 (IQR 33–126) compared to 18.5 (IQR 10.5–51.5) in the placebo group (p = 0.189). At 12-week follow-up, the relapse rate per 100 person-days was higher in the placebo group [3.25 (1.40–6.41]) than in the rifaximin group (1.33 [0.43–3.10]) (Table 2).

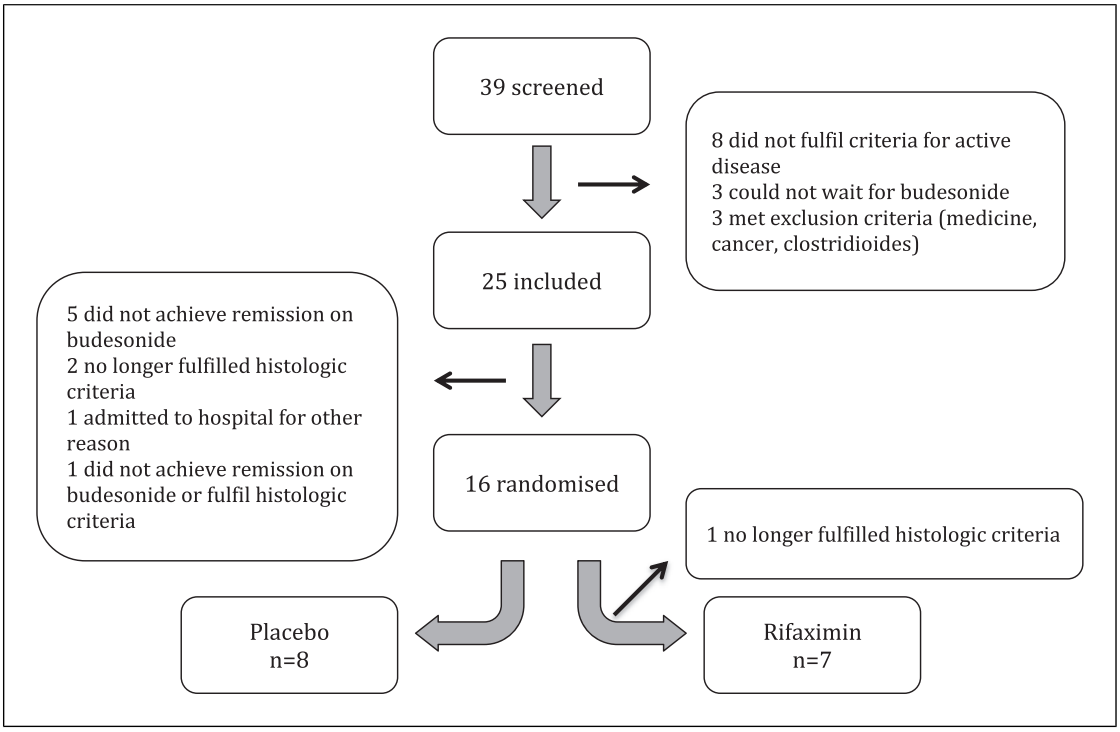

Fig. 2. Flowchart showing patient enrolment.

Table 1. Patient characteristics at baseline

	Placebo (*n* = 8)	Rifaximin (*n* = 7)
Female, *n* (%)	7 (87.5)	5 (71.4)
Male, *n* (%)	1 (12.5)	2 (28.6)
Age, mean (SD), years	64.7 (5.6)	61.6 (7.6)
Smoking status, *n* (%)		
Current smoker	2 (25)	3 (42.9)
Former smoker	6 (75)	2 (28.6)
Never smoked	0 (0)	2 (28.6)
Medications, *n* (%)		
PPI (p.r.n.)	2 (25)	0 (0)
Non-steroidal anti-inflammatory drugs	0 (0)	1 (14)
SSRI	0 (0)	0 (0)
Months since diagnosis, median (IQR)	15.8 (0.6–44)	7.2 (2.5–16.8)
Cumulated budesonide dose in mg, median (IQR)	1,273 (0–2,430)	378 (0–595)
Days since last biopsy, median (IQR)	4.5 (−7 to 17)	54 (0–206)
Stool frequency per day, mean (SD)	5.4 (2.5)	4.8 (1.5)
Short Health Scale score, mean (SD)	23.2 (5.6)	21.1 (8.3)

The probability of being in remission in the two treatment groups at a given time is shown in the Kaplan-Meier curve (Fig. 3). With a log-rank test p value of 0.0996, the study showed no statistically significant difference.

The mean SHS score at 4-week follow-up in the rifaximin group was 7.4 (SD 4.8) and 5.9 (SD 3.4) in the placebo group. At 8-week follow-up, the mean SHS score was 9.0 (SD 7.0) in the rifaximin group and 11.0 (SD 7.3) in the placebo group. None of these differences in mean scores were statistically significant.

No serious adverse events were observed throughout the study, and none led to study discontinuation. In the

Table 2. Remission, relapse, and relapse rate per 100 person-days at 12-week follow-up

Group	Remission, *n*	Relapse, *n*	Total	*p* value	Person-days at risk*	Relapse rate (95% CI)	Relapse rate ratio (95% CI)
Placebo	0	8	8	0.2	246	3.25 (1.40–6.41)	0.41 (0.11–1.42)
Rifaximin	2	5	7		376	1.33 (0.43–3.10)	

*Person-days at risk represent the total time that patients in the two treatment groups were at risk of experiencing relapse.

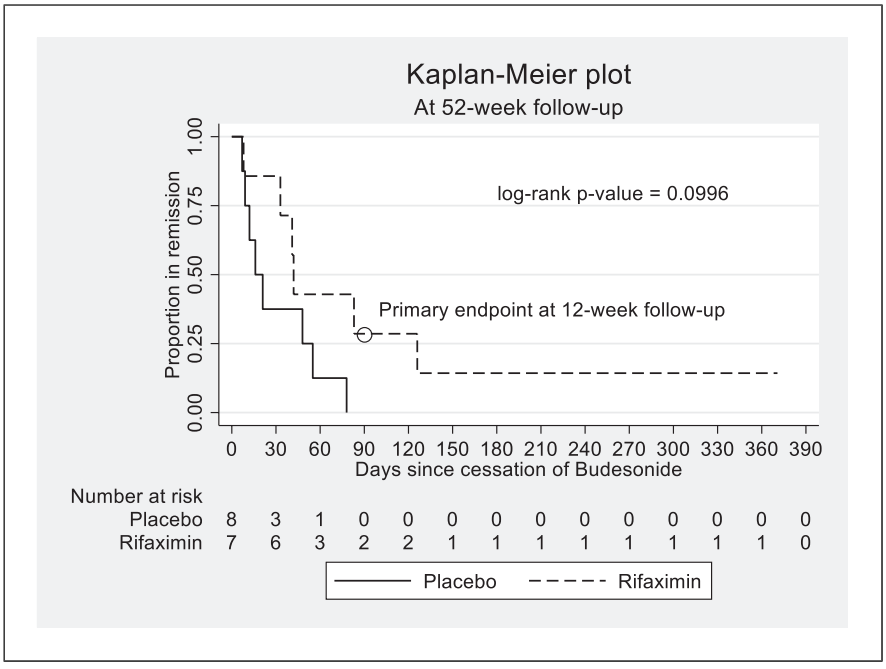

Fig. 3. Kaplan-Meier plot of the proportion of patients in remission at 52-week follow-up in the two treatment groups and showing the number at risk at different time points.

rifaximin group, 1 patient reported myalgia and arthralgia, whereas another reported oedema and shingles. In the placebo group, 1 patient reported headache, vertigo and itchy skin, another reported common cold, and a third reported dental abscess and fall.

Discussion

The main purpose of this study was to investigate the effect of rifaximin on the relapse of symptoms after budesonide cessation in CC. Two patients in the rifaximin group were still in remission at week 12 and none in the placebo group. The time to relapse of symptoms seemed prolonged in the rifaximin group. Although there seemed to be a tendency in favour of the rifaximin group that could provide support for the hypothesis, the study could not demonstrate any statistical significant difference in the probability of being in clinical remission between the rifaximin and placebo treatment group. However, low statistical power reduces the chance of detecting a true effect, and the small sample size is a major limitation of the study. The two groups were comparable; however, there was a longer duration and higher cumulated budesonide dose in the rifaximin group. A previous study demonstrated that a high stool frequency at baseline and a long duration of diarrhoea were risk factors for symptom relapse in CC [24]. We cannot exclude the possibility of difference in disease duration affecting the results in favour of the rifaximin group. The study confirmed the high risk of relapse of symptoms once budesonide treatment was ceased as more than 90% of the patients experienced relapse of symptoms within 130 days. CC has a considerable impact on patients' quality of life as reflected in the SHS score at baseline. Patients that fail to respond to budesonide treatment and also patients with repeated need for budesonide treatment represent a challenge in the handling of CC.

Previous studies have reported alterations in the gut microbiota associated with microscopic colitis, but their role in the pathogenesis of CC is still not well defined [7]. However, it could be involved in barrier dysfunction and mucosal inflammation. Therefore, the potential role of microbiota manipulation in treatment of CC has received increasing attention.

Previous studies have shown that rifaximin has eubiotic properties [25] and can be effective for chronic diarrhoea associated with irritable bowel syndrome [17, 18, 26] and small intestinal bacterial overgrowth [16]. The present study is the first randomised controlled trial of rifaximin in CC. Treatment dose of rifaximin in this study was guided by previous studies on small intestinal overgrowth [16] and irritable bowel syndrome dominated by diarrhoea [26]. No serious adverse events were reported in this study, and rifaximin could be a safe treatment option for CC.

We recommend more extensive studies on the therapeutic effect of rifaximin including dosing and duration. First-line treatment with rifaximin compared to budesonide could also be beneficial.

Conclusion

This is the first study testing rifaximin in addition to budesonide on remission rates in CC. The study suggests a potential improvement in relapse rates within the rifaximin group compared to the placebo group. It is essential to emphasise that our study has a limited sample size, underscoring the need for caution when drawing definitive conclusions. However, we advocate for continued investigation into the impact of microbiota modulation, including rifaximin treatment, on patients with CC.

Statement of Ethics

The study protocol was reviewed and approved by the Central Denmark Region Committees on Health Research Ethics (approval number 1-10-72-214-18) and the Danish Health Agency and Data Protection Agency. The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and Good Clinical Practice principles. All patients provided written informed consent prior to inclusion.

Conflict of Interest Statement

The authors declares no conflicts of interest.

Funding Sources

The study was supported by a grant from A.P. Møller and Chastine Mc-Kinney Møller Foundation for the Advancement of Medical Science (Grant No. 18-L-0146). Study drug and placebo were delivered by Norgine.

Author Contributions

Sabine Becker drafted the protocol, recruited patient, and performed the database; Louise Bang Grode carried out the statistical analysis; and Ole Kristian Bonderup was the principal investigator and had the idea for the study. Sabine Becker, Louise Bang Grode, and Ole Kristian Bonderup equally contributed to interpretation of the study findings and to the writing of the manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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