

Retrospective comparison of long-term ten-day/month rifaximin or mesalazine in prevention of relapse in acute diverticulitis

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Abstract. – **OBJECTIVE:** Diverticular disease (DD) of the colon has an increasing burden on health services. The effectiveness of rifaximin for the treatment of DD, is not yet established. The aim of this study is to assess the impact of long-term treatment with rifaximin or mesalazine in a 10-day schedule for the prevention of recurrent diverticulitis.

PATIENTS AND METHODS: This is a retrospective study. We identified all consecutive patients with DD and previous acute diverticulitis (AD) in our outpatients' database; 124 patients, were included. The recommended therapy consisted of a ten-day/month treatment with either rifaximin (400 mg bid), or mesalazine (2.4 g/daily). Primary end point was AD recurrence.

RESULTS: Between 2010 and 2014, 72 patients were treated with rifaximin and 52 with mesalazine. During a median follow-up of 15 months (range 1-50), we observed 21 episodes of AD among users of either rifaximin (n=7; 0.54 per 100 person-months), or mesalazine group (n=14; 1.46 per 100 person-months). Kaplan-Meier survival estimates of recurrent AD significantly differed between rifaximin and mesalazine groups ($p=0.015$). The multivariate Cox regression analysis showed that AD recurrence was significantly associated with therapy (rifaximin vs. mesalazine, adjusted HR 0.27; 95% CI: 0.10 to 0.72), age and gender.

CONCLUSIONS: Long-term treatment with rifaximin in a 10-day schedule appears more effective than mesalazine in preventing recurrent AD.

Key Words

Non-absorbable-antibiotics, Rifaximin, Mesalazine, Uncomplicated diverticular disease, Diverticulitis.

Introduction

Diverticular disease (DD) of the colon is common in Western countries and its prevalence increases with age. Even though most people with

DD remain asymptomatic, about 20% will experience symptoms¹. Recent data suggest a lower risk of diverticulitis (4% in 11 years)². However, an increasing prevalence of hospitalization for diverticulitis has been pointed out³.

The two most common and well-recognized complications of DD are acute episodes of diverticulitis characterized by inflammation, micro perforation and abscess formation, and bleedings. Around 25-30% of these patients may experience recurrent episodes^{4,5}.

There is little evidence regarding the appropriate management of diverticulitis after an acute episode^{6,7}. Several treatments are currently used in clinical practice. Rifaximin has been tested in many trials in the treatment of symptoms and the prevention of acute diverticulitis. In a recent meta-analysis of published trials conducted by our group we found that, at one-year follow-up, 64% of patients treated with rifaximin plus standard fiber supplement were symptom-free compared with 35% of patients treated with fiber alone. The number needed to treat (NNT) to achieve symptom relief was 3 for rifaximin versus placebo. In a secondary analysis, a NNT of 59 has been suggested to avoid the first complication of diverticular disease⁸.

It has also been proposed that inflammatory bowel disease (IBD) may be resembled by diverticulitis⁹. Therefore, mesalazine has been investigated in multiple studies as a single agent to achieve and to maintain remission. Previous studies by Morris et al¹⁰ and Kruis et al¹¹ suggested some efficacy of mesalazine in achieving remission, and a small study by Tursi et al¹² also mentioned the efficacy of continuous mesalazine in patients with the recurrent symptomatic diverticular disease. However, more recently, the PREVENT 1 and PREVENT 2 trials¹³ have studied the

use of continuous Multi Matrix System (MMX®) mesalazine in the prevention of recurrent diverticulitis. In each study, 584 patients with resolved diverticulitis were given 1.2, 2.4 or 4.8 grams of MMX mesalazine daily for 2 years and followed for recurrent acute diverticulitis. The results of these large and well-conducted trials showed that mesalazine doesn't prevent recurrent attacks.

In our Gastroenterology Unit, long-term intermittent treatment with rifaximin or mesalazine has been commonly recommended in the prevention of recurrent diverticulitis since 2010, when a dedicated outpatient clinic was launched.

Given that only limited data are available on the comparison of the two treatments, we deemed of interest to assess the impact of therapy with rifaximin or mesalazine in patients with at least one episode of acute diverticulitis.

Patients and Methods

The clinical information of all patients with DD treated in the Gastroenterology Unit of the San Filippo Neri Hospital, Rome, Italy, is recorded in the database "Mal.Dive." (from the Italian acronymous Malattia Diverticolare). We retrospectively extracted from the database all patients with established diagnosis of DD complicated by diverticulitis between 1st January 2010 and 30th November 2014. Patients ≥ 18 years, with at least one documented episode of acute diverticulitis in the previous 24 months that resolved without surgery (index episode) were included in the study. Acute diverticulitis was defined as the presence of all of the following: positive computed tomography (CT) scan of the abdomen/pelvis, elevated white blood cell count, elevated C-reactive protein, and abdominal pain. The exclusion criteria were: age < 18 years, previous abdominal surgery (except appendectomy and hernia repair), history of inflammatory bowel disease or cancer, active psychiatric disease, pregnancy and breast-feeding.

The following demographic and clinical characteristics at baseline were recorded: age, gender, number of previous episodes of diverticulitis, acetylsalicylic acid (ASA), non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulant consumption and associated comorbidities. In our Unit, the recommended therapy of patients with diverticulitis consisted of either ten-day/month treatment with rifaximin 400 mg bid or ten-day/month treatment with mesalazine 2.4 g/daily. Both therapies were then expected to be equally effective, and

the decision on the individual patient was left to two treating physicians (VF and MK). Moreover, all subjects with DD were invited to introduce a high fiber diet (20 g/daily) and to assume *Lactobacillus casei* DG (16 billion/daily) for 15 days every month. Treatment was started after the index episode. Patients were expected to receive follow-up visits at regular intervals (2 times per year).

The main outcome of the study was the proportion of patients who were free of recurrent diverticulitis at the end of follow-up, considered as the earliest of the following dates: the first occurrence of recurrent diverticulitis, last visit recorded in the database up to 30 November 2014. Diverticulitis recurrence was defined as either surgical intervention for DD or the presence of all of the following: positive CT scan of the abdomen/pelvis, elevated white blood cell count, elevated C-reactive protein, and abdominal pain.

Statistical Analysis

The groups of patients receiving rifaximin or mesalazine were compared through *t*-test for continuous variables and χ^2 -test for categorical ones. The cumulative survival probabilities of a recurrent diverticulitis were calculated using the Kaplan-Meier method for patients treated with rifaximin and mesalazine. A log-rank test was used to compare the survival curves in the two groups.

We used Cox regression analysis to estimate the hazard ratio (HR) and 95% confidence interval (95% CI) of the outcome among users of rifaximin in comparison with mesalazine.

Patients' data were censored at the first occurrence of recurrent diverticulitis or at the last visit recorded in the database.

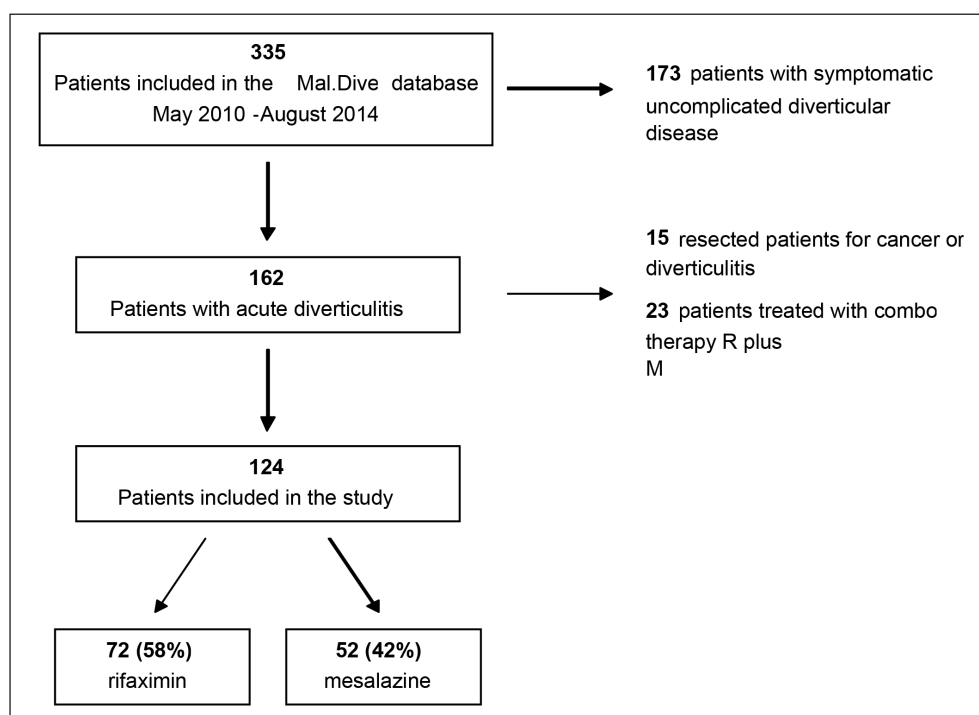
The initial model included as potential confounders: age at first visit (≤ 65 years vs. > 65 years); gender (female vs. male); number of previous episodes of diverticulitis (≥ 2 vs. 1); ASA, NSAIDs or anticoagulant consumption (Yes vs. No); associated comorbidities index level grouped into two categories (≥ 1 vs. 0). The final model was defined by using a stepwise backward approach.

All the analyses were performed with the STATA software (StataCorp, release 11). $p < 0.05$ was considered statistically significant.

Results

Among 335 patients included in our Mal.Dive. database from the 1st January 2010 to 30th November 2014, we included in the study 124 subjects

Figure 1. Patients included in the Mal.Dive database.



(median age of 66 years, range 28-87; 48% females) who experienced one or more resolved episodes of acute diverticulitis in the previous two years (Figure 1). The remaining patients were excluded because they were affected by symptomatic uncomplicated diverticular disease (n=173), were already resected for cancer or diverticulitis (n=15), or were treated with combo therapy rifaximin plus mesalazine (n=23).

Among the 124 selected patients, 72 had received a ten-day/month treatment with rifaximin 400 mg bid, and 52 a ten-day/month treatment with mesalazine 2.4 g/daily. The clinical characteristics of the two groups were similar with regard to age, gender, number of previous episodes of diverticulitis, or ASA/NSAIDs/anticoagulant consumption and comorbidities (Table I). Patients were observed for a total of 2,251 months, with a

Table I. Clinical characteristics of patients included in the study.

		Total	Rifaximin (n. 72)	Mesalazine (n. 52)	<i>p</i>		
		n.	n.	%	n.	%	
Gender	female	60	38	52.8	22	42.3	0.25
	male	64	34	47.2	30	57.7	
Age	≤65	60	33	45.8	27	51.9	0.50
	>65	64	39	54.2	25	48.1	
Comorbidity	no	92	50	69.4	42	80.8	0.16
	yes	32	22	30.6	10	19.2	
Previous episodes of diverticulitis	1	109	62	86.1	47	90.4	0.47
	≥2	15	10	13.9	5	9.6	
ASA/NSAIDs/ anticoagulant	no	97	54	75.0	43	82.7	0.31
	yes	27	18	25.0	9	17.3	

ASA: Acetylsalicylic Acid; NSAID: non-steroidal anti-inflammatory drug

median follow-up of 15 months (range 1-50). The treatments continued in all patients throughout the follow-up period. We observed 21 recurrent episodes of confirmed acute diverticulitis (cumulative prevalence: 16.9%): 7 episodes (9.7%) occurred in the rifaximin group and 14 (26.9%) in the mesalazine group. The corresponding incidence rates were 0.54 and 1.46 per 100 person-months in the rifaximin and mesalazine users respectively. All patients with diverticulitis required hospitalization. Surgery for complicated diverticulitis was required in 4 patients (two in each treatment group).

No side effects were reported by patients receiving rifaximin during the follow-up visits and one episode of repeated nosebleed was experienced by a patient treated with mesalazine; no suspension of the drug use was deemed necessary.

Kaplan-Meier survival estimates of recurrent diverticulitis differed between rifaximin and mesalazine groups ($p=0.015$). At 24 months of follow-up, the estimated cumulative proportions of patients free of recurrences were 83.3% in the rifaximin group and 71.1% in the mesalazine group (Figure 2).

In the multivariate Cox regression, treatment with rifaximin was significantly associated with a reduction in the occurrence of recurrent diverticulitis (adjusted HR 0.27; 95% CI 0.10 to 0.72)

(Table II). Younger age and female gender were associated with an increased risk of recurrent diverticulitis (≤ 65 vs. >65 years: adjusted HR 3.81, 95% CI 1.36 to 10.71; females vs. males: adjusted HR 3.20, 95% CI 1.20 to 8.54).

Discussion

The natural history of DD is poorly understood. On the basis of a review article¹⁴, published in 1975, the lifetime risk of developing diverticulitis is traditionally referred as ranging between 10% and 25%. Previous studies, conducted when population-based colonoscopies were not performed, nor imaging techniques (CT) available, suggested a high recurrence rate and severe clinical presentation, with less chance of conservative treatment⁴.

More recent studies have shown a milder course of the disease. The risk of developing acute diverticulitis in a large cohort of patients with diverticulosis incidentally discovered during a colonoscopy, was 4.3% over a period of 11 years (incidence rate 0.05 per 100 person-months)². Recent prospective data coming from a meta-analysis suggest a 2.8% incidence of diverticulitis in “untreated” symptomatic patients with diverticulosis over a 12-month period⁸.

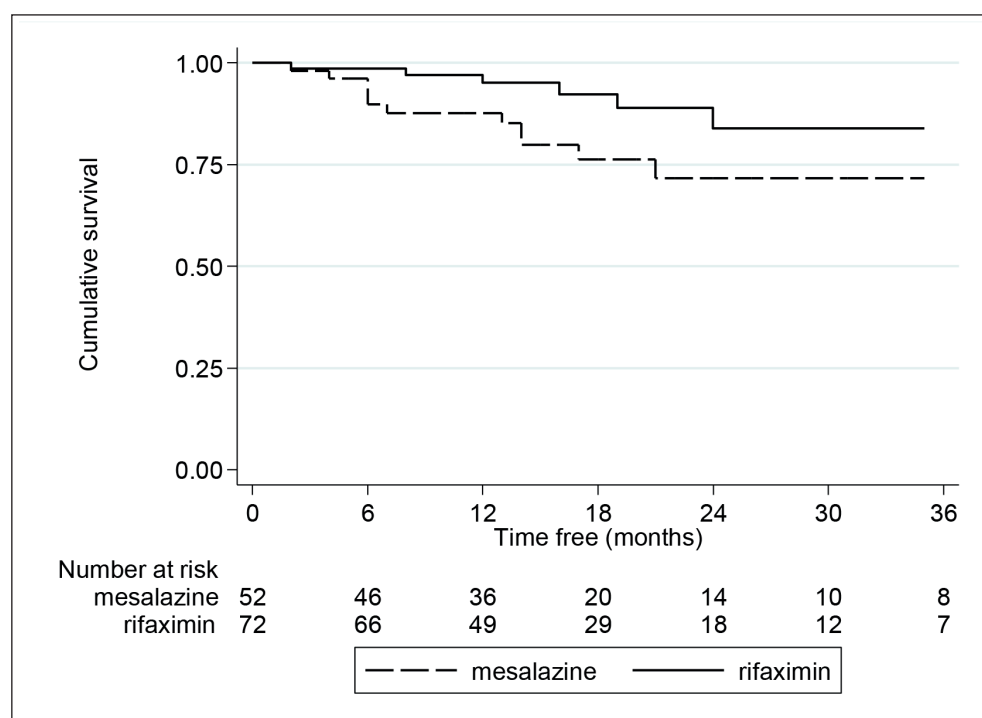


Figure 2. Cumulative survival curves of recurrent diverticulitis by treatment with rifaximin or mesalazine.

Table II. Association between treatment with rifaximin or mesalazine and recurrence of diverticulitis by Cox proportional hazard multiple regression model.

		No. of events	Person time (months)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Therapy	Mesalazine	14	956	1	1
	Rifaximin	7	1,295	0.33 (0.13-0.86)	0.27 (0.10-0.72)
Gender	Male	10	1,279	1	1
	Female	11	972	1.71 (0.70-4.17)	3.20 (1.20-8.54)
Age, years	>65	6	1,159	1	1
	≤65	15	1,092	2.45 (0.94-6.37)	3.81 (1.36-10.71)
Comorbidity	No	18	1,676	1	
	Yes	3	575	0.53 (0.16-1.82)	
N° of previous episodes of diverticulitis	1	18	1,966	1	
	≥2	3	285	1.34 (0.38-4.66)	
ASA/NSAIDs/anticoagulant	No	19	1,882	1	
	Yes	2	369	0.59 (0.14-2.59)	

*the final model for the estimate of adjusted HRs included therapy, age and gender. HR: hazard ratio. 95% CI: 95% Confidence Interval.

However, the first episode of diverticulitis indicates a worsening of the clinical history. Current guidelines of the American Gastroenterological Association¹⁵ estimate the 5-year risk at 20% from a large cohort of 20,136 patients treated medically for a first episode of acute uncomplicated diverticulitis (mean follow-up, 5.5 years)¹⁶.

We observed 21 recurrent episodes of CT-scan confirmed acute diverticulitis, with an overall cumulative incidence of 16.9%. Our estimate, which is based on a median follow-up period of 15 months from 2010 to 2014, indicates a lower incidence rate of recurrent episodes of diverticulitis than previously described⁴.

There is little evidence regarding the appropriate management of diverticulitis after an acute episode. Since recurrent episodes of diverticulitis are common, a treatment aimed at preventing recurrences would be needed. The available literature reports five randomized trials and a meta-analysis, suggesting that cyclic administration of rifaximin may be effective in reducing symptoms (e.g., abdominal pain, bloating), complication frequency and severity of DD^{8,17-21}. These results are explained by the hypothesis that rifaximin influences gut microbiota, reducing its metabolic activity, the degradation of dietary fiber and the production of methane.

On the other hand, mesalazine reduces inflammation in patients with IBD and has been suggested to reduce chronic mucosal inflammation associated with DD⁹. Several studies^{10-12,22} suggested that mesalazine can be effective in the prevention

of diverticulitis recurrence, but two recent trials comparing continuous mesalazine therapy versus placebo denied its role¹³. In these large and well-conducted studies, none of the 3 dosages of mesalazine (1.2, 2.4, or 4.8 g/d) demonstrated a positive effect on the proportion of diverticulitis recurrence-free patients at week 104 compared with placebo (65-68% in the placebo groups; 53-69% in the mesalazine groups). Raskin et al¹³ adopted more sensitive criteria, defining diverticulitis recurrence essentially as a positive CT scan (bowel wall thickening and/or fat stranding), and that could explain the higher risk of a repeated episode when compared to the literature.

Our study shows that rifaximin is more effective than mesalazine in the prevention of recurrent diverticulitis, with a significant difference in the 2-years survival estimates of recurrence-free in favor of rifaximin treatment (83% vs. 71%; $p=0.015$), and an incidence rate of complications which is 3 times lower than in the mesalazine group (0.54 vs. 1.46 per 100 person-months), confirming the protective effect of this non-absorbable antibiotic.

Only one prospective study tested this hypothesis, but it was stopped due to the slowdown in recruiting. Lanis et al²³ expected a 20% annual incidence of new events of diverticulitis in the control group (fiber only) and a 10% incidence in the treated group (fiber plus rifaximin). In the multicentric study (23 gastrointestinal units), they admitted 167 patients. Seventy-six patients in the control group and 56 in the rifaximin group completed a 48-week follow-up. The primary composite endpoint was

the occurrence of recurrences of diverticulitis with or without complications. Acute symptomatic flare was confirmed by whichever instrumental tests routinely used at the patient's referral center.

Their definition of diverticulitis is quite different and "lighter" than the one adopted in our study (presence of all of the following: positive CT scan of the abdomen/pelvis, elevated white blood cell count, elevated C-reactive protein, and abdominal pain). In fact, they had only 7% of hospitalization in the control group and 3% in the rifaximin group, against our figures of 26.9% and 9.7% respectively. Anyway, there is a substantial agreement between the 2 studies on the incidence of the second episode of diverticulitis in the long term (1-3 years) (19% and 27% in the control groups; 10% and 10% in the rifaximin groups).

To estimate the absolute effect of rifaximin on the number of recurrences at 5 years, we applied the data of the largest study on medically treated patients¹⁶ to the Lanas et al²³ and our study. A reduction of 9 and 14 episodes per 100 persons respectively can be obtained (Table III).

However, due to the risk of bias, the evidence should be coded as poor, according to the GRADE scale (http://www.gradeworkinggroup.org/publications/JCE_series.htm).

So, when diverticulitis appears, the risk of a new episode is higher in the following years (>18 times) than the first episode in patients with an occasional finding of diverticulosis, if a constant risk is assumed over time².

Rifaximin is a non-absorbable antibiotic that is commonly used in the therapy of many pathological conditions referred to gastrointestinal dis-

eases, i.e. inflammatory bowel diseases, irritable bowel syndrome, intestinal bacterial overgrowth, and hepatic encephalopathy²⁴. Moreover, rifaximin possesses significant anti-inflammatory/immunomodulatory properties by acting on TNF-alpha and IL-1beta down-regulation in the gut mucosa²⁵.

We boosted the possible effect of rifaximin by the extension of the therapeutic scheme to a ten-day per month. Scarpignato and Pelosini²⁶ demonstrated that pre-existing intestinal microflora recovers within 1-2 weeks after the end of the standard seven-day treatment with rifaximin. Thus, a prolonged schedule in this study has been chosen to guarantee a better modulation of gut microbiota during each month.

We prescribed in all subjects a high fiber diet (20 g/daily), even if the relationship between diverticulosis and dietary fiber is now the subject of reflection²⁷. Some studies^{28,29}, including two large prospective cohorts, have observed an inverse association between dietary fiber intake and diverticular complications.

We also prescribed L. Casei DG 16 billion/daily. The rationale for using probiotics in diverticular disease is based on the theory that a deranged abnormal gut flora (dysbiosis) could precipitate chronic inflammation and recurrent disease^{30,31}.

The low rate of surgery (<5%) observed in both treatment groups of our study suggests that conservative management of recurrent diverticulitis should be preferred, even in patients with a history of several episodes of diverticulitis³².

Only age <65 years and female sex were positively associated with diverticular recurrence. A greater risk of developing diverticulitis at a young-

Table III. Rifaximin rather than no therapy (or mesalazine) in patients with a history of acute uncomplicated diverticulitis. Estimated outcome: number of recurrences at 5 years.

Studies	No. of patients	Risk Ratio (95% CI)	Anticipated absolute effect		Differences (95% CI)
			Without rifaximin	With rifaximin	
RCT					
Lanas	167	0.54 [^] (0.25 to 1.18)	19 per 100 pts	10 per 100 pts	-9 (-14- to +3)
Observational					
This study	124 (0.10 to 0.72)	0.27 [°]	19 per 100 pts	5 per 100 pts	-14 (-17 to -5)

*based on (Anaya DA, Flum DR. Risk of emergency colectomy and colostomy in patients with diverticular disease. Arch Surg 2005; 140: 681-685). Follow-up of 20,136 patients treated medically for a first episode of acute uncomplicated diverticulitis (mean follow-up, 5.5 years), considering a constant risk of recurrence over time. [^]RR: Risk Ratio (control group placebo). [°]HR: Hazard Ratio (control group mesalazine).

er age is consistent with the literature². The possibility of a differential risk between female and male patients is more uncertain, and other studies suggest a greater risk for the male sex³³. NSAID use is considered as a risk factor for diverticulitis and diverticular bleeding³⁴. However, the lack of association observed in our population can be explained by the limited power of the study (only 21 episodes of recurrence were observed).

The study presents several limitations: the design was retrospective, and we cannot exclude that the observed differences were at least partially attributable to the initial differences in the patients' characteristics rather than the treatment. All patients were included in a single center, thus limiting its reproducibility. Moreover, as already mentioned, the power of the study was too limited to either confirm or disprove the role of consistently recognized risk factors (e.g., NSAID use).

However, we were able to guarantee an extensive follow-up, with a median of 15 months and a maximum of four years, which provides an insight into the clinical history of diverticulitis in a "real life" outpatient's clinic.

Conclusions

The administration of rifaximin in a ten-day/month regimen, in comparison with mesalazine, showed a consistent better outcome regarding the recurrence of diverticulitis. Since the evidence derived from a retrospective cohort study, a large randomized controlled trial is highly needed to definitely establish the therapeutic role of rifaximin in preventing recurrence in patients with diverticulitis. A sample of 200 patients would be required to detect a difference of 10% between two groups, with a 3-year survival estimates of recurrence-free of 80% in the placebo group (80% power and 5% significance, two-tailed).

Diverticular disease is now a subject of exciting research. We need to identify patients who will benefit from antibiotics or probiotics, and dietary interventions, that may reduce symptoms, prevent diverticulitis or decrease recurrence rates after acute diverticulitis.

We need to identify better the risk factors that contribute to make worse the clinical history. We need to investigate the clinical impact of NSAIDs and aspirin on the diverticular disease, and to estimate the cost/benefit ratio^{35,36}.

Our findings contribute to estimate the role of unabsorbable antibiotics in preventing relapse of

diverticulitis, and found for the first time a significant gain for the use of rifaximin in this subset of patients.

These data were presented in part at FISMAD, "Italian National Congress of Digestive Diseases", March 27, 2015, Bologna, Italy, and at DDW 2015, May 17, 2015, Washington, USA

Conflict of Interest

The Authors declare that they have no conflict of interests.

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