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CLINICAL TRIAL REPORT

A Randomized Controlled Pilot Study Evaluating the Safety and Efficacy of Nifuroxazide in Patients with Ulcerative Colitis

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Background: The therapeutic potential of nifuroxazide in colitis has been explored in several experimental studies of ulcerative colitis (UC).

Aim: To evaluate the efficacy of nifuroxazide in patients with UC.

Methods: Fifty patients with mild to moderate UC were randomly assigned into two groups (n = 25 each). The placebo group received a placebo alongside mesalamine (1 g three times daily [t.i.d.]) for six months. The nifuroxazide group received nifuroxazide (200 mg twice daily) in combination with mesalamine (1 g t.i.d). A gastroenterologist assessed disease severity using the partial Mayo score (PMS). Serum levels of C-reactive protein (CRP), nuclear factor kappa B (NF-κB), interleukin-6 (IL-6), and signal transducer and activator of transcription 3 (STAT3) were measured before and after treatment. Quality of life was evaluated using the Inflammatory Bowel Disease Questionnaire (IBDQ-32). Primary outcomes: Change in PMS. Secondary outcomes: change in IBDQ-32 and in the level of measured biomarkers.

Results: Baseline measurements were comparable between groups ($p > 0.05$). Post-treatment values showed significant improvements within both groups compared to baseline. However, the nifuroxazide group demonstrated significantly greater improvements than the placebo group, including reductions in PMS ($p = 0.005$) and increases in IBDQ scores ($p = 0.002$). Additionally, significant decreases were observed in IL-6 ($p = 0.03$), NF-κB ($p = 0.03$), CRP ($p = 0.02$), and STAT3 ($p = 0.03$) levels. The placebo group had a response rate of 56% (14/25) and a remission rate of 24% (6/25), whereas the nifuroxazide group achieved a response rate of 76% (19/25) and a remission rate of 56% (14/25), based on PMS.

Conclusion: Co-administration of nifuroxazide with mesalamine improved clinical outcomes, including higher response and remission rates, reduced inflammation by reducing IL-6/STAT3, and enhanced quality of life in patients with UC, compared to mesalamine alone.

Trial Registration Identifier: NCT05988528.

Keywords: nifuroxazide, IL-6, STAT3, PMS, ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) is a chronic condition characterized by recurrent inflammation of the gastrointestinal (GI) tract, primarily driven by an abnormal immune response to the gut microbiota. It encompasses two major forms of idiopathic intestinal disorders—ulcerative colitis (UC) and Crohn's disease (CD)—which differ in their anatomical distribution and the extent of tissue involvement.[1] UC, an idiopathic and chronic inflammatory disease, is marked by

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continuous inflammation of the colonic and rectal mucosa. However, the precise mechanisms underlying UC remain unclear.[2] Due to the increased risk of colorectal cancer associated with UC, there is a pressing need for novel therapies that can slow disease progression and improve clinical outcomes.[3] The pathophysiology of UC involves multiple factors, including epithelial barrier disruption, immune system dysregulation, genetic susceptibility, and environmental influences. A hallmark of IBD is the presence of elevated inflammatory mediators in the affected mucosa, along with increased intestinal permeability.[4,5]

In patients with UC, activated dendritic cells and macrophages are abundant in the colonic mucosa, with their presence positively correlating with disease severity.[6] In experimental colitis models, lamina propria immune cells express Toll-like receptor 4 (TLR-4), which activates nuclear factor kappa-B (NF-κB) in macrophages, leading to the release of proinflammatory cytokines.[7] This proinflammatory cascade plays a key role in disrupting tight epithelial junctions and inducing epithelial cell apoptosis.[8] Among these cytokines, interleukin-6 (IL-6)—a pleiotropic mediator—is critically involved in the pathogenesis of IBD and other inflammatory disorders.[9] Elevated serum IL-6 levels have been observed in patients with IBD.[10,11]

In UC, IL-6 binds to its receptor (IL-6R), initiating trans-signaling through the formation of an IL-6/IL-6R complex that associates with the glycoprotein 130 (gp130) subunit, propagating intracellular signaling.[12] Both IL-6 and IL-6R are expressed by T cells and macrophages during active disease phases.[13] The binding of gp130 to the IL-6/IL-6R complex activates Janus kinases (JAKs), which in turn stimulate downstream signaling via the signal transducer and activator of transcription 3 (STAT3).[14] Activated and phosphorylated STAT3 (p-STAT3) forms dimers that translocate from the cytoplasm to the nucleus, where they regulate various gene expression pathways.[15] Studies have demonstrated that lamina propria mononuclear cells from IBD patients express p-STAT3.[16] Notably, inhibition of IL-6 and STAT3 signaling has been shown to reduce colitis severity in murine models.[17] Supporting this, El-Haggar et al reported that targeting the IL-6/STAT3 axis alleviated inflammation in UC patients.[9] Collectively, these findings underscore the pivotal role of IL-6/STAT3 signaling in the development and progression of colitis.

Current standard treatments for UC aim to induce and maintain remission and include amino salicylates (eg, mesalamine), corticosteroids, immunomodulators, and biologic therapies such as anti-tumor necrosis factor (TNF) agents and integrin inhibitors.[18] However, current treatments are not without limitations. Mesalamine, while generally well tolerated, may be insufficient in moderate to severe cases. Corticosteroids are associated with significant side effects when used long-term, including osteoporosis, hyperglycemia, and immunosuppression.[19] Biologic agents, although effective for some patients, carry risks such as infections and loss of response over time due to immunogenicity. Moreover, a considerable proportion of patients experience incomplete or suboptimal responses, underscoring the need for adjunctive therapies that are both safe and effective.[20]

Nifuroxazide is an oral antibiotic approved for use as an effective antidiarrheal agent, with a favorable safety profile in various gastrointestinal (GI) infections.[21] Beyond its antidiarrheal action, nifuroxazide has been shown to suppress STAT3 activity,[22] underscoring its dual pharmacological role. Its primary therapeutic effect is attributed to its antibacterial activity, which involves inhibition of bacterial enzymes essential for metabolic processes. Moreover, recent studies suggest that nifuroxazide exhibits anti-inflammatory properties by inhibiting Janus kinases (JAKs)—particularly JAK2—and interfering with the STAT3 signaling pathway.[23–25] This mechanism contributes to its potential in modulating immune responses and reducing inflammation in conditions such as inflammatory bowel disease (IBD).[23] Notably, nifuroxazide has been reported to alleviate colonic ulcers in an acetic acid-induced colitis model by regulating IL-6 and STAT3 signaling cascades.[23,26] Nifuroxazide's inhibition of IL-6/STAT3 signaling suggests its potential to modulate the inflammatory pathways that drive UC. This molecular action could lead to a reduction in disease activity, as evidenced by improved outcomes such as decreased UC symptoms, higher remission rates, and reduced levels of inflammatory biomarkers. Based on these observations, the hypothesis of this study is that nifuroxazide, when used in combination with mesalamine, will enhance clinical remission and response rates in UC patients by targeting these key inflammatory pathways, offering a promising adjunctive therapeutic approach. Till now, there is no clinical study that investigated the effect of nifuroxazide in patients with UC.

In summary, the hypothesis of this study is that nifuroxazide, when co-administered with mesalamine, will improve clinical outcomes in patients with UC by enhancing anti-inflammatory effects and increasing response and remission rates.

Patients and Methods

Between August 2023 and December 2024, a total of 50 patients who met the inclusion criteria were enrolled from the Gastroenterology Department at the Faculty of Medicine, Fayoum University. The study received approval from the Institutional Review Board (IRB) of the Faculty of Medicine, Fayoum University (Approval number: R 516). The study design and procedures adhered to the principles of the Declaration of Helsinki and its 1964 amendments. All patients were informed of their right to withdraw from the trial at any time without consequence. Both the type of exposure and the randomization process were blinded to both patients and physicians (double blinded).

Inclusion Criteria

Eligible patients were ≥18 years of age, of any gender, and had an endoscopically confirmed diagnosis of mild to moderate UC. Patients who were either treatment-naïve or already receiving mesalamine therapy were included.

Exclusion Criteria

Patients were excluded if they had severe UC or were receiving treatment with systemic or rectal steroids, immunosuppressants, or biologic agents. To minimize the risk of metabolic complications associated with nifuroxazide, individuals with hepatic or renal impairment were also excluded. Additionally, patients with a history of colorectal cancer or previous colectomy, whether partial or total, were deemed ineligible. Other exclusion criteria included a history of alcohol or drug dependency, as well as known hypersensitivity to any of the study medications.

Study Design

This was a prospective, randomized, double-blind clinical study registered in 2023 under the identifier NCT05988528 on ClinicalTrials.gov. A total of 50 patients were enrolled and randomly assigned into two groups (n = 25 each), as illustrated in the CONSORT flow diagram (Figure 1). Randomization was performed using a computer-generated sequence. All participants met the inclusion criteria and provided written informed consent prior to enrollment.

Group 1 (Placebo Group): Patients in this group received a placebo capsule twice daily along with 1 g mesalamine tablets three times daily (Pentasa® 500 mg, Multi Pharm, Egypt) for six months.

Group 2 (Nifuroxazide Group): Patients in this group were administered 200 mg nifuroxazide capsules twice daily in addition to 1 g mesalamine tablets three times daily (Antinal® 200 mg, Amoun, Egypt) for six months. The placebo capsule was identical in appearance to the nifuroxazide capsule.

Sample Size Calculations

The precise effect size of nifuroxazide medication on changes in PMS has never been studied before. This study was designed to be a pilot one according to Sim and Lewis[27] who advised that a sample size more than 22 in each group for small to medium effect size to decrease combined size. Assuming a 10% dropout rate, a sample size of 25 patients was randomly assigned to each group, setting α-error = 0.05 (2-tailed) and a power of 0.80.

Study Protocol

Patients were closely monitored through monthly in-person visits and weekly follow-up calls, with the hospital's records regularly reviewed for any reported concerns. In accordance with CONSORT guidelines, participants were randomly assigned to one of two treatment groups. One group received mesalamine tablets three times daily along with a placebo capsule twice daily (mesalamine group), while the other received mesalamine tablets three times daily along with a nifuroxazide capsule twice daily (nifuroxazide group). All medications were administered orally, and patients were provided with guidance on nutrition and lifestyle modifications. Patients were advised to maintain their usual diet, and major dietary modifications were discouraged throughout the trial period. Patients were instructed to avoid nonsteroidal

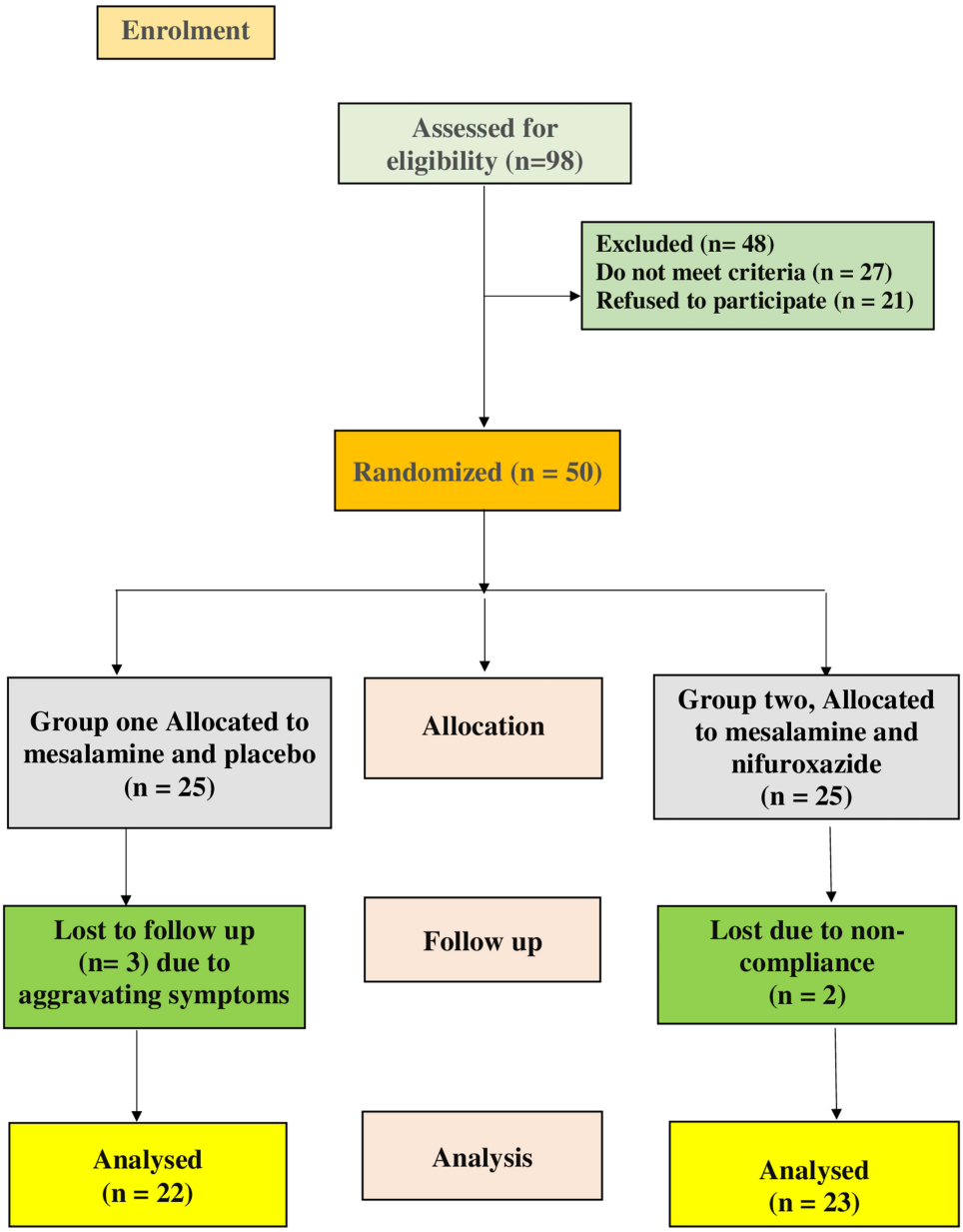

Figure 1 CONSORT flow chart displaying the flow of participants during study.

anti-inflammatory drugs (NSAIDs) and other immunomodulatory agents during the study. The selected dose for mesalamine is 1 g t.i.d[28] and for nifuroxazide is 200 mg twice daily[29] based on previous studies.

Study Outcomes

Primary Outcomes

The primary endpoint of the study was the change in the partial Mayo score (PMS) index, which assessed remission and clinical response in mild to moderate patients with UC.

Secondary Outcomes

Secondary outcomes include changes in the Inflammatory Bowel Disease Questionnaire (IBDQ-32) scores, as well as serum levels of IL-6, NF-κB, C-reactive protein (CRP), and STAT3, which together assess the biological effects of nifuroxazide treatment.

Follow-up

Patients were followed up with monthly in-person visits and weekly phone calls. To rule out any underlying organic dysfunction, a complete blood count, liver and kidney function tests, and a detailed medical history were collected during the initial visit. Additionally, serum levels of the biomarkers IL-6, NF-κB, CRP, and STAT3 were measured.

Evaluation of Colitis

The Partial Mayo Score (PMS) index was employed to assess the severity of the disease. PMS is a non-invasive assessment tool used to determine the severity of UC. The composite score is calculated from three subcategories: stool frequency, rectal bleeding, and the physician's overall assessment. The total score ranges from 0 to 9.[30] PMS scores were recorded both prior to the initiation of treatment and at the conclusion of the study. A reduction of ≥1 point in the rectal bleeding sub score or an absolute rectal bleeding sub score of 0 or 1 was considered a clinical response, as was a decrease in the overall PMS of ≥2 points and ≥30% from baseline. A PMS score of less than two, with no single sub score higher than one, was deemed to indicate clinical remission.[31]

Assessment of Quality of Life

The most popular measure for assessing disease-specific quality of life in randomized clinical studies for ulcerative colitis is the IBDQ-32. The four categories of functioning and well-being that the IBDQ-32 assesses are emotional and social function, bowel and systemic symptoms.[32] Reviews of the IBDQ-32's measurement properties provide evidence supporting its responsiveness, construct validity, reliability, and content validity.[33,34] The total score (scoring range: 0–224) can be calculated using the sum of the 32 components Higher domain and overall scores imply better health related quality of life (HRQoL).

Sample Collection

Prior to the initiation of the study and again six months after the intervention, venous blood samples (10 mL) were drawn from the antecubital vein. The samples were transferred gradually into test tubes and allowed to clot, then centrifuged at 4500 g for 10 minutes using a Hettich Zentrifugen EBA 20 centrifuge. The resulting serum was divided into two aliquots: one was stored at −80°C for subsequent cytokine level analysis, and the other was used for routine assessments of hepatic and renal function.

Biochemical Analysis

Commercially available enzyme-linked immunosorbent assay (ELISA) kits were used to measure serum levels of IL-6 (catalog no. 201–12-0091), NF-κB (catalog no. 201–12-0691), CRP (catalog no. 514003), and STAT3 (catalog no. 201–12-0651), following the manufacturer's instructions. The kits were supplied by SunRed, located in Shanghai, China, with the CRP kit provided by Spectrum Diagnostics. The intra-assay and inter-assay coefficients of variation were as follows: IL-6, 9.2% and 10.4%; NF-κB, 8.9% and 10.8%; CRP, 8.9% and 9.9%; and STAT3, 9% and 11%, respectively.

Statistical Analysis

Statistical analysis was performed using Prism version 9 from GraphPad Software, Inc. (San Diego, California, USA). The Shapiro–Wilk test was applied to assess the normality of continuous variables. To compare within-group differences, the Wilcoxon test was used for non-parametric data, and the Student's *t*-test was applied for parametric data, both before and after treatment. Between-group differences, pre- and post-treatment, were assessed using the Mann–Whitney *U*-test for non-parametric data and the unpaired Student's *t*-test for parametric data. Qualitative variables were presented as counts and frequencies, while quantitative variables were expressed as median, interquartile range, and mean ± standard deviation (SD). For categorical data, the Fisher exact test and the Chi-square test were used. All p-values were two-tailed, with a value of less than 0.05 considered statistically significant.

Results

Analysis of Baseline Demographic Data

The clinical, demographic, and laboratory data for the mesalamine and nifuroxazide groups are reported in Table 1. These data included variables such as gender distribution (males/females), body mass index (BMI), liver function enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), hemoglobin (Hgb), serum albumin, UC disease duration, number of smokers, serum creatinine (Sr Cr), and disease site (rectum only [proctitis], the splenic flexure or the left side of the colon [left-sided colitis], or both [proctosigmoiditis]). At baseline, there were no statistically significant differences between the two groups for any of these variables ($P > 0.05$). Three patients were lost to follow-up in the mesalamine group due to worsening symptoms, and two patients were dropped from the nifuroxazide group due to non-compliance with the study procedures. Therefore, statistical analysis was conducted per protocol, except for disease activity scores (PMS and IBDQ-32), which were analyzed using an intention-to-treat approach.

Effect of Studied Drugs on Clinical Outcomes

The results in Table 2 provide a detailed analysis of clinical markers, including symptoms and disease activity scores, and the impact of study medications on patient outcomes in individuals with UC. It compares the PMS before and after treatment for both the mesalamine and nifuroxazide groups, as well as the statistical significance between the two groups post-treatment. Baseline measurements for PMS were comparable between the mesalamine-only group and the mesalamine plus nifuroxazide group, indicating similar disease severity at the start of the study ($P > 0.05$). Following treatment with mesalamine alone, there was a statistically significant improvement in clinical parameters, with a reduction of 3 in the PMS. The Wilcoxon test revealed significant changes within this group, reflecting the effectiveness of mesalamine in managing UC symptoms. In contrast, the nifuroxazide group showed even greater

Table 1 Clinical, Demographic and Laboratory Data of the Patients

Parameter	Placebo Group (n=25)	Nifuroxazide Group (n=25)	P value
Age (years)	45.34 ± 12.18	49.20 ± 9.19	0.212
Sex (M/F)	12 /13	14 /11	0.571
BMI (kg/m^2)	23.36 ± 1.63	23.30 ± 1.139	0.897
Serum ALT (IU/L)	27.60 ± 6.49	28.92 ± 3.98	0.390
Serum AST (IU/L)	32.80 ± 6.93	31.76 ± 9.58	0.662
SrCr (mg/dL)	0.94 ± 0.13	0.95 ± 0.10	0.585
Hgb (mg/dl)	13.16 ± 1.01	13.71 ± 1.48	0.129
Albumin (g/dl)	4.465 ± 0.938	4.429 ± 0.649	0.874
Disease duration	1.6 (0.85–2.6)	1.8 (0.85–2.85)	0.490
Smoking (no.)	4	5	0.999
Site of disease (no.)			
Proctitis	9	9	0.999
Left-sided	9	7	0.544
Proctosigmoiditis	7	9	0.544

Notes: Data was presented as mean ±SD, median, interquartile range, and numbers, Placebo group, UC patients treated with mesalamine and placebo, Nifuroxazide group, UC patients treated with mesalamine plus nifuroxazide, Significance at ($p < 0.05$).
Abbreviations: M, Male; F, Female; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hgb, haemoglobin, Sr Cr, serum creatinine.

Table 2 Effect of Study Medications on Partial Mayo Score Index (PMS)

Character	Placebo Group (n=25)			Nifuroxazide Group (n=25)			*P* Value	Effect Size
	Before Treatment	After Treatment	*P* value	Before Treatment	After Treatment	*P* value	After Treatment	Rank-Biserial Correlation Coefficient (*r*)
Partial Mayo score index (PMS)	5 (3.5–5)	2 (1–3)	<0.0001*	5 (3–5.5)	1 (0–2)	0.0001*	0.005**	0.375
Response (n, %)	14 (56%)			19 (76%)			0.037***	
Remission (n, %)	6 (24%)			14 (56%)			0.02***	

Notes: Data was presented as mean and standard deviation, numbers, median and interquartile range, Placebo group, UC patients treated with mesalamine and placebo, nifuroxazide group, UC patients treated with mesalamine plus nifuroxazide. (*) level of significance within the same group using Wilcoxon test. (**) level of significance between groups using Mann Whitney test. (***) level of significance between groups using Chi-square test. Significance at ($p < 0.05$).

improvements compared to baseline values, with a statistically significant reduction of 4 in the PMS, indicating a more pronounced effect of the combination therapy. The Mann–Whitney *U*-test was used to assess differences between groups after treatment, and the analysis revealed statistically significant differences for all evaluated clinical parameters ($P < 0.05$), indicating that patients receiving nifuroxazide in addition to mesalamine experienced better outcomes than those treated with mesalamine alone.

In the mesalamine group, the response rate for PMS was 56% (n = 14/25), and the remission rate was 24% (n = 6/25). In the nifuroxazide group, the response rate for PMS was 76% (n = 19/25), and the remission rate was 56% (n = 14/25) (Table 2).

Effect of Studied Drugs on Quality of Life

A comprehensive analysis of disease-specific quality of life via IBDQ's social, systemic, digestive, emotional domains, as well as the total IBDQ scores experienced by patients in the mesalamine and nifuroxazide groups during the study are presented in Table 3. The improvement in the social domain after treatment with either mesalamine alone (an increase of 6 points) or with mesalamine and nifuroxazide (an increase of 5 points) were statistically significant compared to the baseline scores of each group. However, there was no statistical difference in the final outcomes of this social domain between the two groups post-treatment ($P > 0.05$). The systemic, digestive, and emotional domains, as well as the total IBDQ score showed a similar trend to that reported for biochemical and clinical markers. The improvements noted in the nifuroxazide group (2, 19, 6, 33 points for systemic, digestive, emotional domains, and the total IBDQ score, respectively) exceeded the significant improvements observed in the mesalamine group (6, 26, 16, 49 points for systemic, digestive, emotional domains, and the total IBDQ score, respectively).

Table 3 Effect of Study Medications Impact on Disease-Specific Quality of Life via the Inflammatory Bowel Disease Questionnaire (IBDQ-32) Scores Subscales

Character	Placebo Group (n=25)			Nifuroxazide Group (n=25)			##*P* Value	Effect Size
	Before Treatment	After Treatment	#*P* Value	Before Treatment	After Treatment	#*P* Value	Ater Treatment	Rank-Biserial Correlation Coefficient (r)
Social domain	13 (10–18)	19 (12–24.5)	0.002	15 (10.5–20)	20 (14–23.5)	0.003	0.866	0.023
Systemic domain	17 (11–19.5)	19 (17–21.5)	0.0006	17 (11.5 –22)	23 (19.5–26)	0.001	0.004	0.389
Digestive domain	32 (29–36)	51 (36–58)	<0.0001	34 (26.5–37.5)	60 (50.5–64)	<0.0001	0.009	0.359
Emotional domain	25 (18–36)	31 (19–50)	0.02	25 (14.5–34.5)	41 (31–55)	0.0007	0.035	0.294
Total IBDQ score	89 (75–98.5)	122 (100–140.5)	<0.0001	94 (77–112)	143 (125–154.5)	<0.0001	0.002	0.426

Notes: Data was presented as median and interquartile range, Placebo group, UC patients treated with mesalamine alone, nifuroxazide group, UC patients treated with mesalamine plus nifuroxazide, (#) level of significance within group using Wilcoxon test. (##) level of significance between groups using Mann Whitney test, (IBDQ), inflammatory bowel disease questionnaire, Significance at ($p < 0.05$).

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Effect of Studied Drugs on Biological Markers

The effect of study medications on various serum parameters in patients with UC is presented in Table 4. Baseline levels of IL-6, NF-κB, CRP, and STAT3 were comparable between the two groups ($P > 0.05$). After treatment with mesalamine alone (n = 22) or nifuroxazide (n = 23), there was a statistically significant reduction ($P < 0.05$) in the levels of these inflammatory markers compared to baseline values. Post-treatment comparisons between the two groups revealed statistically significant differences for all four serum parameters ($P < 0.05$), indicating that the combination of nifuroxazide with mesalamine was more effective in reducing inflammation.

Analysis of Side Effects Associated with the Studied Drugs

Regarding the side effects observed for each treatment intervention, Table 5 presents the incidence of various side effects, including nausea, vomiting, skin rash, abdominal pain, headache, and dizziness, allowing for a comparison between the two treatment regimens. Overall, although the nifuroxazide group reported lower percentages of subjects experiencing side effects, there were no statistically significant differences in any of the investigated side effects between the two groups ($P > 0.05$).

Table 4 Effect of Study Medications on Serum Biomarkers

Parameter	Placebo Group (n=22)			Nifuroxazide Group (n=23)			*P* Value	Effect Size
	Before Treatment	After Treatment	*P* Value	Before Treatment	After Treatment	*P* Value	After Treatment	r
IL-6 (pg/mL)	127.7 (117.5–146.3)	113.8 (93.95–143)	0.02[A]	121.4 (116–149)	98.6 (63.8–113.5)	0.0002[A]	0.03[B]	0.308
CRP (mg/L)	38 (12.75–74.5)	20.15 (9.75–60.4)	0.04[A]	36 (15–68)	13 (6–42.3)	<0.0001	0.02[B]	0.324
NF-κB (ng/mL)	22.26 (10.35–28.8)	16.60 (13.88–19.85)	0.03[A]	22 (12.5–24.87)	12.79 (7.8–16.47)	0.0005[A]	0.03[B]	0.304
STAT3 (pg/mL)	256.5 (198–276.5)	220 (135.5–257.5)	0.001[A]	266 (168–282)	132 (78.2–230)	0.003[A]	0.03[B]	0.308

Notes: Data was presented as mean ±SD, median and interquartile range. Placebo group, UC patients treated with mesalamine and placebo, Nifuroxazide group, UC patients treated with mesalamine plus nifuroxazide, IL-6, interleukin 6, CRP, C-reactive protein, NF-κB, nuclear factor Kappa B, STAT3, signal transducer and activator of transcription factor 3. ([A]) level of significance within the same group by Wilcoxon test. [(B)] Level of significance between groups using Man Witney test. Significance at ($p < 0.05$). Rank-biserial correlation coefficient (r) using effect size for the Mann–Whitney *U*-test.

Table 5 Analysis of Drug Related Side Effects Between the Studied Groups

Side effect	Placebo group; n=22 (%)	Nifuroxazide group; n=23 (%)	*P* value
Nausea	3 (13.6%)	2 (8.7%)	0.665
Vomiting	4 (18.2%)	3 (13%)	0.699
Skin rash	2 (9.1%)	2 (8.7%)	0.999
Abdominal pain	2 (9.1%)	2 (8.7%)	0.999
Headache	4 (18.2%)	3 (13%)	0.699
Dizziness	4 (18.2%)	3 (13%)	0.699

Notes: Data was presented as numbers, Placebo group, UC patients treated with mesalamine and placebo, nifuroxazide group, UC patients treated with mesalamine plus nifuroxazide, Significance at ($p < 0.05$) using fisher exact test.

Discussion

Ulcerative colitis (UC) is a chronic and debilitating immune-mediated inflammatory disorder that primarily affects the colonic mucosa. Patients experiencing acute flare-ups often present with symptoms such as weight loss, diarrhea, and rectal bleeding.[35] Currently, there is no cure for UC, and available therapies are associated with various side effects. Therefore, exploring alternative treatment options is essential for managing this disease.

Repurposing, also known as drug repositioning, is an effective strategy for discovering new uses for existing pharmaceuticals that have already been approved. This approach has shown success in treating a variety of conditions, including Parkinson's disease, depression, UC, breast cancer, and colon cancer.[36–39]

Despite nifuroxazide's traditional approval for short-term use in treating acute diarrhea, new evidence of its immunomodulatory effects led to an extension of its administration in this trial to six months. Preclinical results indicating possible advantages in chronic inflammatory disorders served as the foundation for the justification for this extended use.[26,40] Throughout the study period, every patient was meticulously watched for tolerability and safety. This is the first clinical trial that contributes important information to the growing body of research on nifuroxazide's potential as a treatment for UC through investigating its effects in patients with UC. Our findings indicate that the addition of nifuroxazide to mesalamine significantly reduced the PMS and improved patients' quality of life, as reflected in the IBDQ-32 domains. Additionally, compared to the control group, the nifuroxazide group exhibited a significantly higher response and remission rate. These results align with previous studies that evaluated nifuroxazide's effects in animal models of colitis.[23,26] Similarly, Yousra et al reported that nifuroxazide decreased the disease activity index, reduced diarrhea and bleeding scores, and alleviated mucosal damage in colitis.[23]

The nifuroxazide treatment group showed a significant improvement in the PMS, with a marked decrease in both diarrhea and bleeding scores compared to baseline values and the control group. While both groups experienced significant improvements in the IBDQ-32 compared to their initial scores, notable differences between the groups were observed, except in the social domain. It is well-established that UC severely impacts health-related quality of life (HRQoL) and imposes a substantial economic burden.[41] Hoivik et al reported that the HRQoL of UC patients was lower than that of the general Norwegian population,[41] a finding consistent with our results, which demonstrated a significant decrease in IBDQ scores among UC patients. A separate study found that nifuroxazide significantly reduced inflammatory biomarkers and alleviated inflammation, apoptosis, and histopathological damage in animal models of colitis.[23] Additionally, prior studies have shown that mesalamine has a beneficial effect on HRQoL, with notable improvements from baseline values.[42] Moreover, our findings align with previous research on the use of anti-inflammatory agents as adjunct treatments for IBDs. Studies have demonstrated that atorvastatin, pentoxifylline, fenofibrate, and metformin exert a protective effect on the colon and enhance the therapeutic efficacy of mesalamine.[9,39,43,44] These findings help highlight the potential benefits of nifuroxazide in reducing the PMS, lowering bleeding scores, and improving HRQoL.

In the current study, the mesalamine group demonstrated a significant reduction in PMS, serum IL-6, CRP, NF-κB, and STAT-3 levels compared to pre-treatment values. Given that mesalamine is commonly used to treat mild to moderate cases of ulcerative colitis (UC), these observations can be confidently attributed to the effects of mesalamine itself.[45] These findings align with previous studies that have investigated the impact of mesalamine on STAT-3 in colitis.[44,46] Mesalamine exerts anti-inflammatory and apoptotic properties through a PPAR-gamma-dependent mechanism, which inhibits the synthesis of inflammatory cytokines.[47] As noted by El-Haggar et al, mesalamine significantly reduced STAT-3 gene expression and serum IL-6 levels in patients with mild to moderate UC.[9]

Accumulated research suggests that the pathophysiology of UC is primarily driven by the proliferation of a coordinated inflammatory cascade. UC has been associated with several dependent and independent inflammatory signaling pathways, including the NF-κB/IL-6/STAT-3 pathway.[9,48] In the current study, the nifuroxazide group showed a significant decrease in IL-6 serum levels after treatment, compared to baseline and control groups. These findings are consistent with earlier studies.[23,26] IL-6 plays a crucial role in the pathophysiology of UC. As a key cytokine, IL-6 regulates the adaptive immune response in UC, and its interaction with IL-6R mediates IL-6 trans-signaling in IBD patients. This interaction recruits the gp130 component, which, upon phosphorylation and activation by JAK1, leads to

the translocation of p-STAT3 to the nucleus.[49] Musso and Dentelli observed that pSTAT3 is expressed in effector T-cells and lamina propria macrophages in mucosal biopsy specimens from UC patients.[50] Furthermore, Carey et al reported that increased IL-6/STAT-3 regulation correlates with higher expression of chemokines and chemokine-positive T effector cells in patients with IBD.[15] In parallel, our results revealed significant upregulation of IL-6 and STAT-3 expression at baseline in UC patients, with levels markedly reduced after treatment with nifuroxazide and mesalamine, compared to mesalamine alone. Inhibition of the IL-6/STAT-3 signaling pathway has been shown to reduce the severity of colitis, as demonstrated by Han X et al.[17] Additionally, T-cells lacking STAT-3 exhibit resistance to IL-6-induced proliferation and survival.[51] Therefore, modulating the dysregulated IL-6/STAT-3 pathway may be a valuable treatment strategy to reduce mucosal inflammation in UC. Interestingly, nifuroxazide therapy significantly reduced STAT-3 levels, which could be attributed to its effects on IL-6 expression. In this context, Won and Kim demonstrated that nifuroxazide's inhibition of IL-6/STAT-3 signaling prevented the formation of hepatic cellular carcinoma xenografts.[52] As a potent STAT-3 inhibitor, nifuroxazide reduces inflammation and protects against diabetic nephropathy in rats.[22] By decreasing Jak kinase autophosphorylation, nifuroxazide effectively suppresses STAT-3 function and prevents the constitutive phosphorylation of STAT-3 in multiple myeloma cells, leading to the down-regulation of the STAT-3 target gene Mcl-1.[53] Furthermore, nifuroxazide's suppression of the STAT-3 signaling pathway enhances antitumor immunity and inhibits the progression of colorectal cancer.[54] These mechanistic pathways may help explain the protective role of nifuroxazide in UC patients by targeting the IL-6/STAT-3 axis.

In comparison to mesalamine alone, the current study demonstrated that combination therapy with nifuroxazide and mesalamine significantly reduced CRP levels. These results align with previous studies conducted in the same field.[23,26] CRP has long been recognized as one of the primary serum markers of disease activity in IBD.[55] Schoepfer et al thoroughly examined CRP's role in assessing disease activity, finding that active UC patients had higher CRP levels than non-active patients, and endoscopic activity could be predicted with 69% accuracy.[56] Moreover, CRP serves as an important marker for monitoring disease progression, enabling adjustments in treatment according to the treat-to-target approach.[57] CRP plays a crucial role in the immune system, with multiple functions. It is primarily produced in the liver in response to elevated pro-inflammatory cytokines such as IL-6 and TNF-α.[55] IL-6 has been identified as the key factor stimulating CRP production in hepatocytes during inflammation.[58] CRP is a major acute-phase protein, and while its baseline level is typically around 1 mg/l, it increases rapidly during the acute phase of infection or inflammation. Once the inflammatory process is controlled, CRP levels decrease accordingly.[59] Studies by Ali et al and El-Far et al have reported elevated CRP levels in animal models of colitis, with nifuroxazide significantly reducing CRP levels in these models,[23,26] consistent with our findings. These observations further support the notion that nifuroxazide has anti-inflammatory properties and may be beneficial in treating colitis.

Ulcerative colitis (UC) is characterized by an imbalance that favors a pro-inflammatory state, during which both immune and epithelial cells markedly increase cytokine production. This excessive cytokine release contributes to mucosal damage and tissue destruction. A critical regulator in this process is NF-κB, which controls the gene expression of various pro-inflammatory cytokines implicated in UC pathogenesis, including TNF-α, IL-1β, and IL-6.[60] Elevated expression of NF-κB, accompanied by increased levels of TNF-α and IL-6, has been shown to play a significant role in colon tissue damage.[61] Remarkably, suppression of NF-kB activation was linked to hindering STAT3 activity.[62] In the present study, the combination of nifuroxazide and mesalamine significantly reduced serum NF-κB levels compared to mesalamine monotherapy, which was accompanied by a decrease in colonic inflammatory infiltration. Additionally, nifuroxazide lowered the elevated levels of CRP, an acute-phase protein that serves as a marker of ongoing inflammation and tissue damage. The pronounced suppression of UC-associated inflammation may be attributed to the combined inactivation of STAT3 and NF-κB signaling pathways. Notably, recent studies have demonstrated the renoprotective effects of nifuroxazide in diabetic nephropathy through the simultaneous inhibition of STAT3 and NF-κB activation.[63] Our results were in line with El-Far et al, as they reported that nifuroxazide dampens colon ulcer in a dose dependent manner through inactivation of STAT3 and NF-κB.[23]

It's interesting to note that baseline demographic information and side effects did not significantly change between the two trial groups; consequently, mesalamine and nifuroxazide are primarily responsible for the therapeutic benefit.

While these biomarkers are important indicators of inflammation, their reductions do not necessarily correlate directly with clinical outcomes such as symptom improvement, remission, or mucosal healing. Further studies are needed to confirm whether these biomarker changes are truly indicative of clinically meaningful benefits, such as improved quality of life or long-term disease control.

Finally, nifuroxazide could offer an alternative or adjunctive therapy, especially in mild to moderate cases of UC, where biologics and JAK inhibitors may not be routinely indicated due to their higher cost and potential for side effects. Given nifuroxazide's favorable safety profile, affordability, and its potential to enhance the anti-inflammatory effects of mesalamine, it could be a cost-effective option in resource-limited settings.

Despite the promising findings, this study has several limitations that must be considered:

1. Lack of Long-Term Follow-Up: The study was conducted over a 6-month period, which limits our ability to assess the long-term efficacy of nifuroxazide in sustaining remission or preventing disease relapse. Longer follow-up is needed to evaluate the durability of the treatment effects.
2. Off-label and Extended Use of Nifuroxazide: The off-label and extended use of nifuroxazide beyond its approved duration of therapy. While no significant safety concerns were observed, the lack of prior published clinical studies using nifuroxazide over such a prolonged period necessitates cautious interpretation of the results.
3. Absence of Endoscopic and Histologic Validation: While clinical and biomarker measures were used to assess disease activity, mucosal healing was not directly evaluated due to the lack of colonoscopy and histologic assessments. Endoscopic and histologic validation of mucosal healing would provide a more comprehensive assessment of treatment effectiveness, and this should be addressed in future studies.
4. Small Sample Size and Single-Center Design: The sample size of 50 patients limits the statistical power and generalizability of the findings. Additionally, the study was conducted at a single center, which may restrict the external validity of the results. Larger, multicenter studies are needed to confirm the findings and improve generalizability across diverse populations.
5. No Comparison to Other Established Therapies: The study did not compare nifuroxazide to other established therapies for UC, such as biologics or JAK inhibitors. The absence of this comparison limits our ability to assess whether nifuroxazide offers comparable benefits or superior cost-effectiveness in treating UC.
6. Potential Confounding Factors: Factors such as diet, microbiota composition, and concomitant medications could influence UC outcomes but were not controlled for in this study. These variables should be considered in future research to better isolate the effects of nifuroxazide.

We recommend that future large studies should adopt longer follow-up periods to assess the effectiveness and safety of intervention medications to evaluate the long-term safety profile and tolerability of nifuroxazide in population.

Conclusion

In conclusion, the study suggests that the combination of mesalamine and nifuroxazide enhanced the treatment outcomes for patients with UC, compared to mesalamine alone. The addition of nifuroxazide was associated with greater reductions in inflammatory markers, clinical symptoms, and improvements in quality-of-life metrics. While side effect profiles were comparable between the two treatments, the combination therapy appeared to be well-tolerated. However, these findings should be interpreted with caution, given the small sample size and the absence of histologic or endoscopic validation of disease improvement. Further research, including larger-scale, multicenter randomized controlled trials, and endoscopic assessments, is necessary to confirm these preliminary findings. Moreover, the potential cost-effectiveness and ease of use of nifuroxazide could provide valuable adjunctive therapy, particularly in resource-limited settings, pending confirmation of its clinical benefits in larger cohorts.

Data Sharing Statement

Upon an appropriate request, any data can be obtained from the corresponding author.

Ethical Approval

The Institutional Review Board of Fayoum University's Faculty of Medicine gave its approval to the study (R 516). The study complies with the ethical guidelines provided by the 1964 revisions to the Helsinki Declaration.

Ethical Consent

Written informed consent was acquired by each study participant.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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