EFFICACY OF RIFAXIMIN IN DIARRHEA PREDOMINANT IRRITABLE BOWEL SYNDROME

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ABSTRACT

Background: It has been shown in multiple studies that gut micro biota plays a major role in diarrhea predominant irritable bowel syndrome. Here we evaluated the efficacy of rifaximin in irritable bowel syndrome.

Objective: To determine the efficacy of rifaximin in diarrhea predominant irritable bowel syndrome.

Study design: Comparative study.

Place and Duration: A Multicenter study from January 2016 to December 2016.

Material and Methods: In a double-blind, placebo-controlled study, patients who had IBS without constipation were randomly assigned to either rifaximin at a dose of 550 mg or placebo, three times daily for 2 weeks, and were followed for an additional 4 weeks. The primary end point was the proportion of patients who had adequate relief of global IBS symptoms, and the key secondary end point was the proportion of patients who had adequate relief of IBS-related bloating, were assessed weekly. Adequate relief was defined as self-reported relief of symptoms for at least 2 of the 4 weeks after treatment. Other secondary end points included the percentage of patients who had a response to treatment as assessed by daily self-ratings of global IBS symptoms and individual symptoms of bloating, abdominal pain, and stool consistency during the 4 weeks after treatment.

Results: Significantly more patients in the rifaximin group than in the placebo group had adequate relief of global IBS symptoms like bloating, stool frequency and stool consistency during the first 4 weeks after treatment (62% vs. 20%, $P = 0.01$). In addition, significantly more patients in the rifaximin group had a response to treatment as assessed by daily ratings of IBS symptoms, bloating, abdominal pain, and stool consistency. The incidence of adverse events was similar in the two groups.

Conclusions: Among patients who had IBS without constipation, treatment with rifaximin for 2 weeks provided significant relief of IBS symptoms, bloating, abdominal pain, and loose or watery stools.

Key Words: Irritable bowel syndrome, rifaximin, diarrhea.

INTRODUCTION

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder characterized by recurring symptoms of abdominal pain, bloating, and altered bowel function in the absence of structural, inflammatory, or biochemical abnormalities.[1] IBS often does not respond to current treatment options, including dietary and lifestyle modifications, fiber supplementation, psychological therapy, and pharmacotherapy.[2,3] Because no reliable biologic or structural markers have been identified, the effects of pharmacotherapy are typically assessed by asking patients to report whether they had adequate relief of IBS symptoms (with a binary response of yes or no).[4] Given the limitations of available therapies, there is an unmet medical need for novel therapeutic approaches.

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Patients with IBS may have alterations in the intestinal microbiota,[5,6,7] thus leading investigators to consider targeting the intestinal micro biota for the treatment of this condition. Although some patients have had improvement with neomycin therapy, clinical trials have shown that it has marginal efficacy, and side effects limit the use of the drug.[8] The use of systemic antibiotics has been reported with mixed results.[9]

The disorder affects approximately 15%-20% of the world population and is predominantly found in women.[10] Despite the high prevalence of IBS in the general population, understanding of the etiology, pathogenesis and treatment is limited. Although many IBS sufferers do not seek medical care, IBS has been estimated to account for 20%-50% referrals to gastroenterology clinics.[11] Diagnosis of IBS is made through the exclusion of organic disease. Information on the prevalence of bowel dysfunction and health care utilization for bowel complaints has been obtained from questionnaire surveys.[12]

Rifaximin is an oral, non-systemic, broad-spectrum antibiotic that targets the gut and is associated with a low risk of bacterial resistance.[10,11,12] It has shown

efficacy in small-scale studies of IBS. A more recent study that included patients who had IBS without constipation were assigned to either rifaximin at a dose of 550 mg or placebo, three times daily for 2 weeks. These patients were followed for an additional 10 weeks. The primary endpoint was adequate relief of IBS symptoms. The proportion of patients who had adequate relief of IBS-related bloating and gas was assessed weekly. Adequate relief was defined as self-reported relief of symptoms for at least 2 of the first 4 weeks of treatment. The improvement was reported as 40.8% versus 31.2% for placebo ($p = 0.01$). The outcome of treatment with rifaximin was that significant relief of IBS symptoms, including bloating, abdominal pain and loose or watery stools, was provided for 2 weeks after treatment among patients who had IBS without constipation.[13] Another recent study comprised 106 of 150 patients with IBS (71%) treated with rifaximin. Assessment at week 4 following commencement of therapy showed that rifaximin provided significant improvement of the following IBS-associated symptoms: bloating, flat-ulence, diarrhea, pain.[14] The aim of this study to determine the efficacy of rifaximin in irritable bowel syndrome.

METHODS

Study patients

Eligible patients were at least 18 years of age who were diagnosed as IBS and had current symptoms of IBS particularly, symptoms of abdominal pain and discomfort, and did not have adequate relief of global IBS symptoms and of IBS-related bloating at both the time of screening. Eligible patients rated the average daily amount of abdominal pain and bloating as a score of 2 to 4.5 on a 7-point Likert scoring system (with 0 indicating not at all; 1, hardly; 2, somewhat; 3, moderately; 4, a good deal; 5, a great deal; and 6, a very great deal) and rated the average daily consistency of their stools as 3.5 or more on a 5-point scale for stool consistency (with 1 indicating very hard; 2, hard; 3, formed; 4, loose; and 5, watery) over the course of at least 7 days.

Exclusion criteria were constipation-predominant IBS, a history of inflammatory bowel disease, diabetes, unstable thyroid disease, previous abdominal surgery (other than cholecystectomy or appendectomy), human immunodeficiency virus infection, and renal or hepatic disease. All patients provided written informed consent before study-related procedures were initiated.

Study design and procedure

The protocols were approved by ethics committee at each center. After a screening phase, eligible patients were randomly assigned to either rifaximin or placebo group, in a 1:1 ratio. After completing the 14-day study treatment period, patients were evaluated for 4 additional weeks.

Efficacy and safety end points

The primary end point was the proportion of patients who had adequate relief of global IBS symptoms for at least 2 of the treatment free 4 weeks. This end point was determined from the response (yes or no) to the following question, which was asked weekly: "In regard to all your symptoms of IBS, as compared with the way you felt before you started the study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms?" The threshold for clinical relevance — adequate relief during at least 2 weeks per month — was defined prospectively. The key secondary end point, the proportion of patients who had adequate relief of IBS-related bloating during the primary evaluation period, was determined from the response (yes or no) to the weekly question, "In regard to your symptoms of bloating, as compared with the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptom of bloating?" The onset and duration of relief of bloating were also assessed in an analysis of monthly response, as described above for the primary end point. An exploratory end point, was the proportion of patients who had relief of the composite of abdominal pain and discomfort and loose or watery stools (as measured by improvement in stool consistency), on the basis of daily assessments. Relief was defined as a decrease of at least 30% from baseline in weekly mean ratings of IBS-related abdominal pain or discomfort and a weekly mean stool consistency score of less than 4 (with 4 indicating loose stools and lower scores indicating more formed stools) for at least 2 of the 4 weeks during a given month.

Statistical analysis

In this study about 120 patients were included in study, 60 were in the rifaximin group while 60 were in placebo group. All efficacy and safety analyses were performed on a modified intention-to-treat population, which included all patients who received at least one dose of the study drug Binary data (i.e., data on the proportion of patients who had or did not have adequate relief of symptoms) were analyzed with the use of logistic regression; fixed-effect terms included the Study group and the analysis center. There were five analysis centers, which we formed prospectively by grouping the study centers according to geographic region in order to assess the effects of geographic location on the end points. For the analysis of ordinal data (i.e., data on the number of months in which patients had relief for at least 2 weeks per month), we used the proportional- odds model for the ordinal outcome. The number of consecutive months with relief during the first 3 months after treatment was summed for each patient, so that each patient received a score of 0, 1, 2, or 3.

RESULTS

Study patients

A total of 120 patients who had IBS without constipation were enrolled in the study. More than 95% of the patients completed the entire 6-week study. The baseline characteristics of the patients were similar in

the two studies and across treatment groups. The rate of adherence to the study drug, defined as the use of at least 70% of the dispensed tablets, was at least 97% in both study groups in both studies. Significantly more patients in the rifaximin group than in the placebo group met the criteria for the primary end point of adequate relief of global IBS symptoms for at least 2 of the first 4 weeks after treatment (62% vs. 20%, P = 0.01). On the basis of daily assessments of IBS symptoms, the proportion of patients with a response to treatment, as rated on a 7-point scale during the primary evaluation period, was significantly greater in the rifaximin group than in the placebo group.

Adequate Relief of IBS-Related Bloating

Significantly more patients in the rifaximin group than in the placebo group met the criteria for the key secondary end point, adequate relief of IBS related bloating for at least 2 of the first 4 weeks after treatment (62% vs. 20%, P = 0.01). On the basis of daily assessments of IBS related bloating as rated on a 7-point scale during the same primary evaluation period, a significantly greater proportion of patients in the rifaximin group (62 %) than in the placebo group had relief.

Relief of IBS-Related Abdominal Pain and Loose or Watery Stools

A significantly greater proportion of patients in the rifaximin group than in the placebo group had relief of IBS-related abdominal pain and discomfort during the primary evaluation period (62% vs. 20%, P = 0.01). In an assessment of the composite end point of abdominal pain or discomfort and loose or watery stools, significantly more patients in the rifaximin group than in the placebo group had relief during the primary evaluation period.

Safety

The safety profile of rifaximin was similar to that of placebo (Table 2). Serious adverse events were recorded not recorded in any patients in the rifaximin group. There were no cases of Clostridium difficile– associated diarrhea or ischemic colitis.

DISCUSSION

Treating IBS is important because the symptoms cause substantial impairment in health-related Quality of life, leading to increased use of health resources and reduced work productivity.[15-18]

These two phase 3 studies showed that a short course of rifaximin leads to sustained amelioration of the symptoms of IBS without constipation in a subgroup of affected patients. The antibiotic effect of rifaximin is the presumed mechanism for its sustained beneficial effects in patients with IBS. A response to antibiotic therapy in patients with IBS has been shown to correlate with normalization of the results of lactulose hydrogen breath tests.[8,13] However, there is debate about which antibiotic related effect is most important. On the basis of existing data, there are three reasonable explanations: rifaximin affects gut bacteria and reduces bacterial products that negatively affect the host, the effect on gut flora reduces local mucosal engagement of bacteria such as the immune responses of the host, or the antibiotic alters both the bacteria and the host response. Whatever the final pathway, the durable effects suggest that rifaximin is affecting an underlying cause of IBS that is linked to an alteration in the intestinal microbiota.[7,19,20] Some patients in both of our studies did not have a response to treatment, a finding that is consistent with the results of other placebo-controlled clinical trials involving patients with IBS and that may reflect differences in the underlying cause of the symptoms.[21-23]

Similar percentages of patients in the rifaximin group and in the placebo group had adverse events. In this short-term study, the incidence of infections was similar in the two groups, and there were no cases of C. difficile–associated diarrhea or ischemic colitis.

CONCLUSION

In summary, the results of these studies showed that treatment with rifaximin at a dose of 550 mg three times daily for 14 days provides better relief of symptoms of IBS than does placebo for up to 10 weeks after completion of therapy.

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