The impact of rifaximin on the hospital burden and infections in patients with hepatic encephalopathy: a retrospective observational study

J. De Graeve[1], E. Vanderstraeten[1], T. Delvaeye[1], S. De Lepeleere[1], T. De Somer[1], C. Van Steenkiste[1, 2]

(1) Gastroenterology & Hepatology, AZ Maria Middelares, Gent, Belgium; (2) Gastroenterology, UZ Antwerpen, Edegem, Belgium.

Abstract

Background and study aims: **Advanced liver disease frequently culminates in hepatic encephalopathy (HE), which can be classified as covert or overt HE, with subtle or clinically obvious changes respectively. 30-40% of patients with cirrhosis develop overt HE, which negatively affects the patients' quality of life. Next to lactulose, rifaximin-α has been prescribed as a second line therapy to treat and reduce the risk of recurrence of overt HE. In this study, we aimed to evaluate the effect of rifaximin-α therapy, both on the number of occurring infections and on the evolution in hospital admissions of patients with overt HE.**

Patients and methods: **A total of 66 cirrhotic patients, treated for at least 6 months with rifaximin-α at AZ Maria Middelares, between October 1st 2014 and January 1st 2020, were included in the study analysis. Medical records of all patients were evaluated over a period of 6 months prior and after initiation of rifaximin-α therapy.**

Results: **Data analysis revealed that the included cirrhotic patients were severely ill, with a mean model for end-stage liver disease (MELD) score of 21, and a median Child Pugh score of 11. Among these patients, rifaximin-α treatment significantly downgraded the total number of infections, with a main effect on respiratory infections. Furthermore, rifaximin-α therapy led to a significant decrease in HE-related, as well as in other liver-related hospital admissions.**

Conclusions: **This study confirms the potential value of rifaximin-α in reducing the number of developing infections and hospital admissions in a severely ill cirrhotic patient population.** (Acta gastroenterol. belg., **2022,** 85, **433-437**).

Keywords: end-stage liver disease, rifaximin-α, intensive care, healthcare utilization.

Introduction

Hepatic encephalopathy (HE) is a severe neuro-psychiatric complication associated with patients that suffer from advanced liver disease, i.e. cirrhosis (1,2). Covert HE occurs in a population of patients with cirrhosis that do not show clinically obvious symptoms, whereas overt HE is seen in patients with cirrhosis that develop changes in behavior, motoric functions and consciousness, hence majorly affecting the patients' quality of life (1,2). Targeting approximately 30-40% of patients with cirrhosis, overt HE is a lethal complication associated with cirrhosis and has a survival rate of 40-55% 6 months after diagnosis (3,4). The pathophysiology is complex with multiple hits, but it is estimated that the accumulation of neurotoxins, which derive from bacteria in the gut, play a major role (2,5). Hence, current treatments for HE mostly intend to modify gut microbiota, or remove toxins in the gut. The first line treatment for HE consists of lactulose, a non-adsorbable disaccharide, that ultimately aims at reducing the amount of produced ammonia out of proteins. Rifaximin-α (Targaxan, Norgine), a poorly adsorbed oral antibiotic, showed to be effective in reducing gut absorption and production of ammonia, and in contrast to lactulose, it was also found to reduce the risk of recurrence of overt HE in different studies (6,7,8).

Rifaximin-α has been recommended as second line therapy after a second episode of overt HE, as an 'add-on' therapy to lactulose for the prevention of recurrence of overt HE (1,2,5,6). Here, we aimed to retrospectively investigate the impact of rifaximin-α on the hospital burden and infections in a real-world setting, i.e. by analyzing medical data obtained from a heterogenous cirrhotic patient population with HE and a high model for end-stage liver disease (MELD) score, over a period of 6 months before and after initiation of rifaximin-α. Importantly, we were able to present the ability of rifaximin-α to reduce HE-related hospital admissions, as well as the amount of occurring infections in patients with severe cirrhosis and HE, confirming its potential as a second line therapy for overt HE.

Methods

Study design and patients

In this retrospective observational monocentric study, we aimed to identify all patients who were treated with Rifaximin-α from October 1st 2014 until January 1st 2020 at AZ Maria Middelares, Ghent, Belgium. Each patient included in the study was diagnosed with cirrhosis and was using rifaximin-α at the dosage of 550mg, twice daily as a secondary prophylaxis for overt HE, in combination with lactulose. All patients were evaluated over a period of 6 months before and after rifaximin-α initiation. The study protocol was approved by the ethical committee at AZ Maria Middelares, Ghent, Belgium.

Correspondence to: C. Van Steenkiste, AZ Maria Middelares, Buitenring Sint-Denijs 30, 9000 Gent. Fax: 09 246 71 09.
Email: christophe.vansteenkiste@azmmsj.be

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Data collection

All medical data were collected from the patient's electronic data file, and included patient demographics (gender, age), comorbidities, etiology of liver disease, MELD score, Child Pugh score, presence of hepatocellular carcinoma (HCC), liver transplantation, West Haven classification (to score maximum grade of HE), presence of ascites and antibiotic prophylaxis regarding spontaneous bacterial peritonitis (SBP).

The patient outcome variables were the amount of HE-related hospital admissions, the number of liver-related admissions (other than HE-related), the amount of liver- and HE-related intensive care unit (ICU) admissions and the number of emergency department admissions. Following the number of admissions, the length of stay of these admissions was also analyzed, as well as the number of outpatient clinic visits and the number and type of infections that occurred among our patient population.

Definitions

Child Pugh scores were determined using HE West Haven grading, bilirubin values (mg/dl), ascites severity, albumin values (g/l) and international normalized ratio (INR) (9). HE severity was graded using West Haven criteria (10), and MELD scores were calculated with the patient's values for serum bilirubin (mg/dl), serum creatinine (mg/dl), and the INR. Patients hospitalized with a primary liver related problem, such as variceal bleeding, ascites or HCC among others, were categorized as liver-related hospital admissions. HE-related hospital admissions included patients with chronic liver disease hospitalized with HE.

Statistics

Data of each patient were gathered from 6 months before to 6 months after Rifaximin-α treatment initiation and was compared between these 2 timeframes per patient. Hence, each patient served as their own control. Data analysis was performed using SPSS Software (Version 27, IBM), in which categoric variables were compared using a Wilcoxon test, and continuous variables were compared using a paired Student's t-test.

Results

Patient characteristics

Between October 1st 2014 and January 1st 2020 at AZ Maria Middelares, a total of 105 patients with confirmed cirrhosis were treated with rifaximin-α at the dosage of 550 mg twice daily. Of these 105 patients, a total of 39 patients were excluded: 22 patients were administered rifaximin-α for acute chronic liver failure (not as secondary prophylaxis) and died within 6 months after initiation of rifaximin-α; 3 patients were transplanted and again had very short administration period of rifaximin-α before transplantation and started rifaximin-α for non-secondary prophylaxis indications; 14 patients dropped treatment within 6 months due to financial problems or due to improvement of HE symptoms. As such, a total of 66 patients remained and were included for further study analysis.

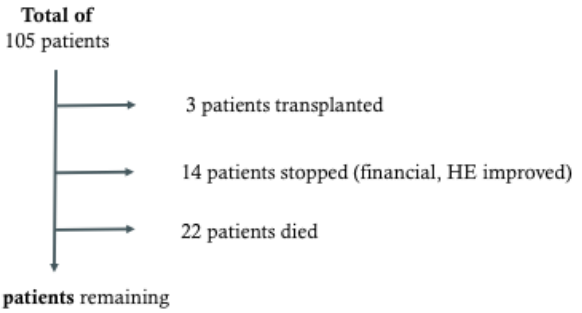

Figure 1. — Patient selection.

Among the study population, the mean age was 67 years (standard deviation (SD) 9.3) at baseline (before rifaximin-α treatment), 43 were male (65.2%) and 23 were females (34.8%). The mean MELD and median Child Pugh score among patients was 21.0 (SD 8.4) and 11.0 (interquartile range (IQR) 5.3) respectively, with the latter being subdivided in class A (1.5%), B (37.9%) and C (60.6%) (11). Furthermore, when patients were classified according to the West Haven classification at the time of rifaximin-α initiation, most patients were scored as having HE West Haven grade 2 (68.2%) and grade 3 (30.3%). Overall, these data point towards a severely ill population of patients with advanced cirrhosis being included in this study (Table 1). Of all these patients, 80.3% was suffering from an alcoholic liver disease, and 13.6% from non- alcoholic steatohepatitis (NASH) (Table 1). Almost half the amount of patients (43.9%) also suffered from cardiac comorbidities, such as coronary artery disease, heart failure or arrhythmia, and 22.7 % of the patients was diagnosed with Diabetes Mellitus type 1 or 2. These demographic data again point out the severely ill population of patients with cirrhosis being included in this study (Table 1).

Beneficial effect of rifaximin-α treatment on the West Haven HE grade

As expected, rifaximin-α treatment had a positive effect on the grade of hepatic encephalopathy using the mean HE West Haven grading before and after rifaximin-α treatment, with scores of 2.3 and 0.7, respectively, indicating a significant decrease (p=0.0001) upon rifaximin-α.

The positive impact of rifaximin-alfa on the hospital burden

To check whether rifaximin-α had an effect on the amount of hospital admissions, data were evaluated 6

Table 1. — **Patient clinical characteristics at baseline, before rifaximin initiation**

	Patients (n = 66)
Male/Female, n (%)	43/23 (65.2/34.8)
Age in years, mean (± SD)	67 (± 9.3)
Underlying etiology of liver disease, n (%)	
Alcoholic liver disease	53 (80.3)
NASH	9 (13.6)
Viral	3 (4.5)
PBC	2 (3.0)
Hemochromatosis	1 (1.5)
Budd Chiari	1 (1.5)
Cryptogenic	1 (1.5)
Liver disease severity scores	
MELD score, mean (± SD)	21 (8.4)
Child Pugh score, median (± IQR)	11 (5.3)
Child Pugh class, A/B/C %	1.5/37.9/60.6
Comorbidities, n (%)	
Cardiac (coronary artery disease, heart failure, arrhythmia)	29 (43.9)
Nephrological (CKD)	10 (15.1)
Pulmonary (asthma/COPD)	9 (13.6)
Diabetes Mellitus (type 1 and 2)	15 (22.7)
Malignancy (other than HCC)	13 (19.7)
Multiple (more than 1)	21
HE (West Haven grading), n (%)	
Grade 1	1 (1.5)
Grade 2	45 (68.2)
Grade 3	20 (30.3)
Grade 4	0 (0)
Ascites, n (%)	42 (63.6)
Prophylaxis SBP, n (%)	10 (15.2)
HCC, n (%)	14 (21.2)

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; SBP, spontaneous bacterial peritonitis; SD, standard deviation; IQR, interquartile range.

months prior and 6 months post rifaximin-α treatment. When comparing the number of HE-related hospital admissions per patient, a significant reduction could be observed between 6 months before (1.6 (SD 1.2)) and 6 months after (0.4 (SD 0.88)) initiation of rifaximin-α treatment. In this category, a significant reduction in the length of stay (expressed as 'bed days') was also apparent between pre-and post- rifaximin-α treatment (23.1 days vs 7.3 days) (Table 2). The number of HE-related admissions at ICU per patient on the other hand, was also reduced, but did not show significance pre- versus post-rifaximin-α treatment. However, the amount of bed days related to HE-related admissions at ICU was significantly less 6 months after compared to 6 months prior to rifaximin-α treatment (0.2 days vs 3.8 days). Next, we also evaluated the difference in number of liver-related admissions, other than HE-related admissions, whether or not at ICU, 6 months before and after rifaximin- α treatment. In both categories, rifaximin-α treatment led to a significant lower number of admissions per patient (Table 2). Finally, after evaluating the number of outpatient clinic visits and emergency department visits, the latter also presented a significant reduction (0.9 (SD 1.4)) when compared to the period of 6 months before rifaximin-α treatment (1.9 (SD 2.1)) (Table 2). Overall, these data show and confirm the potential of rifaximin-α in reducing hospital admissions, bed days and emergency department attendances.

Rifaximin-α treatment significantly reduces the number of infections

Patients diagnosed with cirrhosis have an intrinsic immune dysfunction and hence acquire infections more quickly. To investigate the impact of rifaximin-α treatment on the number of developed infections, data were compared 6 months prior to 6 months after initiation of rifaximin-α treatment. Importantly, the total number of infections among all patients was reduced from 61 infections prior to rifaximin-α treatment to 21 infections post- rifaximin-α therapy. Calculating the mean number of infections per patient 6 months before and after rifaximin-α treatment, a significant reduction could indeed be observed (0.90 vs 0.32) (Table 3). Splitting up the different infections in subcategories, it became clear that respiratory infections in particular were reduced by

Table 2. — **The impact of rifaximin-alfa on the hospital burden**

Mean (±SD)	- 6 months	+ 6 months	p-value
Number of HE-related hospital admissions per patient	1.6 (1.2)	0.4 (0.88)	0.001
Bed days	23.1 (23.5)	7.3 (23.7)	0.001
Number of liver-related* hospital admissions per patient	1 (1.4)	0.4 (0.7)	0.018
Bed days	4.1 (5.8)	6.0 (13.4)	0.913
Number of ICU HE-related admissions per patient	0.4 (0.7)	0.1 (0.4)	0.078
Bed days	3.8 (0.3)	0.2 (1.3)	0.028
Number of ICU liver-related* admissions per patient	0.9 (0.9)	0.3 (0.9)	0.003
Number of emergency department visits	1.9 (2.1)	0.9 (1.4)	0.010
Number of outpatient clinic visits	6.4 (5.6)	4.4 (3.3)	0.130

*Other than HE-related; HE, hepatic encephalopathy; ICU, intensive care unit.

Table 3. — **The impact of rifaximin on the number of developing infections.**

Mean (±SD)	- 6 months	+ 6 months	p-value
Total number of infections per patient	0.90 (1.02)	0.32 (0.63)	0.001
Gastrointestinal	0.14 (0.42)	0.04 (0.21)	0.083
SBP	0.15 (0.36)	0.06 (0.24)	0.083
Respiratory	0.18 (0.38)	0.03 (0.17)	0.034
Urinary	0.18 (0.49)	0.09 (0.38)	0.295
Skin	0.03 (0.17)	0.00 (0.00)	0.157
Bacteraemia/sepsis	0.07 (0.26)	0.06 (0.24)	0.739
Orthopedic	0.03 (0.17)	0.00 (0.00)	0.157

rifaximin-α treatment (p=0.034). A lowering trend was apparent for gastrointestinal infection and SBP, although these differences pre- and post- rifaximin-α treatment did not reach significance (Table 3).

Discussion

The potential value and use of rifaximin-α as a second-line therapy after a second episode of overt HE in cirrhotic patients has been frequently studied (4,5,12,13). The present study is the first to retrospectively evaluate real-world data in a Belgian cohort and focuses on the evidence of efficacy of rifaximin-α on a severely ill cirrhotic patient population with a mean MELD score of 21. This is in contrast to other studies, where patients had MELD scores of 15 (4,12) or between 12.8 and 17.9 (5), suggesting that the patients included in this study had a worse prognosis. Yet, despite this higher MELD score the results of previous studies (4,5) could be reproduced in an ill cirrhotic population.

After comparison of data gathered 6 months prior and 6 months after rifaximin-α treatment initiation in 66 patients, we were able to demonstrate a significant beneficial effect of rifaximin-α therapy on the hospital burden, i.e. on HE- and liver-related hospital admissions, as well as on the number of emergency department visits, and hence confirms earlier reports on rifaximin-α -related beneficial effects (5,13). Moreover, the amount of bed days associated to HE-related admissions was also significantly decreased, 6 months after rifaximin-α initiation. Whereas Oey *et al.* did not observe any effect on the number of ICU hospitalizations (4), our data identified a significant reduction in the amount of liver-related ICU admissions, and more importantly, on the amount of bed days related to HE-associated ICU admissions. Interestingly, the latter results were reported by others too (12). These contrasting findings between different studies might be explained by various factors, e.g. differences in local treatment protocols and/or patient population characteristics, or contrasting criteria for ICU admission.

Furthermore, our data pointed towards a potential beneficial effect of rifaximin-α on the number of developing respiratory infections (p=0.034), and to a lesser and non-significant extent to gastrointestinal infection and SBP. These results are in line with results shown by Oey *et al.*, where a small but non-significant decrease in the amount of SBP was observed in the first 6 months after rifaximin-α therapy initiation (4). To draw firm conclusions on the appearance of different infections upon rifaximin-α treatment, the power, and hence sample size should be increased.

Importantly, rifaximin-α also significantly influenced HE West Haven grading with scores of 2.3 and 0.7 before and after treatment initiation, respectively. These data indicate that rifaximin- α significantly reduced the number of HE episodes.

Most probably, rifaximin-α treatment is not the only factor ameliorating the hospital length of stay and patient's outcome. Indeed, other factors, such as other medications and life-style change contribute to the beneficial effects during hospitalization. Seventy-three percent of all patients already started abstinence of alcohol before being hospitalized, whereas 27% was still drinking alcohol. Interestingly, the latter group displayed more frequent hospitalizations, as well as longer hospital length of stays, however these results did not reach significance (data not shown).

Lastly, our main limitation includes the limited patient population that was included for data analysis; i.e. 66 patients were evaluated in this study, due to which multivariate analysis was impossible. Nevertheless, in most endpoints, e.g. hospitalizations, bed days, and occurring infections, significant changes were already observed.

In real-life we gathered evidence for the positive impact of rifaximin-α on the hospital burden, including less HE-related hospital admissions and liver-related hospital and ICU admissions. Importantly, patients treated with rifaximin-α were also hospitalized for a shorter period, significantly reducing the cost per patient. We also observed a significant decrease in the amount of occurring infections, and patients scored lower at HE West Haven grading. All these data point towards the potential strong value of rifaximin-α as a second line therapy for overt HE.

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