Rifaximin in gut microbiota modification in acute pancreatitis: 15 years of retrospective clinical study

Jacek Tatur[1,A–F], Michał Lipiński[1,A–F], Marta Sznurkowska[1,2,A–D,F], Ewa Józefik[1,B,D,F], Grażyna Rydzewska[1,2,A,C,E,F]

[1] Department of Gastroenterology, Central Clinical Hospital of The Ministry of Interior and Administration, Warsaw, Poland
[2] Collegium Medicum, Jan Kochanowski University of Kielce, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

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Address for correspondence
Michał Lipiński
E-mail: michal7lipinski@yahoo.com

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Abstract

Background. Gut decontamination could have some benefits in preventing infectious complications in acute pancreatitis (AP).

Objectives. To investigate whether the administration of rifaximin could have an impact on the outcomes of AP.

Materials and methods. We conducted a retrospective study on 373 patients with a median age of 50 years that were admitted to our Department of Gastroenterology in the years 2001–2016 with a diagnosis of AP. Patients were subclassified according to the revised Atlanta criteria: mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP). Thereafter, all the patients were divided into 2 groups: in the 1st group (R0) with MSAP and SAP, patients did not receive rifaximin, and in the 2nd group (R1), in the cases of MSAP and SAP, rifaximin was administered to patients at a dose of 3×400 mg (for at least 5 days and up to 7 days). There was no other difference in the treatment between the groups. The median duration of hospital stay, the number of infectious complications and the mortality rate were recorded for both groups.

Results. A significant difference was observed between median durations of hospitalization between the groups with (R1) and without (R0) rifaximin treatment (14 days compared to 24 days, $p = 0.001$) and in the number of patients infected with pancreatic necrosis (7 compared to 1, $p = 0.0487$). However, there was no statistically significant difference between the R1 and R0 group in terms of mortality rate.

Conclusions. The results indicate that rifaximin seems to be a promising novel therapeutic option in MSAP and SAP.

Key words: rifaximin treatment, selective digestive decontamination, gut decontamination, acute pancreatitis therapy

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Background

The knowledge and understanding of the pathogenesis of acute pancreatitis (AP) has improved in recent years. However, severe types of AP still remain difficult to treat, and, when followed by pancreatic infection, are associated with a high mortality rate, as well as a long duration of hospital stay.[1–3] The clinical course of necrotizing pancreatitis is widely acknowledged to present itself with 2 peaks, which are characterized by the highest risk of death. These originate from the subdivision of AP into 2 phases (early and late). The early phase refers to the first 7 days after the outset of AP, and is associated with systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS), due to the release of inflammatory mediators.[4] The late phase occurs after a period of relative stability (usually a few weeks after the onset of AP), and is identified with a significantly higher mortality peak, as a consequence of the addition of septic complications, that being predominantly bacterial infections of pancreatic necrosis.[5,6]

It is reported that the gastrointestinal flora, contributing to the construction of the intestinal barrier, plays an important regulatory role in the progression of AP. The gut barrier and the intestinal flora affect each other in order to engage in the development of the disease.[7] It has been theorized that hypoperfusion of peripheral tissues (including the gut), microcirculatory injury in severe forms of AP and subsequent damage to the enteric mucosa with an increased permeability of the intestinal barrier are the causes of bacterial translocation from the intestine and further contamination of the pancreatic necrosis.[8–11] In consequence, as a response to the potential pathomechanism of infection of the pancreatic necrosis, selective digestive decontamination (SDD) being a method of eradication of enteric pathogens, may be considered an effective prophylaxis of septic complications in AP.[12,13]

In the present study, we attempted to settle whether the use of an oral antibiotic – rifaximin, used in gut microbiota modification treatment, can lead to the reduction of infectious complications, primarily related to the late phase of necrotizing pancreatitis.

Rifaximin is an oral nonabsorbable antibiotic with broad-spectrum antimicrobial activity. It was designed as a synthetic derivative of rifamycin, which irreversibly binds to the β-subunit of DNA-dependent RNA polymerase and consecutively inhibits the synthesis of bacterial RNA and proteins.[14] It is biologically active against a wide range of bacteria, including Gram-positive, Gram-negative, aerobic and anaerobic[15]; nonetheless, it has been shown that rifaximin induces no clinically important bacterial resistance.[16] It has been also demonstrated on animal models that rifaximin modulates the gut microbiota by promoting the growth of symbiotic cultures (*Lactobacillus, Bifidobacterium*), which differs from the mechanism of other antibiotics formerly used in selective digestive decontamination and which is why it can be preferably described as modification of gut microbiota.[15] Rifaximin, as a specific gastrointestinal ligand of the human pregnane X receptor (PXR), has a significant anti-inflammatory effect, reducing intestinal inflammation and restoring epithelial mucosal barrier.[16] Moreover, rifaximin is characterized by low gastrointestinal (GI) absorption (<0.4%),[15] while preserving high antibacterial effect, which attributes to the elimination of the risk of both systemic side effects and interactions with other drugs. All of the aforementioned features prove that rifaximin is a safe and very effective antibiotic in all patients, including the pediatric patients,[17] in the treatment of conditions of the GI tract that include small intestinal bacterial overgrowth (SIBO), irritable bowel syndrome (IBS)[18] and symptomatic uncomplicated diverticular disease (SUDD).[19] The indications for rifaximin treatment registered in Poland are shown in Table 1.

Despite the confirmed efficacy of rifaximin in such conditions, there are no studies assessing its effectiveness through modification of the gut microbiota in patients with AP. Therefore, it is needed to evaluate its use in the aspect of AP treatment.

Table 1. Indications for rifaximin treatment registered in Poland

Indications for rifaximin treatment registered in Poland
Hepatic encephalopathy in advanced liver disease
Traveler's diarrhea
Symptomatic uncomplicated diverticular disease (SUDD)
Diarrhea-predominant irritable bowel syndrome (IBS-D)

Objectives

The purpose of the present study was to analyze whether the modulation of gut microbiota with rifaximin could alter the outcome of patients treated with moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP). The number of infected pancreatic necroses, mortality rate, as well as the time of patients' hospitalization were set as major endpoints of the research.

Materials and methods

A total of 373 patients with AP (242 men and 131 women, median age 50 years, age range 18–96 years) were included in this study. All patients were admitted to the Department of Gastroenterology in Central Clinical Hospital of The Ministry of Interior and Administration, Warsaw, Poland, between 2001 and 2016. The diagnosis and evaluation of the severity of AP were made according to the Revised Atlanta Classification for Acute Pancreatitis (2012).[20] On the basis of these criteria, patients were retrospectively recognized with mild acute pancreatitis (MAP), MSAP or SAP.

Mild acute pancreatitis was characterized by the absence of failure within the pancreas, with no local and systemic

complications. Moderately severe acute pancreatitis was described as transient organ failure, which resolves within 48 h, with local or systemic complications, while SAP indicates persistent organ failure lasting longer than 48 h, with single or multiple complications.[21] The organ failure was defined in accordance with the Modified Marshall Scoring System.[22]

Starting from the cut-off point of the year 2009, the patients admitted to the Gastroenterology Department who started to manifest features of MSAP or SAP received immediate rifaximin therapy through enteral feeding tube along with enteral nutrition. The treatment protocol of rifaximin therapy was arranged as follows; patients were administered rifaximin 3 times per day at a dose of 400 mg (for at least 5 days and up to 7 days), comparably to the maximal dosage of this drug in other registered indications in Poland.

This clinical intervention had received the approval of the hospital ethics committee (approval No. 14/2009 from August 4, 2009). The study complies with the 1975 Declaration of Helsinki. All patients who were treated for severe forms of AP and received rifaximin treatment had signed an informed consent form before participating in the study.

Subsequently, groups of patients that were admitted in different timeframes (2001–2008 compared to 2009–2016) were compared regarding their age, sex and AP severity (Table 2). It resulted in the fact that in the group of patients treated for AP in years 2009–2016, there was a larger number of cases of MAP, which proved to be statistically significant ($p = 0.0346$). Nonetheless, the 2 groups did not differ in both age ($p = 0.3789$) and sex ($p = 0.6776$) distribution.

Finally, 2 other cohorts were compared: patients diagnosed only with MSAP and SAP, admitted in the years 2001–2008, thus not receiving rifaximin (R0 group), and patients admitted in the years 2009–2016 who presented with MSAP and SAP and who were given rifaximin (R1 group) (Fig. 1). There was no other difference in treatment between those cohorts. Both groups (R0 and R1) were analyzed and characterized by their clinical features, including age, sex and severity of AP. There was no statistically significant difference between these groups in regard to age and sex distribution, as well as etiology and severity of AP. The characteristics for the 2 groups are listed in Table 3.

We determined the level of C-reactive protein (CRP) as a predictor for the disease severity. All individuals with CRP level above 150 mg/L and those with the most severe forms of AP on admission underwent a contrast-enhanced computed tomography (CE-CT) examination to confirm or exclude the presence of pancreatic necrosis. The CE-CT was performed not sooner than 4 days after the admission to the hospital. The necrosis of the pancreas was identified as areas of nonviable pancreatic components, commonly associated with necrosis of the peripancreatic adipose tissue in CE-CT findings.[23]

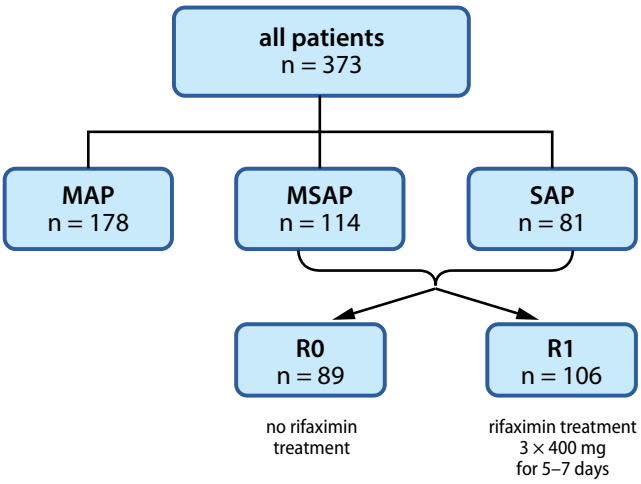

Fig. 1. Distribution of patients with acute pancreatitis (AP) included in the study

MAP – mild acute pancreatitis; MSAP –moderately severe acute pancreatitis; SAP – severe acute pancreatitis; R0 group – group of patients not receiving rifaximin in cases of MSAP or SAP; R1 group – group of patients with MSAP or SAP receiving rifaximin treatment.

Table 2. Profile of patients with AP included in the study

Category	Subgroup	Total	Patients admitted in 2001–2008	Patients admitted in 2009–2016	p-value (statistical method)
All patients, n (%)	–	373 (100.00)	147 (100.00)	226 (100.00)	–
Age [years], median (IQR)	–	50.00 (40.00, 64.00)	51.00 (42.00, 64.50)	50 (38.00, 63.00)	0.3789 (Mann–Whitney U test)
Sex, n (%)	male	242 (64.88)	93 (63.27)	149 (65.93)	0.6776 (χ^2 test with Yates' correction)
	female	131 (35.12)	54 (36.73)	77 (34.07)	
Severity of AP, n (%)	MAP	178 (47.72)	58 (39.46)	120 (53.10)	0.0346 (χ^2 test)
	MSAP	114 (30.56)	53 (36.05)	61 (26.99)	
	SAP	81 (21.72)	36 (24.49)	45 (19.91)	
	MSAP + SAP	195 (52.28)	89 (60.54) (R0 group)	106 (46.90) (R1 group)	–

IQR – interquartile range; AP – acute pancreatitis; MAP – mild acute pancreatitis; MSAP – moderately severe acute pancreatitis; SAP – severe acute pancreatitis; R0 group – group of patients not receiving rifaximin in cases of MSAP or SAP; R1 group – group of patients with MSAP or SAP receiving rifaximin treatment.

We investigated the relationship between administration of rifaximin and duration of hospital stay, as well as the number of infected pancreatic necroses, formerly recognized as pancreatic abscesses. Moreover, the mortality rate was recorded for both groups. The follow-up was continued until death or discharge from the hospital.

Statistical analyses

The Mann–Whitney U test was used in the comparison of the tendencies between groups with regard to continuous variables (age, duration of hospital stay). The χ^2 test with and without Yates' correction was applied when analyzing categorical variables in samples of an average size (sex distribution, age distribution, severity of AP, etiology of AP, number of pancreatic necroses in CE-CT examination), whilst Fisher's exact test was employed in the analysis of small samples (number of infected pancreatic necroses, mortality rate). A value of $p < 0.05$ was considered statistically significant.

Results

Distribution of patients with AP

Mild acute pancreatitis was recognized in 178 (47.7%) patients, MSAP in 114 (30.6%) patients and SAP in 81 (21.7%) patients, in accordance with the Revised Atlanta Classification (2012) described in methodology. From a total number of 195 cases of either MSAP or SAP, 89 patients (45.6%) did not receive rifaximin treatment, thus were further analyzed as R0 group, while 106 (54.4%) patients were given rifaximin and were assigned to the R1 group.

Hospital stay

A statistically significant difference was observed between the R0 and R1 groups in terms of the duration of hospital stay (Table 3). A median hospital stay for patients who did not receive rifaximin (R0) was 24 days, in comparison to the group treated with rifaximin (R1), in which median hospitalization time was 14 days ($p < 0.0001$).

Pancreatic necrosis and infected pancreatic necrosis

Necrosis of the pancreatic tissue was detected by means of computed tomography (CT) in a total number of 87 cases (23.3%), out of which it was present in 42 patients in R0 group (47.2%) and in 45 patients in R1 group (42.5%). No statistically significant difference was observed ($p = 0.5073$).

The overall incidence of infected pancreatic necroses during hospitalization in patients with AP was 7 out of 373 (1.9%). In the R0 group, 6 patients (6.7%) developed abscesses in pancreas, in contrast to only 1 patient (0.9%) in the R1 group. This difference was statistically significant ($p = 0.0487$) (Table 3).

Mortality

The overall mortality rate in patients with AP included in this study was 5.4% (20 out of 373). Seven patients (7.9%)

Table 3. The distribution of age, gender, etiology and severity of AP, duration of hospital stay, number of infected pancreatic necroses, and mortality rate, between R0 and R1 groups

Category	Subgroup	Total	R0 group	R1 group	p-value (statistical method)
All patients, n (%)	–	195 (100.00)	89 (100.00)	106 (100.00)	–
Age [years], median (IQR)	–	54.00 (40.00, 68.00)	52.00 (42.00, 65.00)	57.00 (39.25, 69.00)	0.2585 (Mann–Whitney U test)
Sex, n (%)	male female	135 (69.23) 60 (30.77)	60 (67.42) 29 (32.58)	74 (69.81) 32 (30.19)	0.8381 (χ^2 test with Yates' correction)
Etiology of AP, n (%)	biliary alcoholic	114 (58.46) 81 (41.54)	58 (65.17) 31 (34.83)	56 (52.83) 50 (47.17)	0.0816 (χ^2 test)
Severity of AP, n (%)	MSAP SAP	114 (58.46) 81 (41.54)	53 (59.55) 36 (40.45)	61 (57.55) 45 (42.45)	0.8911 (χ^2 test with Yates' correction)
Hospital stay [days], median (IQR)	–	18.00 (11.00, 27.00)	24.00 (17.00, 31.00)	14.00 (9.25, 22.50)	<0.0001 (Mann–Whitney U test)
Pancreatic necrosis, n (%)	–	87 (44.61)	42 (47.19)	45 (42.45)	0.5073 (χ^2 test)
Infected pancreatic necrosis, n (%)	–	7 (3.59)	6 (6.74)	1 (0.94)	0.0487 (Fisher's exact test)
Mortality, n (%)	–	20 (10.26)	7 (7.86)	13 (12.26)	0.3519 (Fisher's exact test)

IQR – interquartile range; AP – acute pancreatitis; MSAP – moderately severe acute pancreatitis; SAP – severe acute pancreatitis; R0 group – group of patients not receiving rifaximin in cases of MSAP or SAP; R1 group – group of patients with MSAP or SAP receiving rifaximin treatment.

in the R0 group died, in comparison to 13 patients (12.3%) in the R1 group. This difference was not statistically significant (p = 0.3519) (Table 3).

Discussion

Acute pancreatitis is one of the major gastroenterological causes of hospital admission. Seeing that the global incidence of AP varies between 5 and 80 persons per 100,000, the analysis of epidemiological studies puts Poland in the group characterized by the highest incidence rate of 72.1 persons per 100,000.[24] It is reported in literature that men have a higher risk of death in the course of AP than women.[25] However, our study compared 2 final groups of patients (R0 and R1) that did not differ statistically in sex, age, etiology of AP or disease severity distribution, which is why our research supports the hypothesis that it was rifaximin, not any other epidemiological factor, that could have altered the outcome of the disease in the group that underwent rifaximin treatment.

Acute pancreatitis is a condition characterized by an unpredictable clinical course, with a high mortality rate reaching 20% with an infection of pancreatic necrosis[26] and 60% with concomitant multiorgan dysfunction,[27,28] with the majority of deaths being a result of infection of the necrotic tissue, the most severe local complication of the disease.[29] In addition, the mortality level in patients with sterile pancreatic necrosis and organ failure is doubled in patients who develop additional infected pancreatic necrosis.[29] These infecting bacteria are most likely to be relocated from the digestive tract as an integrated effect of several possible pathomechanisms in necrotizing pancreatitis.

It has been illustrated in various reviews that patients with severe forms of AP develop splanchnic hypoperfusion, which is an outcome of fluid depletion in this disease.[30,31] As a result, microinjuries to the intestinal mucosa with subsequent reperfusion injuries induce a dysfunction of the enteric barrier. In a systematic review by Wu et al., 59% of patients with AP were found to have developed a gut barrier dysfunction.[32] This disruption can lead to the translocation of bacteria, mostly from the small bowel[33] to the peritoneal cavity, which may thereon be involved in the pathogenesis of local and systemic infectious complications in AP.[9] Furthermore, the dysmotility of the gut being another result of a decreased blood flow in the digestive tract in AP, as well as the consecutive bacterial overgrowth in the bowels could attribute to a facilitated process of translocation of visceral bacteria to the necrotic tissue in the pancreas. Yet, their role has been described mostly on murine models.[34] This theory of bacterial translocation is endorsed by the fact that the microorganisms isolated from infected pancreatic necroses are mainly Gram-negative aerobic bacteria consistent with the species found in the digestive tract (*Proteus, Escherichia coli, Pseudomonas*)[35]. As such, these bacteria become a subject of interest in studies investigating the possibility of reducing the number of infected pancreatic necroses and mortality rates in AP.

Routine systemic antimicrobial prophylaxis has been established in recent meta-analyses not to bring any benefit in the prevention of infection of pancreatic necrosis, thus it should not be considered as a method of treatment in necrotizing pancreatitis.[36] Guidelines advise against the antibiotic use due to their ineffectiveness, as well asthe higher risk of developing *Clostridium difficile* infection.[27,37–40] Nevertheless, a new effective method of treatment of panecreatic necrosis, with an impact restricted solely to the digestive tract with limited systemic side effects, could be of use and interest in the clinical surrounding.

Studies on animal models reveal that selective digestive decontamination (SDD) decreases the overall mortality rate and the number of infections of pancreatic necrosis in AP, albeit a handful of human studies have explored the effect of antimicrobial prophylaxis through the means of SDD in patients with AP. Luiten et al. reported that the treatment with colistin (200 mg/day), norfloxacin (50 mg/day) and amphotericin (500 mg/day) significantly reduced not only the incidence of infected necrosis and the risk of Gram-negative pancreatic sepsis, but also late mortality rate in patients with SAP, when compared with placebo.[35] Sawa et al. inspected the outcome of patients with SAP, which had been administered polymyxin B (1,500,000 units/day), L-glutamine (3 g/day) and lactulose (90 mL/day) through an enteral feeding tube. This study revealed that SDD reduced the incidence of organ dysfunction and the mortality rate, but the differences were not statistically significant.[12] The results from these major studies have not been well recognized due to the fact that the SDD regimen was repeatedly combined with parenteral antimicrobial treatment.[41]

To our knowledge, there have been no previous clinical studies assessing the purpose of rifaximin use in acute pancreatitis in humans. Preceding analyses demonstrated a possible effect of SDD in severe forms of AP with other antibiotics; however, our study concentrates on the application of rifaximin, which exhibits a peculiar antimicrobial activity and pharmacodynamics. By the eradication of pathogenic bacteria and concurrent promotion of symbiotic cultures, rifaximin shows its properties that are interpreted in literature as eubiotic and not antibiotic.[15] The addition of low GI absorption and the lack of increase of bacterial resistance, as well as the absence of risk of *Clostridium difficile* infections contribute to the wider clinical potential of this medication.

Limitations

Our study has several limitations. It is a retrospective study and the data came from 1 center with a limited number of patients. The 2 cohorts compared in the study (R0

and R1 groups) consisted of patients from different time frames (2001–2008 and 2009–2016). This limitation could have an impact on the immesurable organizational factors contributing to the decline of median length of hospital stay, that are not necessarily associated to the treatment protocol. Nevertheless, it is worth mentioning that the study took place at a tertiary referral center, to which patients from all over the country with the most severe types of AP are referred, hence the relatively high frequency of MSAP and SAP, which appears to be a strength of this research.

Conclusions

It has been found, for the first time, that rifaximin therapy reduced the incidence of infected pancreatic necroses and decreased the time of hospital stay of patients with severe forms of AP (by 86% and 42%, respectively), although it did not significantly affect the mortality ratio.

Our study indicates a possible correlation of rifaximin use with a decrease in the number of pancreatic necroses in AP patients, which is why this subject is currently being investigated in prospective studies in our clinic. Our results allow for a more reliable review of a complex area of gut microbiota modulation treatment with rifaximin in patients with MSAP and SAP. These outcomes indicate that rifaximin seems to be a promising therapeutic option in MSAP and SAP and should be further evaluated in a multicenter randomized prospective study.

ORCID iDs

Jacek Tatur https://orcid.org/0000-0001-8660-6422
Michał Lipiński https://orcid.org/0000-0002-9499-4178
Marta Sznurkowska https://orcid.org/0000-0001-8209-7827
Ewa Józefik https://orcid.org/0000-0003-2425-4008
Grażyna Rydzewska https://orcid.org/0000-0002-1267-7620

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