European Review for Medical and Pharmacological Sciences 2021; 25: 423-430

General practitioners' management of symptomatic uncomplicated diverticular disease of the colon by using rifaximin, a non-adsorbable antibiotic

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Abstract. – OBJECTIVE: Symptomatic uncomplicated diverticular disease of the colon (SUDD) is generally managed by gastroenterologists rather than General Practitioners (GPs). The aim of this study was to assess the efficacy of the treatment of SUDD with rifaximin, a non-absorbable antibiotic, in a primary care setting by GPs.

PATIENTS AND METHODS: This retrospective, observational study investigated the use of rifaximin at a dose of 400 mg b.i.d. for 5, 7 or 10 days monthly, up to 3 months. The symptoms were reported by the patients using a visual analogic scale (VAS) of 0-10.

RESULTS: 286 SUDD patients were enrolled (44.4% of men, average age 70.92±10.98). Respectively, 15 (5.2%) patients received the treatment for 5 days, 205 (71.7%) for 7 days and 66 (23.1%) for 10 days. After three months, a significant reduction of VAS score was observed in almost all symptoms assessed: 135 (47.2%) patients reported no abdominal pain ($p<0.001$) and 23 (8.1%) reported no symptom. Adverse events related to the treatment were recorded in 3 (1.04%) patients, all of them mild and not requiring interruption of the treatment. Acute diverticulitis occurred in 9 (3.1%) patients, but only 2 of them [0.7% (n=2)] underwent surgery due to complicated diverticulitis. Analysis within the different treatment groups (5, 7 and 10 days) shows that rifaximin treatment is effective in reducing the severity of symptoms in almost all groups except for the constipation in the 5-day group.

CONCLUSIONS: Rifaximin can be effectively used by GPs in real-life for the management of SUDD.

Key Words:
Acute diverticulitis, Complications, Primary care, Rifaximin, Symptomatic uncomplicated diverticular disease, Treatment.

Introduction

Colonic diverticulosis is an anatomical alteration of the large intestine, consisting in the outpouching of small pockets of part of the bowel wall[1]. It shows a large prevalence in the general population, especially in industrialized and western countries, reaching up to over 65% of the general population[1-5]. The diverticula are mainly located in the left colon in the western countries, while in the Asian countries they are primarily in the right colon[4,5]. Epidemiological studies have shown that 80% of patients with colon diverticulosis are and will remain asymptomatic, and just 15% of them will experience symptoms, defined as Symptomatic Uncomplicated Diverticular Disease (SUDD)[1,4].

This syndrome is characterized by recurrent abdominal symptoms (for example abdominal pain or changes in bowel habits), attributed to colonic diverticula and with no clinical signs of diverticu-

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litis[1]. Those symptoms look like the symptoms of irritable bowel syndrome (IBS)[1]. However, SUDD symptoms do not fulfill IBS criteria, in particular about the characteristic of the abdominal pain, and a combination of clinical finding permit to pose a correct diagnosis[1,6]. Moreover, it is a frequent and disabling pathology: almost 8% of patients will have diverticulitis[7], and the quality of life is often impaired[7,8]. That's why its management is time consuming, with recurrent doctor's visits. For example, 1,748,508 office visits are performed each year in the United States for the management of diverticular disease[9].

According to the statements coming from three recent International Symposia on Diverticular Disease[10-12], several treatments are currently available and can be used to manage SUDD. Rifaximin, a non-aminoglycoside semisynthetic non-absorbable antibiotic, derived from rifamycin SV, is one of them. Rifaximin inhibits bacterial protein synthesis by binding to the b-subunit of bacterial DNA-dependent RNA polymerase. This activity leads to the suppression of RNA-chain initiation during RNA synthesis[13]. *In-vitro* and *in-vivo,* it shows a strong activity against Gram-positive and Gram-negative bacteria, both aerobic and anaerobic[13,14]. In addition, thanks to a very low systemic absorption[15], its safety profile is excellent, with adverse events observed in less than 2% of patients[16,17].

Some real-life studies have been conducted in order to evaluate the efficacy and tolerability of rifaximin in SUDD patients. All of them were conducted by gastroenterologists[17-22] and none of them fully involved general practitioners (GPs), even though GPs are very often involved in the management of those patients[23-25]. Our aim was therefore to assess the management of SUDD patients with rifaximin by GPs.

Patients and Methods

We conducted a multicenter, retrospective study assessing the outcome of SUDD treated with rifaximin in all eligible SUDD patients who had at least a 3-month follow-up until 31st December 2019.

Patients were considered eligible, if they met the following criteria:

- patients ≥18 years (both male and female);
- had undergone colonoscopy or radiology to detect diverticulosis;
- were at first diagnosis of SUDD. SUDD was defined as the presence of symptoms in patients with diverticulosis, in absence of signs and/or symptoms and laboratory and/or endoscopy and/or radiology evidence of acute diverticulitis, and in absence of any other complication (stenosis, abscesses, fistulas)[1]. Moreover, the presence of long-lasting left lower quadrant pain was considered the mainstay symptom to pose the SUDD diagnosis[1];
- were assessed every month for the first three months on 4 main symptoms (abdominal pain, swelling, constipation and diarrhea) by using a VAS scale, with a score from 0 to 10 (0 = absence of symptoms 10 = maximum intensity of symptoms);
- had given written informed consent before undergoing colonoscopy.

Patients who met any of the following criteria were excluded from the study:

- radiological signs (by abdominal CT or by ultrasounds) of acute diverticulitis (complicated or uncomplicated);
- inflammatory bowel diseases and ischemic colitis;
- prior colonic resection;
- patients with severe liver failure (Child-Pugh C) or with severe kidney failure;
- patients with cancer, of any origin, in treatment with radio- or chemotherapy;
- history of alcohol, drug, or chemical abuse.

The patients who met all these inclusion and exclusion criteria were therefore subdivided according to the duration of course of Rifaximin 400 mg × 2 per day: 5-day course per month, 7-day course per month and 10-day course per month. Other data from these patients were collected, in particular sex, age, BMI, smoking habits, previous appendectomy, comorbidity with any therapies, duration of appearance of abdominal pain, years since the diagnosis of diverticulosis in order to assess which factor could influence the primary and secondary endpoints.

A shared common database was used to collect demographic and clinical data.

The primary endpoint of this study was to assess the effectiveness of a monthly course of rifaximin in reducing the symptoms in patients suffering from SUDD.

Secondary endpoints were:

- the safety of this monthly treatment;
- the difference between the different courses of rifaximin in reaching primary endpoint;
- the occurrence of acute diverticulitis in this population, assessing also potential hospital admittance and length of stay (in days);
- the risk of surgery in this population.

The study was conducted according to the World Medical Association's Declaration of Helsinki. According to the Italian law, a formal consent is not required for this type of study.

Statistical Analysis

Descriptive variables were presented as a mean with a standard deviation for continuous variables or as relative frequency (percentage) with the absolute number for dichotomous or categorical variables. For continuous variables, differences were analyzed using the Wilcoxon test or the Kruskal Wallis test according the grouping of each variable. For dichotomous variables differences were analyzed using the χ^2-test. In order to analyze differences among the 3 treatments groups (according to the duration of cyclic treatment) due to possible baseline imbalance among the three groups both a univariate and a multivariate linear regression were performed and adjusted by the possible confounding factors registered at the baseline.

Results

Baseline Characteristics

Baseline characteristics of enrolled patients (n=286) are reported in Table I.

Diverticulosis was diagnosed by colonoscopy in 241 (84.3%) patients, by ultrasound in 25 (8.7%), by computerized tomography (CT) in 17 (6.0%) and by barium enema in 3 patients (1.0%). In all patients at least an endoscopic or radiologic visualization of diverticula was reported.

Most of the patients reported 2 episodes of SUDD at baseline visit. Also pain duration was evaluated at the baseline visit: 74 (25.9%) patients reported pain that lasted "a few hours" in the week before enrolment, 108 (37,8%) reported it

Table I. Baseline characteristics of studied population.

Age (years)	70.92 ± 10.98 (range 40-97)
Sex	
Male	127 (44.4%)
Female	159 (55.6%)
BMI (kg/m^2)	26.53 ± 3.61 (range (16.16-39.60)
Smoker	50 (17.5%)
Appendectomy	61 (21.3%)
Comorbidity	
Cardiovascular	172 (60.1%)
Respiratory	27 (9.4%)
Metabolic	51 (17.8%)
Rheumatic	39 (13.6%)
Others	103 (36.0%)
Initial diagnosis of diverticular disease	
< 5 years ago	96 (33.6%)
5-10 years ago	109 (38.1%)
11-20 years ago	60 (21.0%)
> 20 years ago	21 (7.3%)
Frequency of SUDD attacks previous year	
2 episodes	224 (78.4%)
3 episodes	31 (10.8%)
4 episodes	16 (5.6%)
5 episodes	9 (3.1%)
> 5 episodes	6 (2.1%)
Previous pharmacological treatment of SUDD/diverticulitis	
No	39 (13.6%)
Yes	247 (86.4%)
Antibiotics	144 (50.3%)
Mesalazine	37 (12.9%)
Prebiotics	116 (37.5%)
Antispasmodics	27 (8.7%)
Others	8 (2.8%)

lasted "several hours" and 104 (36.3%) reported it lasted "a whole day". 247 (86.4%) patients reported previous treatments for SUDD.

At baseline (T0), for symptomatic patients, average VAS score and frequency for abdominal pain, swelling, constipation, diarrhea and their mean value are reported in Table II.

Efficacy

After 3 months of rifaximin treatment (T3), a significant reduction in symptoms severity was observed in most patients as well as a reduction of symptomatic patients, as shown in Table II. Specifically, the average VAS score decreases from 3.21 ± 1.75 to 1.08 ± 1.11 and the number of patients who had at least one symptom decreases from 91.6% (n=262) to 73.8% (n=211). There was also a significant decrease in symptoms score and average VAS score from baseline to the follow-up visits at T1 and T2, even if of smaller amplitude. Finally, constipation score showed a reduction, although not significant (p=0.086), between T2 and T3.

In addition to the intensity of the symptoms, the frequency at which they occur in patients being treated also decreased. Moreover, the number of patients complaining of pain decreased by 35.7% from baseline to the third month of observation. Similarly, the number of patients who complained of swelling decreased by 22.8%, those who complained of constipation decreased by 10.5% and those who complained of diarrhea by 18.6%. In addition, the number of asymptomatic patients increased by 17.8%, and all parameters improved significantly (Table II).

The results of the univariate and multivariate analyses are shown in Table III. Constipation was improved by a longer rifaximin cycle rather than a shorter one, because both the models are consistent with the result of Kruskal Wallis test results for constipation at T3.

Specifically, according the univariate linear regression, abdominal swelling and constipation seem to be improved by a longer cycle of treatment, while diarrhea seem to be worsened. According to the multivariate regression (adjusted by gender, age, BMI, the corresponding score at baseline, the years of disease and the number of recurrences before the treatment), both constipation and the average VAS score seem to be improved by a longer cycle, while diarrhea seem to be worsened.

Safety and Tolerability

The treatment with rifaximin cycles has proven to be very safe and tolerated by patients. Only in three patients (1.04%) we observed adverse events associated with the drug. These were extremely mild, ended after the suspension of the treatment cycle, and did not reappear with the next treatment cycle. In particular, 1 episode of diarrhea and 2 of abdominal bloating have been observed in patients who previously had not experienced these manifestations.

Differences According the Duration of Rifaximin Treatment

Looking at the difference between the three groups of treatment, we observed that at the baseline the three groups have different, statistically significant score levels, except for the severity of constipation, which is similar among the three groups. We found an improvement in the VAS score for all the symptoms studied and for the average VAS score. Nevertheless, some differences

Table II. VAS score and Symptoms in studied population.

VAS Score	T0	T1	T2	T3	p-value*
Pain	5.00 ± 2.62	2.85 ± 2.25	1.87 ± 1.92	1.37 ± 1.76	< 0.001
Swelling	4.09 ± 2.94	2.69 ± 2.36	2.06 ± 2.11	1.55 ± 1.85	< 0.001
Constipation	1.97 ± 2.61	1.41 ± 1.98	1.02 ± 1.61	0.96 ± 1.57	< 0.001
Diarrhea	1.82 ± 2.57	0.95 ± 1.72	0.62 ± 1.28	0.44 ± 1.07	< 0.001
Mean	3.21 ± 1.75	1.97 ± 1.41	1.39 ± 1.19	1.08 ± 1.11	< 0.001
Symptoms frequencies	**T0**	**T1**	**T2**	**T3**	**p-value$^{\alpha}$**
Pain	88.5% (n = 253)	72.7% (n = 208)	61.9% (n = 177)	52.8% (n = 151)	< 0.001
Swelling	77.3% (n = 221)	68.5% (n = 196)	60.5% (n = 173)	54.5% (n = 156)	< 0.001
Constipation	47.6% (n = 136)	43.7% (n = 125)	38.8% (n = 111)	37.1% (n = 106)	< 0.05
Diarrhea	39.9% (n = 114)	29.6% (n = 85)	25.9% (n = 74)	21.3% (n = 61)	< 0.001
At least one symptom	91.6% (n = 262)	84.6% (n = 242)	79.7% (n = 228)	73.8% (n = 211)	< 0.001

*p-value between T0 and T3; Wilcoxon test; $^{\alpha}p$-value between T0 and T3; χ^2 test.

Table III. Analysis of the impact of cycle length on studied symptoms according the univariate and the multivariate models.

Regression models for cycle treatment duration	β univariate	R^2 univariate	*p*-value β univariate	β multivariate**	R^2 multivariate**	*p*-value β multivariate**
Pain	-0.071	0.001	0.735	-0.237	0.157	0.252
Swelling	-0.570	0.024	< 0.01	-0.576	0.327	0.107
Constipation	-0.568	0.033	< 0.01	-0.625	0.414	< 0.001
Diarrhea	0.366	0.030	< 0.01	0.361	0.287	< 0.01
Mean score	-0.211	0.009	0.106	-0.276	0,334	< 0.05

[c]A positive β coefficient shows correlation between a shorter cycle and a symptomatic improvement, while a negative β coefficient shows correlation between a longer cycle and a symptomatic improvement; **Adjusted by gender, age, BMI, the corresponding score at the baseline, the years of disease and the number of reactivation before the treatment.

can be found (Table III). The first was that the 5-day group did not show a statistically significant improvement of constipation at T3 (Table IV). The second was that the longer the treatment cycle, the greater the improvement in abdominal swelling and constipation. In fact, the 10-day treatment group had the greatest improvement and the lowest score among the three groups in these specific symptoms.

Occurrence of Diverticulitis and Length of Hospital Stay

Acute diverticulitis occurred in 9 (3.1%) patients, seven suffering from uncomplicated dis-

Table IV. Efficacy evaluation among the three group of treatment..

Pain	T0	T1	T2	T3	*p*-value* (within group T0 *vs.* T3)
5-days Group (n = 15)	6.73 ± 1.98	4.4 ± 3.043	3.33 ± 2.35	2.00 ± 1.852	< 0.001
7-days Group (n = 205)	4.59 ± 2.58	2.7 ± 2.163	1.82 ± 1.697	1.31 ± 1.491	< 0.001
10-days Group (n = 66)	5.88 ± 2.52	2.95 ± 2.222	1.67 ± 2.323	1.44 ± 2.412	< 0.001
p-valueb (among groups at same time)	< 0.001	0.072	< 0.01	0.085	
Swelling	**T0**	**T1**	**T2**	**T3**	***p*-value* (within group T0 *vs.* T3)**
5-days Group (n = 15)	6.40 ± 2.87	4.93 ± 2.40	3.80 ± 2.45	2.47 ± 1.81	< 0.001
7-days Group (n = 205)	3.87 ± 2.84	2.53 ± 2.23	1.99 ± 1.92	1.61 ± 1.74	< 0.001
10-days Group (n = 66)	4.26 ± 3.05	2.68 ± 2.55	1.89 ± 2.44	1.14 ± 2.13	< 0.001
p-valueb (among groups at same time)	< 0.01	< 0.01	< 0.01	< 0.01	
Constipation	**T0**	**T1**	**T2**	**T3**	***p*-value* (within group T0 *vs.* T3)**
5-days Group (n = 15)	1.87 ± 2.74	1.67 ± 2.44	1.2 ± 1.70	1.87 ± 2.20	0.367
7-days Group (n = 205)	2.06 ± 2.51	1.36 ± 1.86	1.08 ± 1.62	1.02 ± 1.62	< 0.001
10-days Group (n = 66)	1.70 ± 2.87	1.45 ± 2.25	0.79 ± 1.52	0.55 ± 1.11	< 0.001
p-valueb (among groups at same time)	0.128	0.938	0.170	< 0.01	
Diarrhea	**T0**	**T1**	**T2**	**T3**	***p*-value* (within group T0 *vs.* T3)**
5-days Group (n = 15)	3.13 ± 2.66	1.53 ± 1.77	1.07 ± 1.39	0.33 ± 0.90	< 0.01
7-days Group (n = 205)	1.46 ± 2.33	0.73 ± 1.50	0.5 ± 1.02	0.33 ± 0.81	< 0.001

[c]A positive β coefficient shows correlation between a shorter cycle and a symptomatic improvement, while a negative β coefficient shows correlation between a longer cycle and a symptomatic improvement; **Adjusted by gender, age, BMI, the corresponding score at the baseline, the years of disease and the number of reactivation before the treatment.

ease (4 of them required hospitalization) and only 2 (0.7%) from complicated disease requiring surgery (one with a history of 3 episodes and one with a history of 4 episodes of SUDD). The average length of hospital stay for patients who did not undergo surgery was 5 days, while it was 16.5 days for patients undergoing surgery.

Discussion

Current guidelines[10-12] claim that the treatment of SUDD is aimed at symptom-relief and at prevention of complications (mainly acute diverticulitis). Thus, several treatments have been proposed, such as bulking agents, spasmolytics, topical antibiotics, and anti-inflammatory drugs, on the basis of different potential pathophysiological mechanisms[1]. The efficacy of some treatments remains controversial[26]. For example, the use of antibiotics in SUDD patients seems to have no rationale. However, although the mechanism by which rifaximin improves symptoms in SUDD is still unclear, both uncontrolled and controlled clinical studies found rifaximin effective in treating SUDD[27].

Looking at the studies conducted in a real-life setting, rifaximin was found effective in managing SUDD patients[17-22]. Overall, our results indicate that rifaximin is effective in treating SUDD patients in real-life, confirming the good performances reported by the other real-life studies. In fact, the average VAS score and at least one symptom decrease significantly from baseline to T3 except for constipation. Rifaximin confirms therefore its efficacy in treating diarrhea more specifically than constipation in SUDD patients[20]. Looking at the safety, we found that the occurrence of adverse events linked to rifaximin use was in line with other experiences (about 1%)[17,19,28], and none of the patients stopped treatment. This means that recurrent use of rifaximin is safe with a very low risk to cause AEs. Finally, the occurrence of complications, namely acute diverticulitis, was low (about 3%), in line with what reported by Bianchi et al[27] in their meta-analysis.

Although reaching similar results, we would like to pinpoint three significant differences from the previous real-life studies. The first is that this is the first study enrolling patients having a clear definition of SUDD[11], which has often been lacking in the previous real-life studies. This is an important point, because the absence of a clear definition can cause over- or underestimation of the disease, with consequent bias of treatment. Using well-defined criteria, this study confirmed that the vast majority of SUDD patients had abdominal pain not fulfilling IBS criteria[8], and the patient had to be thus managed accordingly.

The second difference from the previous studies is that it is the first real-life study fully conducted by GPs. Some real-life investigations have already been conducted by gastroenterologists[17-22], but no study so far had been conducted by GPs. This is another important point because, even though they are managing the diseases often using the same drugs, significant differences can be found between gastroenterologists and GPs. Notably, in the treatment of gastro-esophageal reflux disease gastroenterologists stated that the most important consideration for the selection of treatment was high safety profile, whereas GPs were focusing on a rapid symptomatic relief[29]. A similar divergent approach can be seen with SUDD. Since GPs are the first doctors consulted by the symptomatic patients, they generally consider symptoms relief the most important target[25]. This very observation is what led us to design a study conducted by GPs.

The third significant difference is that this study is assessing for the first time whether there are differences depending on the duration of the cyclic treatment with rifaximin. This is currently no consensus about the duration of the treatment cycle with rifaximin and, at least in Italy, it can vary from 5 to 10 days monthly. The results of the multivariate analyses, adjusted for confounding factors, found that a longer treatment was the best choice in improving the average VAS score, swelling and constipation, while a shorter cycle is the best in improving diarrhea. These findings are very important for clinical practice and for GPs in particular, because they allow to modulate the duration of the rifaximin treatment: when patients complain of constipation, a longer treatment is needed, while in patients complaining of diarrhea, a 5-day cycle may be enough. Of course, the small sample size of the 5-days group enrolled limits the interpretation of these results. However, it could be the background for further studies assessing the best duration of the cyclic treatment with rifaximin.

This study has several limits. First of all, being designed as a retrospective study, some data, such as concomitant fiber consumption, are missing. The second limit is the lack of a standardized questionnaire to assess the Quality of Life, such as the score DV-QOL[30]. However, we think that the VAS scale adequately overcomes this limit.

Conclusions

This is the first study assessing the efficacy of rifaximin in real-life setting, using well-defined SUDD criteria, and fully conducted by GPs. While confirming the efficacy and safety of this approach, this study also evidenced interesting differences when using different durations in the monthly cycle of rifaximin. Further prospective studies assessing this last specific target are warranted.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Contributorship Statements

Conception and design of the study: Antonio TURSI; Acquisition of data, or analysis and interpretation of data: Rudi DE BASTIANI, Guido SANNA, Luciano BERTOLUSSO, Giovanni CASELLA, Manuela DE POLO, Maria ZAMPARELLA, Carmelo COTTONE, Cesare TOSETTI, Maurizio MANCUSO, Enzo PIRROTTA, Lorenzo LANZAROTTO, Luigi NAPOLI, Marco DE BASTIANI, Giuseppe DISCLAFANI, Patrizia GAMBARO, Riccardo SCOGLIO, Alessandra BELVEDERE, Serena FASULO, Maurizio D'URSO, Edoardo BENEDETTO, Elisabetta BALDI, Federica MARCHESAN, Gennaro ABAGNALE, Leila TURNAVA, Emanuela SALOME', Fabio INGRAVALLE, Antonio TURSI; drafting the article or revising it critically for important intellectual content: Rudi DE BASTIANI, Fabio INGRAVALLE, Antonio TURSI; final approval of the version to be submitted: Rudi DE BASTIANI, Guido SANNA, Luciano BERTOLUSSO, Giovanni CASELLA, Manuela DE POLO, Maria ZAMPARELLA, Carmelo COTTONE, Cesare TOSETTI, Maurizio MANCUSO, Enzo PIRROTTA, Lorenzo LANZAROTTO, Luigi NAPOLI, Marco DE BASTIANI, Giuseppe DISCLAFANI, Patrizia GAMBARO, Riccardo SCOGLIO, Alessandra BELVEDERE, Serena FASULO, Maurizio D'URSO, Edoardo BENEDETTO, Elisabetta BALDI, Federica MARCHESAN, Gennaro ABAGNALE, Leila TURNAVA, Emanuela SALOME', Fabio INGRAVALLE, Antonio TURSI.

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