

The influence of rifaximin on diverticulitis rate and quality of life in patients with diverticulosis

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ABSTRACT:

Diverticulosis, its associated symptoms and complications are one of the most common pathologies of the gastrointestinal tract in more economically developed countries. Presence of diverticuli and their clinical consequences can be divided into four categories: 1) diverticulosis, i.e. an asymptomatic presence of diverticuli that are usually found by accident 2) symptomatic uncomplicated diverticulosis 3) diverticulitis (acute uncomplicated diverticulitis) 4) complications of diverticulitis (conditions requiring hospital stay).

The aim of this study was to retrospectively analyze the efficacy of rifaximin in preventing diverticulitis in patients visiting proctology clinics. The diagnostic criterium for diverticulosis was confirmation by colonoscopy, barium enema or CT colography (virtual colonoscopy) as well as history of at least one documented episode of diverticulitis. History of diverticulosis was evaluated based on medical records, clinical symptoms, elevated level of CRP (>5.0) and/or diagnostic imaging (ultrasound, CT). After setting strict exclusion criteria, 248 patients were qualified for the study out of 686, and they were later divided into two groups: control group (group I – 145 patients) and studied group (group II – 103 patients receiving rifaximin prophylaxis). Diverticulitis rate was comparable in both groups over a period of 6 months before study ($p = 0.1306$) and 6 months of treatment ($p = 0.3044$). Between the 6th and 12th month of treatment, a significantly lower rate of diverticulitis was noted in the group receiving rifaximin compared to control group ($p < 0.0001$). Patients receiving rifaximin reported higher quality of life (which was assessed using the VAS scale) compared to control group after 12 months. The results confirmed the efficacy of rifaximin in prevention of diverticulitis, even in the scheme of repeated courses every 3 months. Not only did application of rifaximin lower the rate of diverticulitis and its complications in patients after an episode of diverticulitis, but also it improved the patients' quality of life. It seems that diverticulitis prophylaxis based on rifaximin can be economically efficient, however, it requires further research.

KEYWORDS:

diverticulitis, diverticulosis, rifaximin, prevention

INTRODUCTION

Diverticulosis, its associated symptoms and complications are one of the most common pathologies of the gastrointestinal tract in more economically developed countries. Diverticulosis has become a lifestyle disease of the 21st century. According to current

epidemiological data, diverticuli of the left part of the colon are observed in more than 20% of patients undergoing colonoscopy [1]. In majority of them, the diverticuli are asymptomatic, however, 20% of patients may develop symptoms, i.e. diverticulosis. [2] Presence of diverticuli and their clinical consequences can be divided into four major clinical presentations. [3,4,5]

1. diverticulosis, i.e. presence of diverticuli that are asymptomatic and usually found by accident. Diagnosis of diverticuli with no accompanying symptoms does not require any intervention, and managing usually includes nutrition counselling, increased intake of soluble fiber, weight control and increased physical activity.

2. symptomatic uncomplicated diverticulosis – it is the most common clinical problem associated with diverticuli. It is a chronic condition with recurring symptoms. They involve stomach pain, irregular stools, bloating [4]. Inflammatory marker levels are not elevated, and there are no abnormalities on imaging [6], which makes this condition distinct from diverticulitis.

The basis of uncomplicated symptomatic diverticulosis is changes to enteral microflora [7], and hence it is recommended, in addition to diet rich in soluble fiber, to introduce cyclic therapy with a non-absorbable (acting locally) antibiotic: rifaximin at the dose of 400mg twice a day for 7 days a month, repeated every month for a year. Only such a regime reaches all therapeutic goals: limits the previously mentioned symptoms, lowers recurrence and complication rates and improves quality of life [5].

Mesalazine is not recommended, similar to systematically acting antibiotics [5,8]. There are studies which prove the positive effect of probiotics, however, due to large diversity of patients and antibiotics used, there are no unequivocal meta-analyses and recommendations for their use [9].

3. diverticulitis (acute uncomplicated diverticulitis) associated with systemic inflammatory response, which clinically presents as: fever, chills, abnormal laboratory results (increased ESR, CRP, calprotectin) and diagnostic imaging (ultrasound, computed tomography – as the ‘gold standard’), which present thickening of intestinal wall and inflammatory infiltrate in the surrounding adipose tissue. Clinical course of acute diverticulitis can vary ranging from mild cases requiring out-patient care to severe and/or complications requiring hospital admission [4]. Diverticulitis requiring hospital stay is observed in 15-20% of patients with diverticulosis [10,11].

Mild and moderate diverticulitis can be treated in an out-patient setting, and therapeutic recommendations include liquid and easily digested diet, proper hydration, analgesics, antipyretics and antispasmodics. No significant differences were observed between patients receiving and not receiving antibiotics, and hence system antibiotic therapy should be reserved for patients in severe condition admitted to the hospital [4,5], or for patients from high-risk groups, e.g. with immunodeficiency (HIV, AIDS, on immunosuppressant drugs, steroids),

with co-morbidities (e.g. chronic kidney disease, chronic obstructive pulmonary disease) or elderly patients [20].

According to current recommendations published in Colorectal Disease in 2014, as well as recommendations by the Polish Society of Surgeons and Polish Society of Gastroenterology from 2015 regarding diagnosis and treatment of diverticulosis, prevention of recurrence should be introduced in all patients after an episode of acute diverticulitis. The only medication with efficacy confirmed by prospective studies with randomization in preventing recurrent diverticulitis and complications is rifaximin used repeatedly every month [4,5]. For prophylaxis of diverticulitis, it is recommended to use fiber, although only soluble fiber. [4] Only soluble fiber undergoes fermentation to SCFA (short-chain fatty acids), including butyric acid, which ‘nourishes’ colonocytes, provides fiber-rich diet and nourishes colonocytes at the same time. As a prophylactic method for diverticulitis, apart from dietary recommendations and increased physical activity, use of probiotics is considered, although their efficacy has not been proven and there are no unequivocal recommendations, similar to their therapeutic use. [9] There are also single reports of efficacy of microencapsulated sodium butyrate in preventing diverticulitis. [12] However, the efficacy of prophylactic use of mesalazine has not been proven and according to current recommendations, the use of mesalazine is not recommended [4].

4) complications of diverticulitis requiring hospital admission. The risk of such complications amounts to 3.5 to 4.0 / 100,000 / year [13]. Although several scales have been developed for clinical assessment and evaluation of complications, the most popular and commonly used one is diverticulitis complication scale proposed by Hinchey et al. in 1978 [14]. The classic division of diverticulitis complications according to Hinchey includes 4 degrees [14]:

- 1) para-colic abscess (inflammation with localized perforation)
- 2) distant abscess (pelvis, retroperitoneal space)
- 3) diffuse (generalized) purulent peritonitis
- 4) fecal peritonitis

In the case of 1st and 2nd degree, minimally invasive strategy is recommended, limited to diet, percutaneous drainage of abscess under ultrasound guidance (if there is a safe access), and/or systemic antibiotics. Surgical intervention is indicated when this strategy is ineffective. 3rd and 4th degrees are indications for peritoneal cavity inspection, however, its mode (laparotomy vs. laparoscopy) is a subject to discussion [15].

Considering that diverticulitis and especially its complications lower the quality of life and sometimes requires admission to the hospital or surgical intervention, prophylaxis is important.

The aim of this study was to analyze the efficacy of rifaximin in prevention of diverticulitis in patients visiting proctology clinics.

MATERIALS AND METHODS

The study was retrospective. For the assessment, patients were qualified who had been diagnosed with diverticulosis and treated at the outpatient proctology clinics of the authors' affiliated centers in the years 2011-2015. The study was conducted based on the permission by the Bioethics Committee (Poznań University of Medical Sciences). The diagnostic criteria for diverticulosis were confirmation by colonoscopy, barium enema or CT colography (virtual colonoscopy) as well as history of at least one documented episode of diverticulosis. History of diverticulosis was evaluated based on medical records, clinical symptoms, elevated CRP (>5.0) and/or diagnostic imaging (ultrasound, CT). A total of 686 patients who met those criteria were treated at the clinics. The next stage of qualification was to exclude previous gastrointestinal surgeries, abdominal tumors, other neoplasms with chemotherapy and/or radiotherapy in the past 5 years, inflammatory bowel disease, immunosuppressive therapy, psychiatric disorders. Applying those criteria, 453 were qualified for further study. For the final analysis of medical records, the following patients were included who:

- had had at least 3 visits over 12 months at the six-month intervals (± 2 months)
- there was information regarding location of diverticuli in their medical documentation – 1) limited to the sigmoid 2) in other location in colon with or without their presence in the sigmoid
- after each visit, they gave unambiguous information regarding their quality of life expressed on the VAS scale (visual analogue scale) ranging 0-10, where 0 denotes the worst possible while 10 – the best possible quality of life,
- had not been receiving rifaximin (group I – control) or they used it according to the regime 2x400mg for 7 days that was repeated at least every 3 months (group II)
- information regarding history of diverticulitis and its complications were unequivocally formulated in the medical documentation, including criteria of diverticulitis diagnosis, presence of clinical symptoms, elevated CRP (>5.0) and/or results of diagnostic images (ultrasound, CT)
- possessed documents verifying their hospital stay; as a hospital stay, we assumed admission to the hospital (every admission to the surgical ward) and admission to the Emergency Department for more than 12 hours.

All the mentioned criteria were finally met by 145 patients from control group (group I) and 103 patients receiving rifaximin prophylactically (group II).

STATISTICAL ANALYSIS

For comparison of quality of life in patients with diverticulitis, we used the Friedman test (non-parametric test for more than 3 groups and related observations). For comparison of changes in diverticulitis rate between patients receiving and not receiving rifaximin at three points of time (at 6-month intervals), we used the repeated measures logistic regression test, which allows to include related parameters of the same patient at three points time due to implementation of changing effects.

RESULTS

The study included 248 patients with diverticulitis: group II (n=103) consisted of patients who received rifaximin prophylactically and group I (n=145) consisting of patients who did not receive rifaximin and they served as control group.

Table 1 shows characteristics of each group.

Diverticulitis rate was similar in both groups over 6 months prior to the study ($p=0.1306$) and during 6 months of treatment ($p=0.3044$). Between the 6th and 12th month of treatment, significantly lower rate of diverticulitis was observed in patients receiving rifaximin compared to control group ($p<0.0001$). The analysis results are shown in Table 2.

Relationship between the studied period (between 6th and 12th month) and rifaximin use was statistically significant ($p=0.0001$). Patients receiving rifaximin more than 6 months presented statistically less episodes of diverticulitis (regardless where it was treated – at the outpatient clinic or the hospital) than a representative control group receiving no rifaximin prophylaxis (Fig.1). The same relationship was observed in groups divided with respect to treatment setting (out-patient or hospital).

Patients who received rifaximin reported significantly higher quality of life (assessed on VAS scale) than in control group after 12 months of rifaximin therapy. It should be noted that initial quality of life was similar in both groups and although in control group there was no significant difference in quality of life ($p=0.783$), the difference was gradually increasing in study group ($p<0.0001$). The comparison of quality of life of patients is shown in Fig.3.

DISCUSSION:

Diverticulosis is a huge health problem but also an economic problem as well, considering all clinical manifestations. Its pre-

valence is gradually increasing in the more economically developed countries, which is mainly due to increasing life expectancy and processed food consumption. In the US, diverticulosis is diagnosed in about 70% of patients in their 80s, and 300,000 patients are admitted to the hospital each year, every stay lasting for 5 days on average. It generates costs as high as 2.4 trillion USD per year. [2] Epidemiological data from both Europe and the US indicate increasing number of hospital admissions due to diverticulosis over decades [16]. Diverticulosis may, however, develop in much younger individuals and, according to the authors' observations, severe complication of diverticulosis, i.e. vesicoenteric or enterovaginal fistulae, are often found in patients as young as 30 years old.

Complications of diverticulosis, especially 3rd and 4th degree according to Hinchey classification, are still a common indication for laparotomy and Hartmann's operation. For many patients, this surgical treatment actually means formation of a permanent stoma, because restoration of intestinal continuity may not be technically possible or the patient's general condition disqualifies him from further planned procedures. It is worth mentioning that in the authors' opinion, surgeons should aim for primary anastomosis and possible formation of a decompressive colostomy. Its elimination and restoration of intestinal continuity is definitely easier and associated with lower risk of perioperative complications than reconstructive procedures requiring dissection of the distal end of the large intestine, which is often short and inflamed.

It should be remembered that surgical intervention itself in the context of diverticulosis is associated with high risk of complications (ca. 40%) and morbidity (ca. 10%) [17,18]. A much less invasive strategy is laparoscopic peritoneal lavage with following drainage and systemic broad-spectrum antibiotics (targeted after obtaining cultures). It should be emphasized that there are no unequivocal recommendations for this method and the group of patients in whom it can be applied is limited [15,19]. Necessity for surgical intervention or hospital admission are not the only problems met by people suffering from diverticulosis. Recurrent diverticulitis, even when uncomplicated, certainly causes huge discomfort to patients, who are forced to limit their normal daily activity, and negatively influences their quality of life. Those patient are often stressed and fear the next episode of diverticulitis. They also fear potential consequences of inflammation, particularly surgical interventions leading to stoma formation. The risk of recurrence and complications is increased in patients with comorbidities (chronic kidney disease, chronic obstructive pulmonary disease) as well as receiving immunosuppressant therapy, including steroids. [20] Considering the risk of recurrence of symptoms and associated clinical consequences, more attention is currently given to prevention of diverticulitis recur-

rence and its complications. One possible prophylactic method is surgical resection of the part of colon containing diverticuli. This method was relatively popular in Western Europe in 1990s, however, now it is no longer recommended. In the analysis on a large population of 87,461 patients with no immunological disorders with history of at least one episode of diverticulitis, 5,604 patients (6.4%) underwent segmental resection of colon. On the long-term consequence analysis, the group undergoing resection did not experience significant difference in everyday functioning and quality of life. [21] Moreover, the number of elective resection surgeries did not influence the rate of consecutive surgical interventions, percutaneous interventions or hospital admissions [22]. One important conclusion is that elective resection may potentially be effective only in selected groups of patients, however, currently there is very limited data to precisely define those groups. [21] In the light of lacking unambiguously confirmed efficacy of surgical prevention for diverticulitis, as well as all potential complications associated with surgery, non-invasive forms of prophylaxis are being searched for.

One of the easiest methods is certainly lifestyle modification, especially increased physical activity, cessation of smoking and diet rich in soluble fiber. Although those recommendation sound trivial, those are risk factors contributing to formation of diverticuli, development of diverticulitis, its complications and recurrences [23]. Another recommendation aiming to prevent potential complications and improve quality of life is avoiding constipation. On one hand, it is based on dietary recommendations, on the other hand, however, it includes laxatives, especially bulk-forming, lubricant and hyperosmotic agents. There are no unequivocal recommendation regarding their use, in clinical practice a great variety of individual reactions to them and therapeutic outcomes can be observed.

Pharmacological prophylaxis concepts are based on the assumption that one of the most probable mechanism responsible for inflammatory response in the intestines is a change to enteral microflora (dysbiosis). Chronic local inflammation, changed

Tab. 1. Characteristic of groups of patients included in the study: patients without diverticulitis prophylaxis (group I) and with prophylactic rifaximin (group II).

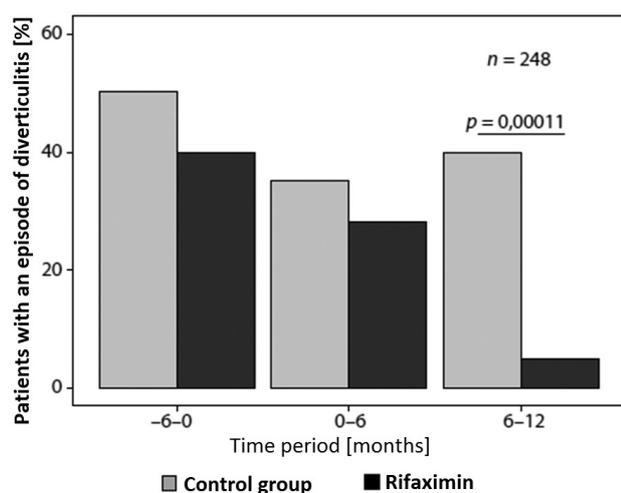
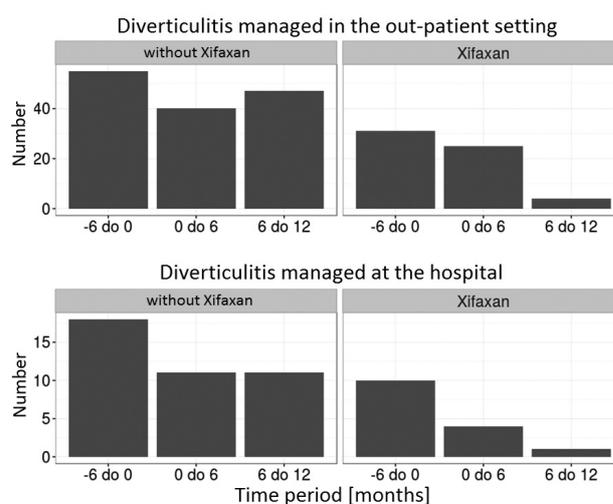
| | | CONTROL GROUP (GROUP I) | GROUP RECEIVING RIFAXIMIN PROPHYLACTICALLY (GROUP II) | P |
|---------------------|--------|----------------------------|--|--------|
| Demographics | | | | |
| Sex | Male | 68 (53,54%) | 59 (46,46%) | 0,083 |
| | Female | 77 (65,25%) | 41 (34,75%) | |
| Age | | 63,78 (+/- 8,04) | 64,85 (+/- 8,8) | 0,3272 |
| Duration of disease | | 6,68 (+/- 4,16) | 7,32 (+/- 4,58) | 0,2577 |

Tab. II. Assessment of diverticulitis rate, its complication and quality of life in patients without prophylaxis (group I) and receiving rifaximin prophylaxis (group II).

| | DURING LAST 6 MONTHS PRIOR TO INTRODUCTION OF RIFAXIMIN / ENROLLMENT IN THE STUDY | DURING FIRST 6 MONTHS AFTER INTRODUCING RIFAXIMIN / ENROLLMENT IN THE STUDY | DURING 6TH TO 12TH MONTH AFTER INTRODUCING RIFAXIMIN / ENROLLMENT IN THE STUDY |
|---|---|---|--|
| Group I (control) – number of reported episodes of diverticulitis treated in out-patient setting | 55/145 (38%) | 40/145 (28%) | 47/145 (32%) |
| Group II (rifaximin prophylaxis) – number of reported episodes of diverticulitis treated in out-patient setting | 31/103 (31%) | 25/103 (24%) | 4/103 (4%) |
| Group I (control) – number of reported episodes of diverticulitis with hospital admission (including ED) | 18/145 (12%) | 11/145 (8%) | 11/145 (8%) |
| Group II (rifaximin prophylaxis) – number of reported episodes of diverticulitis with hospital admission (including ED) | 10/103 (10%) | 4/103 (4%) | 1/103 (1%) |
| Group I (control) – number of reported episodes of diverticulitis requiring surgical intervention (all procedures) | 0 (chorzy operowani nie byli włączeni do badania) | 4/145 (3%) | 5/145 (4%) |
| Group II (rifaximin prophylaxis) – number of reported episodes of diverticulitis requiring surgical intervention (all procedures) | 0 (chorzy operowani nie byli włączeni do badania) | 2/103 (2%) | 0/103 (0%) |
| Group I (control) – quality of life assessed on VAS scale 0-10 (on average) | 5,4 | 5,4 | 5,5 |
| Group II (rifaximin prophylaxis) – quality of life assessed on VAS scale 0-10 (on average) | 5,6 | 6,3 | 7,2 |

ED – Emergency Department

VAS – visual analogue scale

**Fig. 1.** Patient diagnosed with and treated for diverticulitis at three time points – 6 months prior to study, 6 month after initiation of rifaximin and after 12 months of rifaximin prophylaxis – in patients with no prophylaxis (control group) and patients receiving rifaximin prophylaxis.**Fig. 2.** Diverticulitis rate with respect to treatment setting (out-patient or hospital) in patients with no prophylaxis (control group) and patients receiving rifaximin prophylaxis.

profile of intestinal mucous, excessive growth of bacteria, as well as increased permeability to bacteria caused by fecal stasis in diverticuli, they all lead to translocation of bacteria. The presence of bacteria in the surrounding adipose tissue leads to stimulation of inflammatory response, release of inflammatory mediators including adipokines and chemokines, and as a consequence triggering neural cascade (sensitization of afferent and efferent neurons), which results in smooth muscle overgrowth and increased visceral sensitivity, and hence triggering mechanisms causing clinical symptoms of diverticulosis, mainly pain.

In order to influence the above-mentioned processes and normalize bacterial flora, various prophylactic schemes based on probiotics have been proposed. Despite numerous studies and attempts to standardize their use, no unambiguous evidence confirming efficacy of probiotics in preventing diverticulitis and their complications has been found. [9] Similar to prebiotic trials, e.g. butyric acid [12], which showed efficacy in studies based on single centers and too small groups of patients in order to recommend it as standard prophylaxis. Among other methods influencing bacterial microflora and possibly associated with diverticulitis, fecal microbiota transplant should be considered, however, there are no data regarding the influence of stool transplant on diverticulosis. On one hand, normalization of intestinal microbiome can be a positive factor preventing diverticulitis, on the other hand, there are suggestions about potential induction of diverticulitis by changing bacterial flora [24].

The only method with a confirmed effectiveness in preventing diverticulitis and its complications is use of rifaximin, which not only eliminates pathogenic intestinal flora but also it prevents its excessive growth. Rifaximin restores eubiosis, i.e. balance of intestinal flora, and due to recently discovered and described other mechanisms of action (apart from bactericidal effect), it is referred to as an eubiotic [25]. Despite direct antibacterial effect, rifaximin can also modulate immune response of the host (anti-inflammatory effect) as well as intestinal microbial activity (e.g. metabolism, adhesion, virulence). The efficacy of prophylactic rifaximin has been confirmed in numerous studies [4,5,10,20]. The recommended standard of its use is strictly based on repeated courses (one course: 2x400mg for 7 days) every month for a year. In clinical practice, the intervals between courses are often prolonged, which is due to lack of understanding of the chronic character of the disease by the patient, non-compliance with recommendations, or subjective improvement which causes lack of motivation to obey prophylaxis rules. For this reason, education of the patient is so important in this chronic recurrent disease. In this study, patients received rifaximin every 3 months. Such dosing constituted a compromise between recommendations and clinical reality. The study suggests that even such prophylaxis can be beneficial. However, it is expected

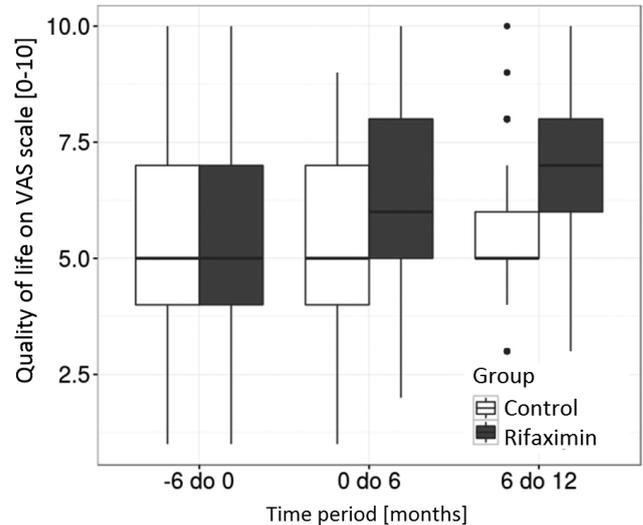


Fig. 3. Increase in quality of life in patients with diverticulosis after 12 months of prophylactic use of rifaximin.

that strictly applying recommendations reviewed by scientific societies could yield better results.

The efficacy of cyclic use of rifaximin in prevention of recurrent diverticulitis is a confirmation of a change to microflora, which is the chief causative agent for symptoms, diverticulosis and potential further complications. Mild inflammation of the intestines is only a reaction to quantity and composition of microflora. Therefore, attempts to solely suppress inflammatory response (symptomatic treatment) are ineffective – clinical trials show lack of effectiveness of prophylactic use of mesalazine [4], which is therefore not recommended as part of prevention of diverticulitis in patients with diverticulosis [26].

In our study, prophylactic use of rifaximin in courses repeated four times a year resulted in statistically significant decrease in diverticulitis rate in patients treated in both out-patient and hospital setting. The percentage of necessary surgical intervention in group with rifaximin was 0, while in group with no rifaximin it was 4% (5 interventions). It was too low to evaluate statistical significance. Our attention was drawn by the second studied parameter, i.e. quality of life in groups with or without rifaximin therapy. In the group of patients receiving rifaximin, the quality of life improved significantly over one year period of observation. It is probably due to decrease in number of diverticulosis episodes.

We observed that everyday ailments and discomfort caused by diverticuli are lower in patients receiving rifaximin, which eradicates bacteria, resolves inflammation and alleviates symptoms,

including pain. Quality of life in patients who did not receive rifaximin remained stable, which can be explained by the previously described mechanism of increased visceral sensitivity caused by chronic changes in intestinal microflora in patients with diverticulosis who do not receive rifaximin.

Analyzing the results of our study, it is worth noting that the rate of diverticulosis in patients who developed an episode of diverticulitis was high, and some patients even developed complications. It can be due to specific conditions under which proctology clinics operate. Those clinics are located at multispecialty hospitals, where patients with other comorbidities are hospitalized and hence they are at a higher risk of recurrence and complications. Furthermore, patients are usually referred to those clinics after an episode of diverticulitis, which also increases the risk of next episodes. Patients, in whom episodes are frequent, are certainly more determined to seek medical treatment, they are often referred as an urgent case requiring early visit. Another parameter that deviates from literature data is the number of patients requiring hospital admission due to diverticulitis or its complications. It is certainly high, which can be due to a number of reasons. One of them is the organization of health care in Poland, where patients with abdominal symptoms are sent to Emergency Departments, where they require laboratory tests, consultations and administration of basic drugs, and hence their stay usually lasts more than 12 hours.

Analyzing specific features of patients with diverticulosis visiting proctology clinics, deficits of health awareness in this group of patients should be kept in mind. They are often not informed well enough that their condition is chronic and recurrent, they also lack awareness about fiber-rich diet or cyclic use of drugs and/or supplements. Repeated and appropriate education and implementing planned prophylaxis would be sufficient and it would allow to avoid visits in a proctology clinic.

The study we presented certainly has limitations. The main limitations include: retrospective character of the study, relatively low number of patients, lack of uniform diagnostic criteria (it was verified based on medical documentation). Lack of data on associated comorbidities makes it harder to assess in which group of patients rifaximin prophylaxis is the most effective. Also, there is no analysis of long-term clinical results or an answer to the question how long the effect of rifaximin lasts regarding prevention of recurrent diverticulitis and its complications.

Despite those limitations, the study confirms the efficacy of rifaximin in preventing diverticulitis, even in the regime with repeated courses every 3 months. Use of rifaximin in patients after an episode of diverticulitis not only lowers diverticulitis and complication rates, but also it improves quality of life. It seems that prophylaxis based on rifaximin can be economically efficient, however, it requires further research.

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