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Non-interventional study evaluating efficacy and tolerability of rifaximin for treatment of uncomplicated diverticular disease

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Summary Patients with symptomatic uncomplicated diverticular disease represent a spectrum of patients who report recurrent abdominal symptoms, however are lacking substantial colonic inflammation in contrast to patients with acute diverticulitis. This non-interventional study investigated the efficacy and tolerability of rifaximin, a broad-spectrum poorly absorbable antibiotic, in cyclic treatment of these patients. Adult patients with uncomplicated diverticular disease in care of physicians in private practice intended to be treated with rifaximin were included. Patients with acute diverticulitis and symptoms suggestive of more severe intestinal inflammation were excluded. Data of 1,003 patients treated in cycles of 7–10 days per month over a period of 3 months were evaluated. In total, 75 % of patients had more than three episodes of symptoms in the last year before inclusion in the study. However, two-third of patients did not receive any treatment before. Over the 3-month treatment period with rifaximin, all assessed symptoms of diverticular disease, such as abdominal pain, diarrhoea and flatulence, improved significantly. There was an overall good compliance to the scheme of cyclic drug administration of rifaximin. During the study, 24 adverse events in 20 patients were recorded, of which 6 adverse events showed a causal relationship to the use of rifaximin (0.6 %). We conclude that cyclic rifaximin shows good clinical efficacy and tolerability in patients with symptomatic uncomplicated diverticular disease treated in a routine private practice outpatient setting.

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Keywords Antibiotics · Abdominal symptoms · Uncomplicated diverticular disease · Rifaximin · Non-interventional study

Nicht-interventionelle Studie zur Evaluierung der Wirksamkeit und Verträglichkeit von Rifaximin in der Therapie der unkomplizierten Divertikelerkrankung

Zusammenfassung Patienten mit symptomatischer unkomplizierter Divertikelerkrankung repräsentieren eine Krankheitsentität der Divertikelerkrankung mit chronisch rekurrierenden Symptomen, jedoch dem Fehlen einer wesentlichen Entzündung im Kolon im Unterschied zu Patienten mit akuter Divertikulitis. Die vorliegende nicht-interventionelle Studie untersuchte die Wirksamkeit und Verträglichkeit von Rifaximin, einem nicht-absorbierbaren Breitbandantibiotikum, in der zyklischen Anwendung bei Patienten mit symptomatischer unkomplizierter Divertikelerkrankung. 193 niedergelassene Internisten, Chirurgen sowie Allgemeinmediziner in ganz Österreich haben an der Studie teilgenommen. Von den teilnehmenden Ärzten wurden 1003 Patienten mit symptomatischer Divertikelerkrankung eingeschlossen, welche in Zyklen von 7–10 Tagen pro Monat mit Rifaximin behandelt wurden. Der Beobachtungszeitraum betrug 3 Monate. Patienten mit Zeichen einer schweren Entzündung oder Symptomen vereinbar mit akuter Divertikulitis, waren von der Studie ausgeschlossen. Über den Behandlungszeitraum von 3 Monaten kam es zu einer signifikanten Reduktion aller erhobenen Symptome der Divertikelerkrankung, wie abdominale Schmerzen, Diarrhoe und Flatulenz. Insgesamt wurden 24 unerwünschte Wirkungen bei 20 Patienten detektiert. Davon wurden 6 unerwünschte Wirkungen in einem kausalen Zusammenhang zur Studienmedikation gesehen (0,6 %). Zusammenfassend konnte in dieser nicht-inter-

ventionellen Studie eine gute Effektivität und Toleranz von Rifaximin in der Behandlung der symptomatischen unkomplizierten Divertikelerkrankung bei Patienten im niedergelassenen Bereich festgestellt werden.

Schlüsselwörter Antibiotika · Abdominale Symptome · Unkomplizierte Divertikelerkrankung · Rifaximin · Nicht-Interventionelle Studie

Introduction

Diverticular disease is one of the most common gastrointestinal diseases in the Western world [1]. The clinical spectrum of the disease spans from the asymptomatic diverticulosis to acute inflammation termed as diverticulitis. Complications of the latter can be sometimes life threatening [2, 3]. The prevalence of diverticulosis, meaning the existence of multiple inflammation-free diverticula, increases with age. Although this disease is rather unusual in patients younger than 40 years, it occurs in approximately one-third of subjects older than 45 and in two-third of subjects older than 85 years [4, 5]. It is suggested that this increase in prevalence may be due to factors such as a low-fibre diet alterations in gastrointestinal motility as well as other environmental factors of a 'Western' life style [5, 6]. Only approximately 20 % of the carriers of diverticula will show any symptoms of this disease during their life [3–5].

The nomenclature of symptomatic diverticular disease causes certain confusion. Many classifications cover only acute diverticulitis and recurrent diverticulitis contrary to asymptomatic diverticulosis [1, 3, 7]. However, there is a considerable number of patients with diverticular disease having chronic symptoms such as lower abdominal pain, flatulence, bloating, tenesmus, diarrhoea and abdominal tenderness without marked diverticular inflammation [4, 7]. These symptomatic patients, termed as having 'chronic symptomatic uncomplicated diverticular disease' in this article (Fig. 1), are often referred to as having symptomatic diverticular disease or uncomplicated diverticulitis in the literature [4, 8–10]. This form of diverticular disease includes patients with persistent symptoms after an episode of acute diverticulitis and patients that suffer from mild mucosal inflammation around the diverticular openings as evident on colonoscopy, termed as segmental colitis associated to diverticulosis (SCAD) [11, 12]. There seems to be at least some overlap and transition of patients with 'chronic symptomatic uncomplicated diverticular disease' and SCAD to the group of patients with acute diverticulitis.

The treatment of diverticular disease aims to relieve occurring symptoms and to prevent diverticulitis and its major complications [13]. As treatment for these patients' fibre supplementation, amino-salicylates, probiotics and antispasmodics are used, with variable success [6, 8, 14]. A novel therapeutic concept is the periodic administration of non-absorbable antibiotics, such as rifaximin, with or without addition to a high-fibre diet. This form of therapy proved to be successful in controlled studies showing a significant improvement of symptoms and a tendency in the avoidance of complications [4, 9, 14–16]. Most of these studies used a cyclic regimen of rifaximin administration, applying rifaximin for 1 week followed by a treatment break of 3 weeks, which is again followed by subsequent cycles of rifaximin. This cyclic form of drug administration is rather uncommon in medical practice, and patient compliance in routine practice is questionable, as rifaximin application in other indications like in hepatic encephalopathy is not cyclic [17].

In this non-interventional study (NIS), we therefore studied patients with symptomatic uncomplicated diverticular disease intended to be treated with cyclic administration of rifaximin in an outpatient setting. We reviewed patient compliance, efficacy and tolerability of this treatment approach in this indication.

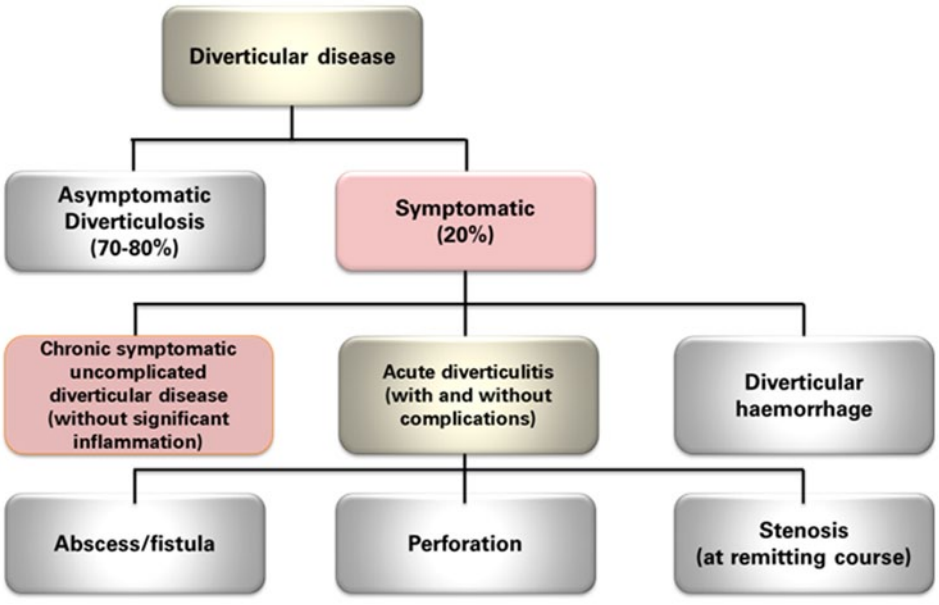

Fig. 1 Nomenclature of diverticular disease. Patients included in this non-interventional study included only patients with chronic symptomatic uncomplicated diverticular disease

Patients, materials and methods

Between June and December 2011, internists, surgeons as well as general practitioners across Austria were contacted and invited to participate in this NIS. Of 347 physicians, who decided to take part in the study, 193 (55.6 %) actively participated and included patients. Professional background of physicians collecting data was as follows: internal medicine (11 %), surgery (4 %) and general medicine (85 %).

This NIS included male and female patients older than 18 years, suffering from uncomplicated symptomatic diverticular disease and who were intended to be treated with cyclic administration of rifaximin in an outpatient setting. Patients with suspected diverticulitis as well as severe colitis and infectious diarrhoea with fever or blood-stained stools were excluded from the study. Pregnant and breastfeeding patients and patients with hypersensitivity to the active ingredient were also excluded.

A total of 1,054 patients (55.4 % female and 44.6 % male) were recruited; 51 patients were excluded from data analysis because of incomplete data (29 patients) or diagnosis of acute diverticulitis (22 patients), which was contrary to inclusion criteria. In total, data of 1,003 patients were included for analysis.

The planned study period per patient was 3 months. Patients underwent four clinical visits (baseline and three follow-up visits with an interval of 1 month). According to the actual Austrian regulation for NISs, the study protocol was approved by the ethics committee of the Medical University Graz. Informed consent was obtained from the patients before inclusion in the study. This NIS was conducted according to the Austrian regulations and the actual version of Declaration of Helsinki.

Patients included in the study were treated by cyclic administration of rifaximin (Colidimin®, Gebro Pharma Ltd., Fieberbrunn, Austria). Cyclic administration was defined as rifaximin treatment for a period of 7–10 days, followed by a 3-week treatment break.

There were two possible modes of data collection: an electronic Case Report Form (eCRF; data of 724 patients reported by 123 physicians) and data collection by paper questionnaires (279 patients reported by 70 physicians). The following information was collected: concomitant diseases and therapies, condition of health, any possible adverse events, dietary and physical recommendations, dosage, duration of treatment, symptoms, condition of health and treatment compliance of patients at all visits. At baseline visit, information regarding demographics, history of diverticular disease, evaluation of symptoms, concomitant diseases and therapies, condition of health and dietary and physical recommendations was collected. At final visit, information regarding cycles of rifaximin treatment, continuation of treatment and condition of health was collected; efficacy and tolerability were assessed using a 5-point rating scale (excellent, very good, good, moderate and poor), and compliance by a 4-point rating scale (very good, good, satisfactory and not sufficient). At each visit, the patients were asked about their following symptoms: 'lower abdominal pain', 'flatulence', 'tenesmus', 'diarrhoea' and 'abdominal tenderness or sensitivity to touch', and rated using a severity scale of 0–3 points (0 = no symptoms, 1 = mild: symptoms are tolerable; 2 = medium: symptoms impair normal activities; and 3 = severe: symptoms restrict normal activities). Total symptom score was calculated by summarising the individual symptoms at each time point (maximal value: 15).

The reported adverse events were coded according to MedDRA SOCs (version 14.1 and 15.0) by the pharmacovigilance manager at Gebro Pharma GmbH. Statistical analyses were done by using Wilcoxon matched pairs test (total symptom score) and Bowker's test for symmetry (assessment of individual symptoms) to evaluate statistical significance of changes in assessment of symptoms at baseline and final visit. All other parameters were evaluated with descriptive statistical methods. The results were specified as quantity and percentage or as mean ± standard deviation (MW ± SD).

Results

Baseline characteristics

Demographic data of patients included (n = 1,003), with history regarding to diverticular disease and previous therapy, are reported in Table 1. Most patients reported multiple episodes of symptoms from diverticular disease within the previous year at baseline visit. Diverticular disease was present for at least 2 years in two-third of patients (Table 1). A pre-treatment of any kind for diverticular disease was reported in only one-third of patients (34 %).

At baseline visit, accompanying therapies and concomitant diseases were reported in 32 % of patients. At final visit, no change in concomitant medication or diseases was present in 94 % of the patients.

At beginning of the study, diet interventions and exercise recommendations were indicated in 69 % of all patients. As measures were specified, they included as follows: 35 % high-fibre diet, 33 % increased intake of fluids, 30 % exercise and 2 % other treatments (multiple choices possible). At final visit, 81 % of the patients stated that they did not change their diet scheme or exercises during the study.

Reported treatment regimen for rifaximin

In 96 % of patients, a dosage of 800 mg of rifaximin per day (400 mg bid) was prescribed by the treating physician. Only in 4 % of patients, a different dosage or no information of dosage was reported. At study end, still 84 % of the patients received a dosage of 800 mg/day. A total of 90 % of the patients started rifaximin therapy with the recommended treatment duration of 7–10 days. At study end, 80 % of the patients still followed this treatment regime.

Table 1 Patients' characteristics at baseline. Data represent number of patients (percentage of patients in parenthesis) or means ± SD for age, height, weight and BMI. Multiple choices are possible for pre-treatment

Age (years)	60 ± 15 (range 18–95)
Sex	
Female	556 (55.4 %)
Male	447 (44.6 %)
Height (cm)	170 ± 8 (range 150–198)
Weight (kg)	76 ± 14 (range 48–141)
BMI (kg/m²)	26.4 ± 4.0 (range 17–59)
Initial diagnosis of diverticular disease	
1 year ago	308 (31 %)
2–4 years ago	320 (32 %)
5 or more years ago	340 (34 %)
Not specified	35 (3 %)
Frequency of symptoms in the last year[a]	
0	25 (3 %)
1–2	188 (19 %)
>3	756 (75 %)
N.a.	34 (3 %)
Previous episodes of diverticulitis	
Yes	235 (23 %)
No	758 (76 %)
N.a.	10 (1 %)
No. of previous diverticulitis episodes	
1–2	116 (49 %)
>3	62 (26 %)
N.a.	57 (25 %)
Pre-treatment of diverticular disease	
No	663 (66 %)
Yes	338 (34 %)
Change of diet	210 (27 %)
Probiotics	164 (21 %)
Proton-pump-inhibitors (PPIs)	127 (16 %)
Systemic antibiotics	102 (13 %)
Rifaximin	95 (12 %)
5-aminosalicylic acid (5-ASA)	51 (7 %)
Others	34 (4 %)

BMI body mass index, *N.a.* not applicable
[a]Episode of symptoms is defined as symptoms suggestive for diverticular disease lasting for ≥3 days

Approximately two-third of patients (63 %) were treated within three cycles, 9 % of patients received one and 11 % received two treatment cycles. A total of 30 % of patients resumed the therapy with rifaximin after the end of the study.

Treatment compliance was reported as very good and good in 94 % of the patients at the first follow-up, 91 % at the second follow-up and 90 % at the final visit.

Symptoms

A statistically significant symptom reduction was evident for all symptom parameters evaluated (Table 2). At the end of follow-up ($n=943$), >90 % of the patients reported only mild or no symptoms except for flatulence (88 %). The total symptom scores at baseline and follow-up are shown in Fig. 2. Total symptom scores decreased from 7.2 ± 2.7 at baseline continuously over the 3-month observation period to 1.5 ± 1.6 at the final visit. Wilcoxon matched pairs test ($p<0.001$) revealed a significant reduction of sum of symptom scores form baseline to final visit. There was also a decrease in the symptom score from baseline to the follow-up visits after 1 and 2 months; however, this was not statistically significant.

Efficacy and tolerability of therapy

After the treatment period of 3 months, the efficacy and tolerability of rifaximin were evaluated by the treating physician. The assessment of efficacy was evaluated as excellent in 44 % and very good in 37 % of the cases. Tolerability was assessed in 50 % as excellent and in 34 % as very good.

During the study, 24 adverse events in 20 of 1,003 patients were recorded, of which 6 adverse events showed a causal relationship to the use of rifaximin (0.6 % adverse drug reaction): 5 gastrointestinal adverse events (flatulence/1 patient; abdominal pain/1 patient; nausea/3 patients) and 1 skin and subcutaneous disease (rash/1 patient).

Discussion

The aim of this NIS was to investigate the use of cyclic rifaximin therapy in patients with uncomplicated diverticular disease in an outpatient setting in Austria. NISs help acquiring, deepening and broadening the knowledge for administration of a medication in the routine usage.

Cyclic administration of drugs such as the use of rifaximin in clinical studies for diverticular disease (7–10 days of rifaximin followed by 3 weeks of pausing the drug, followed by additional similar cycles) is rather uncommon. Therefore, it was important to investigate whether this scheme of drug therapy is feasible in routine clinical practice.

As most participating physicians were no specialists for diverticular disease, their adherence to prescription of cyclic form of drug administration was good. At the end of the study period, in >80 % of patients, the correct dose and duration of administration as well as more than two cycles of rifaximin were prescribed. Also the compliance of patients with the prescribed rifaximin therapy was reported as good and very good in approximately 90 % of patients at all study visits.

Table 2 Assessment of the symptoms at the start (n = 1,003) and end of the study (n = 943): Bowker's test for symmetry showed p < 0.001 for all assessed symptoms (baseline vs. final visit)

Symptoms	Lower abdominal pain		Flatulence		Tenesmus		Diarrhoea		Abdominal tenderness or sensitivity to touch	
	$p<0.001$		$p<0.001$		$p<0.001$		$p<0.001$		$p<0.001$	
	Baseline visit (%)	Final visit (%)	Baseline visit (%)	Final visit (%)	Baseline visit (%)	Final visit (%)	Baseline visit (%)	Final visit (%)	Baseline visit (%)	Final visit (%)
No symptoms	46 (4.6)	653 (69.2)	47 (4.7)	389 (41.3)	186 (18.5)	736 (78.0)	277 (27.6)	722 (76.6)	85 (8.5)	654 (69.4)
Mild	370 (36.9)	213 (22.6)	309 (30.8)	447 (47.4)	418 (41.7)	133 (14.1)	395 (39.4)	151 (16.0)	479 (47.8)	212 (22.5)
Medium	518 (51.6)	15 (1.6)	484 (48.3)	43 (4.6)	346 (34.5)	12 (1.3)	259 (25.8)	6 (0.6)	360 (35.9)	10 (1.1)
Severe	67 (6.7)	0 (0.0)	161 (16.1)	2 (0.2)	51 (5.1)	0 (0.0)	70 (7.0)	2 (0.2)	77 (7.7)	5 (0.5)
Not applicable	2 (0.2)	62 (6.6)	2 (0.2)	62 (6.6)	2 (0.2)	62 (6.6)	2 (0.2)	62 (6.6)	2 (0.2)	62 (6.6)

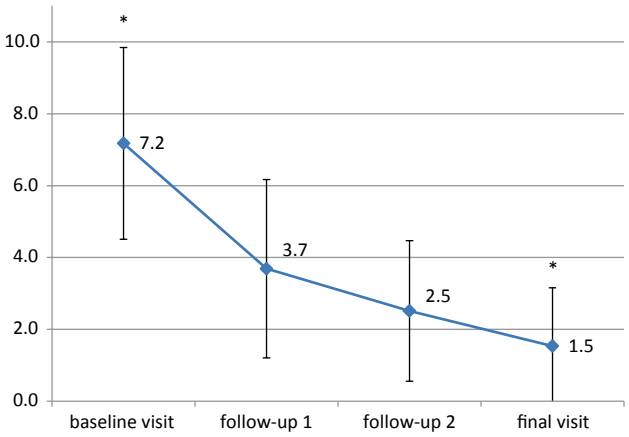

Fig. 2 Total symptom score (sum of all symptom parameters) at baseline and during follow-up visits on cyclic rifaximin therapy. Values are reported as means ± SD. * Baseline visit versus final visit, $p<0.001$

In this NIS, cyclic rifaximin therapy was associated with a marked reduction in all assessed symptoms of uncomplicated diverticular disease. Beside rifaximin therapy, in two-third of patients, additional dietary interventions for diverticular disease were recommended. These data have to be interpreted with caution because of the based study design: lacking a control group and blinding of patients and physicians as well as symptom assessment by the treating physician. However, the observed improvement of symptoms was comparable with controlled studies using cyclic rifaximin administration for diverticular disease [4, 15, 18]. We want to draw attention to the fact that the majority of our patients were frequently symptomatic over a time period of at least 2 years without any therapy before inclusion. Previously, treatment options for these patients were very limited. This study showed that cyclic rifaximin administration is an effective treatment option in routine clinical practice for these patients.

Because of the large number of patients ($n = 1{,}003$), this study provides information for occasional and rare side effects of rifaximin. The rate of adverse events as described in literature is less than 1 % [19]. During this NIS, a very low rate of 24 adverse events in 20 patients occurred. Of these, only 6 showed a causal relationship with the intake of rifaximin (0.6 % adverse drug reactions). Most of them were gastrointestinal symptoms (flatulence, abdominal pain and nausea) and one skin rash. Although other mild side effects might be underreported due to the NIS design, we assume that it is unlikely that additional severe adverse events were not reported. More than 80 % of participating physicians considered the tolerability of rifaximin as excellent or very good.

There is some confusion about the nomenclature of symptomatic diverticular disease [1, 7]. Many classifications as, for example, the widely used classification of Hansen and Stock in the German-speaking countries do not separate a symptomatic form of diverticular disease without marked inflammation from acute diverticulitis with phlegmon of the whole intestinal wall and surrounding mesenteric tissue or abscess formation [20]. In the English literature, chronic symptomatic diverticular disease is referred to as uncomplicated diverticulosis or uncomplicated diverticular disease. However, the differentiation from acute diverticulitis is limited. Chronic symptomatic diverticular disease is often preceded by an episode of acute diverticulitis or is associated with some mild mucosal inflammation around the diverticular openings [12].

The disease spectrum of chronic symptomatic diverticular disease without major inflammation is, therefore, not very well known in the medical community in private practice. As rifaximin is poorly absorbed by the intestine, this antibiotic is not suitable for more severe forms of diverticular inflammation. In our opinion, a novel classification of diverticular disease with specific aims reflecting on the spectrum of patients with chronic symptoms without significant inflammation is helpful for clinical practice. A suggested example that might better represent the whole spectrum of diverticular disease is shown in Fig. 1.

Despite the limitations of a NIS as mentioned above, this study confirms the previously reported literature data for cyclic administration of rifaximin for chronic symptomatic diverticular disease, in terms of an excellent safety profile and the substantial improvement of symptoms under daily practice conditions in a large cohort of patients. The scheme of cyclic administration

of rifaximin is furthermore practicable for patients and physicians in private practice.

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Conflict of interest
Data capture and analysis was supported financially by Gebro Pharma GmbH, Fieberbrunn, Austria. Sylvia Stallinger and Norbert Eller are employed by Gebro Pharma. Christoph Högenauer has received gratuities from Gebro Pharma for scientific lectures and consulting.

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