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Full Paper

Efficacy and safety of rifaximin in patients with chronic intestinal pseudo-obstruction: a randomized, double-blind, placebo-controlled, phase II—a exploratory trial

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Chronic intestinal pseudo-obstruction (CIPO) is a rare intractable disease with limited treatment options. Small intestinal bacterial overgrowth (SIBO) often co-occurs with several diseases, including CIPO. While rifaximin (RFX) is effective in treating SIBO, its efficacy for CIPO remains unclear. Here, we aimed to investigate the efficacy and safety of RFX in adult patients with CIPO. Twelve patients were randomly assigned to receive RFX (400 mg three times daily, n=8) or a placebo (PBO, n=4) for 4 weeks. The global symptom score for abdominal bloating (GSS-bloating) and an original whole gastrointestinal symptoms score (O-WGSS) were collected, and a glucose hydrogen breath test (GHBT) and abdominal computed tomography (CT) were performed. No significant differences were observed in the primary endpoint. GSS-bloating improved by 75% and 25% in the PBO and RFX groups, respectively, and O-WGSS improved by 25% in both groups. No significant differences were observed in secondary and other endpoints, including the SIBO eradication rate in the GHBT and small intestinal volume on CT. In a post hoc analysis of SIBO-positive patients with CIPO (4/4 and 4/8 in the PBO and RFX groups), SIBO was eradicated in 25% and 75% of the patients (PBO and RFX groups, respectively) at the end of treatment, indicating a high eradication rate in the RFX group. Furthermore, the small intestinal gas volume decreased in the RFX group, and no severe adverse events occurred. Although no significant improvements were observed in subjective indicators, RFX may be beneficial in alleviating SIBO and reducing the small intestinal gas volume in SIBO-positive patients with CIPO.

Key words: chronic intestinal pseudo-obstruction (CIPO), rifaximin (RFX), small intestinal bacterial overgrowth (SIBO), systemic scleroderma (SSc)

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INTRODUCTION

Chronic intestinal pseudo-obstruction (CIPO), an intractable disease, manifests as persistent small bowel distention with air-fluid-level and chronic abdominal symptoms due to intestinal obstruction without any mechanical cause [1–6]. It is a rare disease, and its epidemiology remains poorly understood. A previous epidemiological investigation in Japan reported that the prevalence of CIPO was approximately 1/100,000, showing the rarity of the disease [7].

Patients with CIPO often exhibit persistent abdominal bloating (97.5%), which leads to a substantially impaired quality of life (QOL). CIPO can affect the entire gut, from the esophagus to the rectum, but it predominantly affects the small intestine. A sustained increase in intraluminal pressure causes malabsorption, leading to malnutrition and blood stream infections, which are sometimes fatal [6, 8].

CIPO can be classified as idiopathic or secondary. Idiopathic CIPO, also known as chronic idiopathic intestinal pseudo-obstruction (CIIP), develops without any underlying diseases and accounts for approximately 70% of CIPO cases. Secondary CIPO, meaning CIPO that is secondary to an underlying disease, is mostly associated with systematic scleroderma (SSc) [9].

The main objectives of CIPO treatment are to relieve abdominal symptoms and improve the nutritional status. Pharmacological therapies, such as treatment with prokinetics, are often used to alleviate abdominal symptoms; however, they are mostly ineffective. Therefore, decompression therapies, such as trans-nasal intestinal tube insertion and ileostomy or colostomy, are often required. However, decompression therapy using trans-nasal small intestinal tubes places a high burden on patients, as it causes immense nasal pain and requires long-term hospitalization. Furthermore, surgical options, including palliative ileostomy and colostomy, are highly invasive and difficult to perform because they cannot control the drainage volume and can cause excessive drainage and dehydration.

Recently, percutaneous endoscopic gastro-jejunostomy (PEG-J) has been reported to be effective for alleviating subjective and objective symptoms in patients with CIPO [10]. PEG-J is less invasive and is advantageous in controlling the amount of drainage; however, it has some disadvantages, including the occurrence of reflux esophagitis and chemical dermatitis as well as an insufficient decompression effect on the distal small bowel, which cannot be covered by the PEG-J tube. Therefore, effective noninvasive treatments that alleviate abdominal bloating without serious complications are urgently needed in clinical practice.

Small intestinal gas, the main cause of abdominal bloating, is often generated from small intestinal bacterial overgrowth (SIBO). SIBO often co-occurs with various diseases (including CIPO) [11], particularly SSc, with a prevalence rate of 43% [12]. In our experience, treatment of SIBO using metronidazole (MNZ) is effective for alleviating abdominal bloating in CIPO cases. However, there is a lack of evidence for the efficacy of MNZ in CIPO treatment, and there are some concerns, including the development of MNZ-induced encephalopathy, with long-term administration [13].

Recently, the efficacy of rifaximin (RFX), a rifamycin-derived antibacterial agent that inhibits bacterial RNA synthesis and is effective against gram-positive, gram-negative, aerobic, and anaerobic bacteria, has been reported for SIBO. A meta-analysis showed that RFX is effective for SIBO, with an eradication rate of at least 70% [14]. Therefore, RFX could alleviate abdominal bloating in patients with CIPO by eradicating SIBO. However, the precise incidence of SIBO in patients with CIPO and efficacy of RFX in them have not been investigated. Demonstrating the efficacy of RFX in patients with CIPO would enable the development of a breakthrough strategy for the management of CIPO. The aim of this exploratory study was to investigate the efficacy and safety of RFX for abdominal symptoms in patients with CIPO.

MATERIALS AND METHODS

Trial design

This was a randomized, double-blind, placebo-controlled, single-center, phase IIa exploratory trial.

Eligibility

Inclusion criteria

Consecutive patients (20–75 years) who were diagnosed with CIIP according to all relevant diagnostic criteria proposed by the Japanese Ministry of Health, Labour and Welfare [9], (1) to (7) in Supplementary Table 1, or diagnosed with CIPO secondary to SSc according to the same diagnostic criteria, (1) to (6) in Supplementary Table 1, were recruited among outpatients visiting Yokohama City University Hospital from November 2019 to May 2021.

The severity of abdominal bloating was assessed using the global symptom score (GSS) questionnaire and a four-point Likert scale (0, no symptoms; 1, mild, with symptoms easily tolerated; 2, moderate, with symptoms sufficient to cause interference with normal activities; and 3, severe, with incapacitating symptoms and inability to perform normal activities) [15–17]. Patients were considered eligible for inclusion if they had a GSS of 2 or 3 at visits 1 and 2 described below.

Exclusion criteria

Patients were excluded if they 1) underwent gastrostomy, including PEG-J, ileostomy, or colostomy; 2) underwent decompression therapy using trans-nasal small intestinal tube insertion within 4 weeks of entry; 3) had malignant tumors; 4) had severe psychiatric diseases; 5) had diabetes mellitus with hemoglobin A1C levels >10%; 6) had severe liver dysfunction; or 7) were pregnant or breastfeeding. The detailed exclusion criteria are presented in Supplementary Table 2.

Protocol

The trial schedule is summarized in Supplementary Table 3. This study comprised a provisional registration period (weeks −4 to 0), a 4-week treatment period (weeks 0 to 4), and an 8-week follow-up period (weeks 4 to 12). Patients were required to visit the study site a total of six times:

visit 1 (week −4) to obtain informed consent
visit 2 (week 0) for registration and initiation of treatment
visit 3 (week 2) at 2 weeks after the initiation of treatment
visit 4 (week 4) at the end of treatment
visit 5 (week 8) at 4 weeks after the treatment period
visit 6 (week 12) at 8 weeks after the treatment period

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After providing written informed consent (visit 1), the patients completed the GSS questionnaire and underwent a blood test. They also completed the GSS questionnaire at visit 2 (week 0), and patients with a GSS for abdominal bloating (GSS-bloating) of ≥2 at both visits were enrolled in the study. The eligible patients were randomly assigned to either an RFX or placebo (PBO) group. After randomization, the patients received 400 mg RFX or PBO orally three times per day for 4 weeks. From visits 2 to 6, in addition to the GSS questionnaire, three other instruments were administered: an original whole gastrointestinal symptoms score (O-WGSS) questionnaire and original general health condition score (O-GHCS) questionnaire, both of which were different from the GSS questionnaire and scored on a five-point Likert scale (0, very good/significantly improved compared with the symptoms at enrollment; 1, good/slightly improved; 2, no change; 3, bad/slightly worsened; and 4, very bad/significantly worsened), and the Short Form-8 (SF-8). Furthermore, data pertaining to blood tests, nutrition indices (albumin, prealbumin, and cholinesterase), serum endotoxin levels [18, 19], and small intestinal volumes (measured using abdominal computed tomography [CT]) were collected. A patient's condition was considered to have improved if their GSS-bloating and O-WGSS were both ≤1 at visit 4. The volume of the small intestine was calculated using a SYNAPSE VINCENT system (Fujifilm Medical, Tokyo, Japan) and three-dimensional (3D) CT images [10].

A glucose hydrogen breath test (GHBT) was performed at visits 2, 4, and 6 to assess the presence or absence of SIBO. In accordance with previous studies [20, 21], the participants were administered 50 g of glucose dissolved in 200 mL of water just before examination. Using a Breath Gas Analyzer (BGA-1000D), the hydrogen concentration in exhaled breath samples was measured nine times every 15 min. The participants were instructed to abstain from smoking and fast for 12 hr before the GHBT (sugar-free water intake was permitted; gum and candy were not allowed). An increase in H_2 level of >12 ppm over the baseline value was considered to indicate that a patient was positive for SIBO.

Stool samples were also collected at visits 2 and 4, and gut microbiota measurements were performed according to our institutional manual (Techno Suruga Laboratory Co., Ltd., Shizuoka, Japan).

Endpoints

The primary endpoints included 1) the proportion of patients with improved GSS-bloating and 2) the proportion of patients with improved O-WGSS at visit 4 (score 0 or 1) in each group. The secondary endpoints and other endpoints are presented in Supplementary Table 4.

Rationale for determining the drug dose, duration, and endpoints

Previous studies have shown that RFX administered at doses of 600, 800, and 1,200 mg/day are well tolerated, with a dose-dependent improvement in patients with SIBO [22–24]. The approved dosage of RFX for hepatic encephalopathy in Japan is 400 mg three times per day, and the safety of this dosage for 12 weeks has already been demonstrated in the Japanese population. Although the target disease was different, we considered it acceptable to administer RFX at a dose of 400 mg three times per day in this study.

The duration of RFX administration was set to between 7 and 28 days based on a previous review [14]. From our clinical experience, it requires 3 or 4 weeks to confirm the efficacy of MNZ for CIPO treatment. Therefore, we chose 4 weeks as the duration of RFX administration in this study.

As CIPO is a rare disease, no specific assessment method has been established in guidelines or by academic societies. Original scales are often used for the assessment of abdominal bloating. Therefore, the GSS, which is often used in studies, such as double-blind controlled trials or large clinical trials [15–17], was selected for the assessments in this study. According to an epidemiological survey in Japan, "abdominal bloating" is the most common symptom in patients with CIPO, accounting for 97.5% of all cases [9]. Considering the small number of target patients owing to the rarity of this disease, the degree of alleviation in abdominal bloating, which is observed in almost all patients with CIPO, was selected as the primary endpoint.

Randomization and masking

Eligible patients were randomly assigned to either the RFX or PBO group (2:1). After randomization, they were administered 400 mg RFX or PBO orally three times per day. Randomization was performed using a centrally administered, validated allocation system. RFX and PBO were provided as identical film-coated tablets in identical containers labeled with code numbers. Both the physicians and patients were blinded to the assignment.

Population set

The full analysis set (FAS) comprised all eligible patients, except 1) those with serious good clinical practice (GCP) violations (violations of consent acquisition and the clinical trial procedure) and 2) those who were never administered the study products. The per-protocol set (PPS) comprised all patients from the FAS population with no violations of the inclusion criteria and without concomitant use of prohibited drugs or treatments. The safety analysis set (SAS) consisted of patients who were administered at least one dose of the study product.

Statistical analyses

The sample size was 12 (PBO, 4; RFX, 8). This was determined using a feasibility study considering the rarity of CIPO with a prevalence of 1 in 100,000 and the fact that our hospital is the only specialized institution for CIPO research and treatment in Japan. To obtain more data from the RFX group, the ratio of PBO group patients to RFX group patients was set to 1:2, and allocation was performed using the minimization method to ensure that each group comprised patients with both CIIP and secondary CIPO. Group comparisons were performed using Fisher's direct probability calculation method.

Post hoc analysis included determination of the 1) SIBO eradication rate (%), 2) change in the amplitude of hydrogen gas concentration (amplitude = maximum H_2 concentration − baseline H_2 concentration; ppm) between before and after treatment (ΔAmplitude), 3) change in small intestinal gas volume on 3D-CT (Δ% volume), and 4) change in endotoxin activity (ΔEA) only in patients diagnosed with CIPO along with SIBO. The Kruskal–Wallis test was applied for the gut microbiota analysis using data obtained before and after administration of the study products. In an exploratory test, the analysis of composition of microbiomes model, which compares representative sequences between

groups, was applied. All statistical analyses were performed using SAS version 9.4 (SAS Institute Japan Ltd., Tokyo, Japan). Safety and tolerability analyses were performed in the SAS population.

Ethics

The study protocol complied with the tenets of the Declaration of Helsinki and ICH E6 (R2) GCP for Clinical Trials guidelines published by the Ministry of Health, Labour and Welfare of Japan. The Institutional Review Board of Yokohama City University approved this clinical trial prior to the initiation of the study (approval number: 19-280, approval date: August 21, 2019). The study protocol was registered at ClinicalTrials.gov (NCT04118699) on September 23, 2019. Written informed consent was obtained from all participants before participation. The trial results are reported in conformity with the Consolidated Standards of Reporting Trials 2010 guidelines.

RESULTS

From November 26, 2019, to May 24, 2021, 15 patients were screened, and 12 eligible patients were randomly assigned to the PBO (n=4) and RFX (n=8) groups. No patients dropped out of the trial during the period from visit 1 to the end of treatment (Fig. 1). A total of 12 patients were included in the analysis of treatment efficacy and safety. Baseline demographics and disease characteristics were similar between the groups (Table 1). All patients in the PBO group (100%) and four of the eight patients in the RFX group (50%) were diagnosed with SIBO (Table 1).

GSS-bloating was improved in 75.0% of the patients in the PBO group (3/4; 95% confidence interval [CI], 19%–99%) and in 25.0% of those in the RFX group (2/8; 95% CI, 3%–65%). There was no significant difference between PBO and RFX (p=0.2), and the same result was observed in the PPS analysis. O-WGSS was improved in 25.0% of the patients in the PBO group (1/4; 95% CI, 1–81%) and in 25.0% of those in the RFX group (2/8; 95% CI, 3–65%). There was also no significant difference between PBO and RFX, and the same result was observed in the PPS analysis (Table 2).

Furthermore, no significant differences were observed between the PBO and RFX groups in the following subjective evaluations, which included the secondary endpoints:

(1) Temporal changes in the improvement ratio (%) of GSS-bloating
(2) Absolute changes in GSS-bloating
(3) Temporal changes in the improvement ratio (%) of O-WGSS (evaluation by participants)
(4) Temporal changes in the improvement ratio (%) of O-WGSS (evaluation by physicians)
(5) Temporal changes in the “good” ratio (%) of O-WGSS
(6) Absolute changes in each GSS other than the abdominal bloating score
(7) Absolute changes in the total GSS
(8) Temporal changes in the improvement ratio (%) of O-GHCS
(9) Temporal changes in the “good” ratio (%) of O-GHCS
(10) Treatment satisfaction rate
(11) Temporal changes in the SF-8 health survey score

There was also no significant difference between the groups regarding the absolute changes in the small intestinal volume on 3D-CT, which was one of the objective evaluations. In terms of nutritional indicators, the folic acid level in the RFX group significantly decreased after treatment (PBO vs. RFX, 4.3 mg/dL vs. −1.0 mg/dL, p=0.02). Furthermore, the serum iron and serum prealbumin levels in the RFX group tended to decrease (PBO vs. RFX, 26 μg/dL vs. −5 μg/dL, p=0.07) and increase (PBO vs. RFX, −1.1 mg/dL vs. 0.7 mg/dL, p=0.1), respectively, after treatment (Table 2). However, no significant changes were observed in the serum albumin levels between the groups.

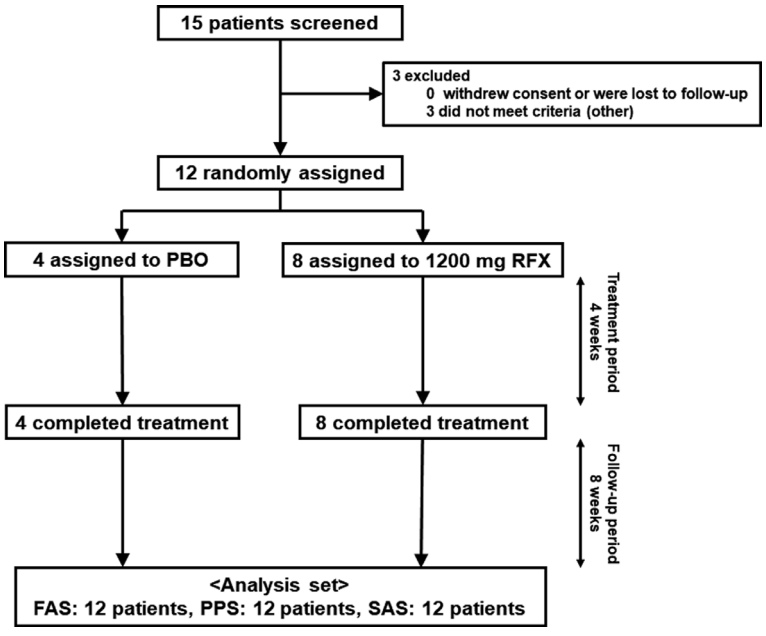

Fig. 1. Trial flow.
PBO: placebo; RFX: rifaximin; FAS: full analysis set; SAS: safety analysis set; PPS: per-protocol set.

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Table 1. Baseline characteristics

Variable	PBO (n=4)	RFX (n=8)
Demographics		
Age (years)	42 (15)	63 (10)
Male (%)	1 (25)	2 (25)
Disease period (years)	6 (5)	5 (5)
Target disease		
Primary CIPO (%)	3 (75)	7 (87.5)
CIPO secondary to SSc (%)	1 (25)	1 (12.5)
Concomitant drug use		
Prokinetic agents (%)	4 (100)	8 (100)
Herbal medicine (%)	4 (100)	8 (100)
Laxatives (%)	4 (100)	8 (100)
Probiotics (%)	2 (50)	5 (62.5)
Antacids (%)	2 (50)	5 (62.5)
Pain killers (%)	1 (25)	1 (12.5)
Sleeping pills (%)	1 (25)	2 (25)
Enteral nutrition (%)	1 (25)	1 (12.5)
Blood endotoxin		
EAA ($\times 10^{-2}$)	18 (16)	15 (10)
Metabolic factors, mean (SD)		
Weight (kg)	52 (9)	46 (7)
BMI (kg/m^2)	19.7 (1)	17.9 (1.7)
SBP (mmHg)	102 (16)	109 (23)
DBP (mmHg)	71 (7)	69 (8)
Heart rate (/min)	77 (6)	69 (12)
Glucose (mg/dL)	94 (8)	100 (16)
Nutrition factors		
Total protein (g/dL)	7.1 (0.3)	6.8 (1.0)
Albumin (g/dL)	4.3 (0.4)	4.0 (0.7)
Pre-albumin (mg/dL)	23 (9)	18 (7)
Cholinesterase (U/L)	336 (136)	260 (123)
Folic acid (ng/mL)	12 (3)	14 (7)
Vitamin B12 (cobalamin) (pg/mL)	189 (74)	807 (554)
Iron (μg/dL)	88 (32)	93 (43)
Electrolytes		
Na (mmol/L)	141 (2)	140 (5)
K (mmol/L)	4.3 (0.5)	4.1 (0.4)
Cl (mmol/L)	106 (0.6)	102 (5)
Ca (mg/dL)	9.2 (0.4)	8.9 (0.9)
Liver function		
AST (U/L)	21 (4)	35 (12)
ALT (U/L)	22 (16)	33 (16)
γ-GTP (U/L)	18 (10)	16 (4)
ALP (U/L)	107 (75)	186 (149)
T-bil (mg/dL)	0.6 (0.3)	0.6 (0.3)
Lipids		
T-Cho (mg/dL)	166 (40)	160 (65)
LDL-C (mg/dL)	99 (32)	82 (42)
HDL-C (mg/dL)	52 (12)	66 (23)
TG (mg/dL)	109 (53)	79 (20)
Inflammation marker		
CRP (mg/L)	0.03 (0.01)	0.03 (0.03)
Renal function		
BUN (mg/dL)	11 (3)	17 (9)
Creatinine (mg/dL)	0.6 (0.1)	0.7 (0.2)

Data are expressed as number (proportion) or mean (standard deviation). ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; CIPO: chronic intestinal pseudo-obstruction; CT: computed tomography; DBP: diastolic blood pressure; EAA: endotoxin activity assay; γ-GTP: gamma-glutamyl transferase; GHBT: glucose hydrogen breath test; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; LDL-C: low-density lipoprotein cholesterol; PBO: placebo; RFX: rifaximin; SBP: systolic blood pressure; SF-8: short form-8; SIBO: small intestinal bacterial overgrowth; SSc: systemic scleroderma; T-Cho: total cholesterol; T-bil: total bilirubin; TG: triglyceride.

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Table 1. Continued

Variable	PBO (n=4)	RFX (n=8)
Hematological examination		
White blood cells (10^3/μL)	5.4 (1.3)	6.0 (2.1)
Red blood cells (10^6/μL)	4.4 (0.3)	4.3 (0.7)
Hemoglobin (g/dL)	13.8 (1.2)	13.8 (2.1)
Hematocrit (%)	42 (3)	42 (6)
Platelets (10^3/μL)	228 (84)	240 (94)
GHBT		
SIBO positive (%)	4/4 (100)	4/8 (50)
Maximum value (ppm)	64 (57)	47 (82)
CT imaging		
Gas volume (mL)	749 (423)	615 (559)
Intestinal fluid volume (mL)	546 (627)	547 (544)
SF-8 quality of life		
Physical component	38 (8)	42 (7)
Mental component	46 (3)	39 (7)

The SIBO eradication rate in the GHBT (an exploratory endpoint) showed no difference between the groups (Table 2). Although the serum endotoxin activity after treatment tended to decrease, there was no significant difference between the groups (PBO vs. RFX, 0.02 vs. −0.03, p=0.4; Table 2). In terms of the gut microbiota, there were no significant changes in α-diversity, β-diversity, intestinal flora, and PICRUSt2 results between the groups (Supplementary Tables 5–7). There were no significant changes in baseline α-diversity between the groups (Supplementary Table 8). However, as shown in Supplementary Table 9, at the phylum level, the proportion of Proteobacteria members in the baseline gut microbiota was significantly higher in the PBO group than in the RFX group. At the genus level, the proportion of *Veillonella* species was significantly higher in the PBO group than in the RFX group, and those of *Oscillospira*, *Ruminococcus*, and *Butyricimonas* species were significantly higher in the RFX group than in the PBO group (Supplementary Table 9).

The results of the *post hoc* analysis of patients with CIPO along with SIBO are summarized in Supplementary Table 10. Both groups had four patients with CIPO who were positive for SIBO. SIBO was eradicated in one patient with CIPO in the PBO group (25%) and in three patients with CIPO in the RFX group (75%) at the end of the 4 weeks of administration, showing a high eradication rate in the RFX group (p=0.2). However, SIBO recurred at visit 6 (8 weeks after the end of drug administration) in the abovementioned three patients (3/3, 100%) in the RFX group (Fig. 2a).

The ΔAmplitude in the GHBT was increased in the PBO group but was significantly decreased in the RFX group (PBO vs. RFX, 131 vs. −108, p=0.03; Fig. 2b). The Δ% volume and ΔEA also tended to decrease in the RFX group; however, no significant differences were observed between the groups (PBO +79% vs. RFX −7% for Δ% volume, p=0.08; PBO 0.02 vs. RFX −0.12 for ΔEA, p=0.10; Fig. 2c).

Adverse events were observed in three (75%) patients in the PBO group and five (63%) patients in the RFX group. Gastrointestinal adverse events were observed in zero (0%) patients in the PBO group and three (38%) patients in the RFX group. No life-threatening events, severe adverse events, or treatment-related deaths occurred during the study period (Table 3).

DISCUSSION

To our knowledge, this is the first randomized, double-blind, placebo-controlled trial on the efficacy and safety of RFX in patients with CIPO (CIIP and CIPO secondary to SSc). The primary endpoints, which was the improvement rates of GSS-bloating and O-WGSS at visit 4, showed no significant differences between the PBO and RFX groups. Furthermore, no significant results were obtained for the secondary and exploratory endpoints, including abdominal bloating, other gastrointestinal symptoms, general health, patient satisfaction, QOL, small intestinal volume on CT scans, and nutritional parameters. The following are some possible reasons for no significant differences in the endpoints. 1) The small number of patients (N=12), owing to the rarity of CIPO and the single-center study design, may have resulted in a β error (type II error). 2) Although the most frequent clinical symptom is abdominal bloating, patients with CIPO often develop overlapping abdominal symptoms, such as abdominal pain and constipation, in addition to abdominal bloating. Therefore, patients may not have been able to distinguish their abdominal symptoms clearly, and the severity of abdominal bloating may not have been accurately reflected in the questionnaires. 3) This was an exploratory study with a short administration period of 4 weeks to ensure patient safety. 4) The GSS was only assessed on a four-point Likert scale, and a finer scale may have been needed for a detailed assessment.

Although there is no specific method for the assessment of abdominal bloating, the GSS is one of the few well-established methods reported previously [15–17]. Therefore, we adopted the GSS for assessment of the primary endpoint in this study. To date, there is no established primary endpoint in clinical trials for CIPO; hence, establishment of gold standard endpoints through clinical trials is required.

Here, the results of our *post hoc* analysis for the SIBO-positive CIPO subgroup (4/4 patients in the PBO group [100%] and 4/8 patients in the RFX group [50%]) revealed that the hydrogen gas concentration, small intestinal gas volume, and serum endotoxin

Table 2. Changes in factors from baseline to four weeks (full analysis set population)

Variable	PBO (n=4)	95% CI	RFX (n=8)	95% CI	p-value
Primary endpoints					
Questionnaires					
Proportion of patients (%) with improved GSS-bloating	3 (75)	19–99	2 (25)	3–65	0.20
Proportion of patients (%) with improved O−WGSS	1 (25)	1–81	2 (25)	3–65	1.00
Secondary endpoints					
Questionnaires					
Temporal changes in the improvement ratio (%) in GSS-bloating, V3/V4/V5/V6	1 (25)/3 (75)/4 (100)/1 (25)		0 (0)/2 (25)/2 (25)/2 (25)		0.33/0.22/0.06/1.00
Absolute changes in GSS-bloating	−0.8 (1.3)		0.4 (0.5)		0.40
Temporal changes in the improvement ratio (%) in O−WGSS (relative evaluation by subjects), V3/V4/V5/V6	1 (25)/1 (25)/1 (25)/2 (50)		2 (25)/2 (25)/2 (25)/2 (25)		1.00/1.00/0.55/0.55
Temporal changes in the improvement ratio (%) in O−WGSS (relative evaluation by physicians), V3/V4/V5/V6	2 (50)/3 (75)/4 (100)/2 (50)		2 (25)/2 (25)/5 (62.5)/2 (50)		0.55/0.22/0.49/0.55
Temporal changes in the “good” ratio (%) in O-WGSS (absolute evaluation by subjects), V3/V4/V5/V6	1 (25)/1 (25)/3 (75)/1 (25)		0 (0)/0 (0)/1 (12.5)/0 (0)		0.33/0.33/0.07/0.33
Absolute changes in each GSS other than the abdominal bloating score					
Diarrhea	0		−0.1 (1.2)		0.80
Upper abdominal pain/discomfort	−0.8 (1.7)		0 (1.2)		0.50
Lower abdominal pain/discomfort	0		−0.1 (0.6)		0.60
Tenderness	−0.8 (1.0)		0.3 (1.0)		0.20
Nausea	−0.3 (0.5)		0.6 (0.7)		0.06
Vomiting	0.3 (0.5)		0 (0.5)		0.50
Absolute changes in total GSSs	−2.5 (5.8)		−0.3 (3.2)		0.40
Temporal changes in the improvement ratio (%) in O-GHCS (relative evaluation by subjects)	1 (25)/1 (25)/2 (50)/2 (50)		1 (12.5)/3 (37.5)/2 (25)/3 (37.5)		1.00/1.00/0.55/1.00
Temporal changes in the “good” ratio (%) in O-GHCS (absolute evaluation by subjects)	1 (25)/1 (25)/2 (50)/2 (50)		1 (12.5)/1 (12.5)/0 (0)/2 (25)		1.00/1.00/0.09/0.55
Treatment satisfaction rate	1 (25)	1–81	3 (38)	9–76	1.00
Changes in SF-8 health survey score					
Physical component	4.9 (9)		−5.8 (8)		0.09
Mental component	2.2 (4.6)		−1.5 (10)		0.40
Changes in the SF-8 health survey score subscale					
Physical function	1.4 (2.8)		−2.5 (11)		0.40
Daily role function (physical)	2.8 (5.6)		−6.2 (8.0)		0.05
Body pain	7.2 (14)		−5.5 (9.4)		0.20
Overall health	7.1 (13)		−4.9 (5.9)		0.20
Vitality	5.6 (7.0)		−2.5 (6.7)		0.10
Social life function	3.5 (6.9)		−7.6 (8.7)		0.05
Daily role function (mental)	1.5 (5.3)		−1.6 (12.3)		0.50
Mental health	2.9 (8)		−1.4 (9.4)		0.40
CT imaging					
Absolute change in small intestinal volume on abdominal 3D-CT	728 (660)		167 (643)		0.20
Blood analysis					
Changes from baseline in serum albumin levels	0.2 (0.3)		−0.06 (0.2)		0.20
Changes from baseline in pre-albumin levels (transthyretin)	−1.1 (1.4)		0.7 (2.4)		0.10
Changes from baseline in cholinesterase levels	3.3 (23)		−19.8 (43)		0.30
Changes from baseline in folic acid levels	4.3 (2.5)		−1.0 (3.5)		0.02
Changes from baseline in vitamin B12 levels (cobalamin)	0.5 (57)		−35 (123)		0.50
Changes from baseline in serum iron levels	26 (21)		−5 (25)		0.07
Exploratory endpoints					
SIBO eradication rate in GHBT	1 (25)		4 (75)		0.50
Changes in serum endotoxin activity ($\times 10^{-2}$)	2 (9)		−3 (12)		0.40

Data are reported as number (proportion) or mean (standard deviation).
CT: computed tomography; GI: gastrointestinal; GSS: global symptom score; GHBT: glucose hydrogen breath test; O-GHCS: original questionnaire of general health condition score; O-WGSS: original questionnaire of whole gastrointestinal symptoms score; PBO: placebo; SF-8: short form-8; SIBO: small intestinal bacterial overgrowth; V3: Visit 3; V4: Visit 4; V5: Visit 5; V6: Visit 6.

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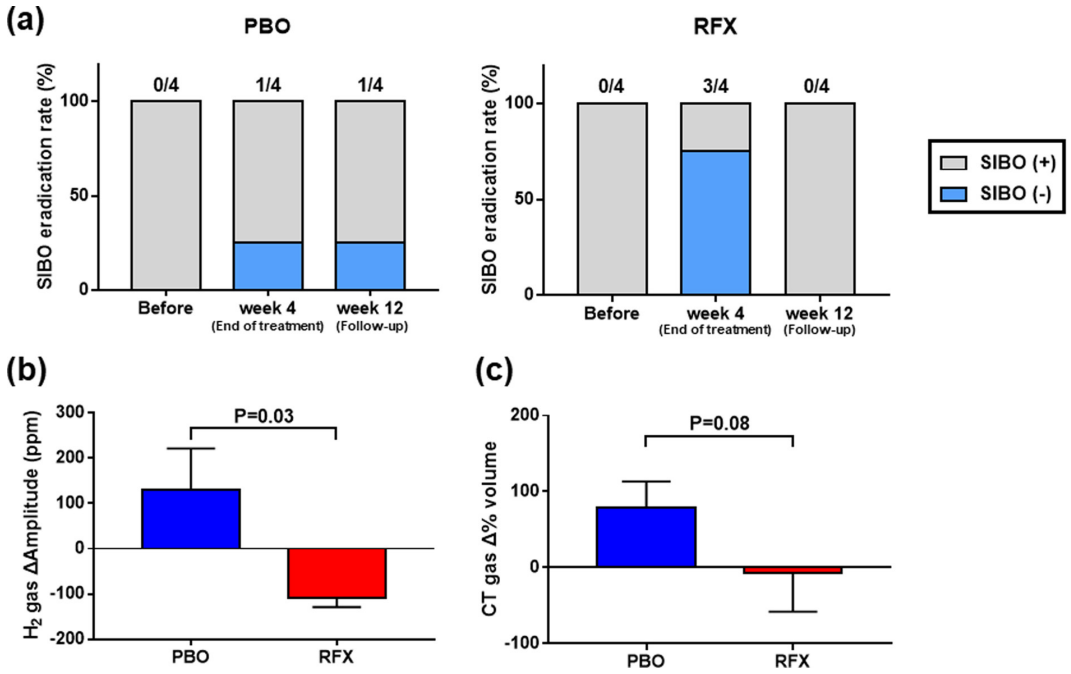

Fig. 2. Changes in small intestinal bacterial overgrowth (SIBO) eradication rate, hydrogen gas concentration, and small intestinal gas volume.

(a) Changes in SIBO eradication rates over time in the PBO (left panel) and RFX (right panel) groups.

(b) Changes in the amplitude of the hydrogen gas concentration (amplitude = maximum H_2 concentration – baseline H_2 concentration, ppm) from before treatment to after treatment (ΔAmplitude) in the PBO and RFX groups.

(c) Changes in small intestinal gas volumes on 3D-CT (Δ% volume) in the PBO and RFX groups.

Data are shown as the percentage or mean ± standard error of the mean (SEM). Statistical significance was set at $p<0.05$. Week 4 represents the end of treatment, and week 12 represents the end of the follow-up period.

PBO: placebo; SIBO: small intestinal bacterial overgrowth; RFX: rifaximin; CT: computed tomography.

activity tended to decrease in the RFX group compared with those in the PBO group. SIBO was eradicated in three patients at the end of the 4 weeks of RFX administration (75%) but reappeared in all three of those patients after the 8-week follow-up period. These *post-hoc* analysis results show that RFX administration could contribute to the alleviation of SIBO and be beneficial for patients with CIPO along with SIBO.

Subjective and objective indicators are often related to each other; however, this trial showed the possibility of RFX efficacy based only on objective indicators. Alleviation of subjective symptoms is definitely important for patients with CIPO; however, improvement of objective indicators, including small intestinal gas volume and GHBT data, is also important. This is because a reduction in small intestinal gas volume or eradication of SIBO leads to the avoidance of invasive decompression procedures, including trans-nasal intestinal tube insertion, PEG-J, and palliative ileostomy. Therefore, the results of the *post hoc* analysis are clinically significant. The observed discrepancy in the results between the subjective and objective indicators may be because of the difficulty in accurately evaluating specific symptoms because of the overlap of several abdominal symptoms. The applicability of subjective indicators as primary endpoints in clinical trials for CIPO may be controversial. Future trials should recruit a sufficient number of patients with CIPO along with SIBO to accurately evaluate the changes in treatment-associated symptoms.

In this trial, the level of serum albumin, which is one of the indices for static nutritional status and has a long half-life (about 21 days) [25], showed no significant difference between before and after RFX administration. The level of serum prealbumin, which is one of the indices for dynamic nutritional status and has a half-life of 2 days [26], also showed no significant difference between before and after RFX administration; however, it tended to increase after RFX administration. These results indicate that a long administration period (more than 4 weeks) may enable accurate evaluations of improvement in nutritional indices.

In the stool assessment, no significant differences were observed in diversity or intestinal flora between before and after RFX/PBO administration. Accordingly, our results are compatible with those of a previous study, which demonstrated the risk of dysbiosis [27] and supported the safety of RFX.

Recent studies have shown that probiotics and antacids (proton pump inhibitors or potassium-competitive acid blockers) can affect the gut microbiota [28–32]. Therefore, it is possible that the natural gut microbiota of the patients in this study were modified by the concomitant drugs at baseline. Baseline comparisons between the groups showed differences in the proportions of species of a phylum (Proteobacteria) and some genera (*Veillonella*, *Oscillospira*, *Ruminococcus*, and *Butyricimonas*) but no change in α-diversity (Supplementary Tables 8 and 9). However, we speculate that this was more likely influenced by the difference in gut microbiota composition among individuals than modification by the concomitant medications, because there

Table 3. Adverse events

Adverse events	PBO (n=4)	RFX (n=8)
Deaths	0	0
Serious adverse events	0	0
Treatment-related serious adverse events	0	0
Discontinuation due to overall adverse events	0	0
Discontinuation due to GI-related adverse events	0	0
Overall adverse events	3 (75)	5 (63)
GI-related adverse events	0	3 (38)
Blood and lymphatic system disorders	0 (0)	1 (13)
Anemia	0 (0)	1 (13)
Ear and labyrinth disorders	1 (25)	1 (13)
Vehicle sickness	0 (0)	1 (13)
Vertigo	1 (25)	0 (0.0)
Gastrointestinal disorders	0 (0)	2 (25)
Constipation	0 (0)	2 (25)
Hepatobiliary system disorders	0 (0)	1 (13)
Liver dysfunction	0 (0)	1 (13)
Immune system disorders	1 (25)	0 (0)
Allergic rhinitis	1 (25)	0 (0)
Infectious diseases and parasites	1 (25)	0 (0)
Nasopharyngitis	1 (25)	0 (0)
Metabolism and nutrition disorders	0 (0)	1 (13)
Total liquid volume decrease	0 (0)	1 (13)
Musculoskeletal and connective tissue disorders	0 (0)	1 (13)
Degenerative spondylosis	0 (0)	1 (13)
Nervous system disorders	1 (25)	1 (13)
Tremor	1 (25)	0 (0)
Vagus nerve disorder	0 (0)	1 (13)

Data are reported as number (proportion).
GI: gastrointestinal; PBO: placebo; RFX: rifaximin.

was no significant difference in baseline drug use between the groups (Table 1).

We surmise that concomitant medications are unlikely to affect treatment efficacy because there were no changes in the types or doses of medications during the 4 weeks prior to screening, as stated in the eligibility criteria. However, we believe that the differences in baseline gut microbiota may have affected treatment responses.

This study has several strengths. 1) It is the first randomized, placebo-controlled, double-blind trial on the efficacy of RFX in patients with CIPO. 2) Our results demonstrated the safety of RFX in patients with CIPO, at least during 4 weeks of administration. 3) Moreover, our results indicate that RFX may be effective for patients with CIPO along with SIBO. This study, however, also has some limitations. 1) There may have been selection bias because it was a single-center trial. 2) The number of patients was too small to perform sufficient statistical analyses. 3) The RFX administration period was too short for adequate assessments of RFX efficacy and safety. Investigations with a long administration period, more than 4 weeks, are required for further research on RFX efficacy for patients with CIPO along with SIBO.

In conclusion, although no significant improvements were observed in abdominal bloating, small intestinal gas volume, and nutritional indices, RFX may have beneficial effects in alleviating SIBO and reducing small intestinal gas volume in SIBO-positive patients with CIPO. Reconsideration of appropriate target patients, endpoints, and the administration period is required in the future for high-quality clinical trials in patients with CIPO.

ETHICS STATEMENT

Study Approval Statement: The study protocol and relevant supporting data were reviewed and approved by the Institutional Review Board of Yokohama City University (approval number: 19-280) on August 21, 2019, prior to the initiation of the study. This trial was registered at ClinicalTrials.gov (NCT04118699) on September 23, 2019. The trial results have been reported in conformity with the Consolidated Standards of Reporting Trials 2010 guidelines.

Consent to participate statement: All patients provided written informed consent prior to their participation in the study.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

HO, TK, and AN contributed to the study design. HO, TK, K Tanaka, K Takahashi, TT, TY, NM, KA, AF, SK, and MY were responsible for data collection. CT interpretation was performed by TH, and KH participated in the data analysis. Biostatistical analyses were performed by TM and SS. HO, TK, AN, and VS contributed to data interpretation. HO and TK were responsible for the preparation of the manuscript, tables, and figures. All authors participated in manuscript writing and reviewing.

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