ORIGINAL ARTICLE

Efficacy of Rifaximin in Prevention of Recurrence of Hepatic Encephalopathy in Patients with Cirrhosis of Liver

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Abstract

Objective: To determine the efficacy of Rifaximin in prevention of repeated episodes of hepatic encephalopathy in patients with liver cirrhosis as compared to placebo.

Study Design: Triple-blind, randomized placebo-controlled trial.

Place and Duration of Study: Department of Gastroenterology-Hepatology, Shaikh Zayed Hospital, Lahore, from October 2012 to April 2013.

Methodology: Patients in remission from recurrent hepatic encephalopathy resulting from cirrhosis were randomly assigned to receive either Rifaximin, at a dose of 550 mg twice daily (63 patients), or placebo (63 patients.) Patients were requested to take the drug orally twice daily for 6 months or until they developed a breakthrough episode of hepatic encephalopathy.

Results: Mean age of patients in treatment and control group was 40.21 ± 2.33 years and 42.87 ± 4.54 years respectively. The most common etiology of cirrhosis was hepatitis C followed by hepatitis B. Patients who remained free of hepatic encephalopathy during study period were 40 out of 63 patients in control group and 35 patients out of 63 patients (p = 0.56). Most of the patients who developed breakthrough hepatic encephalopathy had a MELD score range of 21-25 in both groups. The number of deaths and adverse events was similar in both groups.

Conclusion: Over a 6-month period, treatment with Rifaximin failed to maintain remission from hepatic encephalopathy more effectively than placebo in the studied group.

Key Words: *Hepatic encephalopathy. Lactulose. Rifaximin. Liver cirrhosis. Therapy. Recurrence.*

INTRODUCTION

Hepatic encephalopathy (HE) a common complication of cirrhosis, imposes a formidable burden on the patients and their families. Repeated episodes are debilitating, require repeated hospitalizations and render the patient incapable of performing activities of daily life.[1] An increase in the frequency and severity of such episodes predict an increased risk of death.[2]

Although hyperammonia has been implicated, the exact pathogenesis of HE remains elusive.[3] The aim of treatment has been to reducte the gut-derived ammonia, increased ammonia clearance and control of precipitating factors.[4] Lactulose has been the standard of care while oral antibiotics have been effective only to be associated with toxic effects when used on long-term basis.[5,6]

Rifaximin is a minimally absorbed oral antimicrobial agent. It is derived from rifamycin and has broad spectrum of activity against gram-positive, gram-negative and anaerobic enteric bacteria and has a low risk of inducing bacterial resistance. In randomized studies, Rifaximin, used concomitantly with lactulose was found to be more effective for the prevention of recurrence of HE.[7]

The study population in the western world mostly consists of alcohol induced cirrhosis[8] while in our part of the world it is mostly cirrhosis secondary to viral hepatitis.[9] In addition, the microflora in the gut in eastern populations is different from that of western populations.[10] There could be differences in response to Rifaximin in our population compared to the west. If it is found to be efficacious in the local population, it would help decrease the morbidity of the disease.

The purpose behind this study was to evaluate the efficacy and safety of Rifaximin in the local population for the prevention of recurrent episodes of hepatic encephalopathy.

METHODOLOGY

This study was carried out at the Department of Gastroenterology-Hepatology, Shaikh Zayed Hospital (SZH), Lahore, from October 2012 to April 2013. It was a triple blind randomized placebo-controlled trial. Approval of the study was taken from Institutional Review Board (IRB) of SZH. Patients with cirrhosis of any cause, of all ages and both sexes and with a history of at least two episodes of hepatic encephalopathy in the last 6 months with a Conn score ≥ 2 and a score of 25 or less on the model for end stage liver disease scale

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presenting to OPD or getting admitted to ward were included in the study. Patients admitted with HE, which was precipitated by active Spontaneous Bacterial Peritonitis (SBP), a potassium level of < 2.5 mmol/l, or intercurrent infection, gastrointestinal hemorrhage, constipation and electrolyte imbalance due to diuretic use were enrolled once these conditions were corrected. It was made sure, however, that this episode leading to admission was at least the second episode of HE with Conn score ≥ 2 in the past 6 months. Those patients who had known hypersensitivity to rifamycin and its products, a calcium level > 10 mg/dl, hepatocellular carcinoma and comorbidities such as chronic kidney disease, respiratory insufficiency and cerebrovascular injury were excluded. Patients were counseled regarding the study and its implications and an informed consent was taken for participation in the study.

History and clinical examination were carried out when patient was screened for enrollment. Previous history of HE was assessed clinically with use of Conn score (score 0: no abnormality detected; score 1: trivial lack of awareness or shortened attention span; score 2: lethargy, apathy, disorientation; score 3: somnolence, stupor, confusion; score 4: coma). MELD score was calculated.

Patients meeting inclusion criteria were randomly allocated in a 1:1 ratio to either treatment group (Rifaximin 550 mg) or placebo (Placebo group) group. Each pack specially prepared on request by the pharmaceutical company (Brooke's Pharmaceuticals) was labeled with the name of XIFAXA, coded either A or B and it was clearly mentioned on each pack that the manufactured drug was part of the randomized control trial. At the end of the trial and after statistical analysis, the company was requested to break the code. According to the decoded information, packs labeled 'A' contained placebo and those labeled 'B' contained Rifaximin. The product Rifaximin and Placebo were of the same size, shape and colour with similar packing. Rifaximin and Placebo were manufactured by Brooke's Pharmaceuticals on special request. An honorarium was paid by Brooke's Pharmaceuticals to the Principal Investigator. None of the authors hold any financial interest in Brooke's Pharmaceuticals nor were provided with any kind of remuneration by the aforementioned company.

Patients were requested to take the drug orally twice daily for 6 months or until they developed a break-through episode of hepatic encephalopathy or had to discontinue the drug due to some other reason. Breakthrough episode of HE was defined as Conn score ≥ 2 precipitated by progression of disease, constipation or electrolyte imbalance. All enrolled patients and their care givers were told about the potential side effects of Rifaximin and were advised to get in touch with the investigator if any new symptoms developed while on study drug. Patients developing adverse events including intercurrent infections such as pneumonia, bacterial peritonitis or variceal hemorrhage leading to HE were asked to withdraw the study drug. Concomitant administration of lactulose was permitted during the study. The patients, the investigator and the statistician did not know which patients were receiving Rifaximin and which were being given placebo.

After screening and randomization, patients were required to visit Gastroenterology-Hepatology Outdoor on day 7 and 14 and 2 weeks thereafter through 168 days. Telephonic monitoring was carried out during the weeks without visits to outpatient department. Safety assessments were carried out on each visit in particular infections, including infections of respiratory and gastrointestinal tract. Assessment of response to therapy on day 0 and on subsequent visits was done by Conn score. The information was collected through a specifically designed proforma.

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 20. Mean and SD was calculated for quantitative variables. i.e. age and MELD scores. Frequency and percentages were calculated for qualitative variables i.e. gender, number of episodes of encephalopathy in the past, and number of patients who were prevented from an episode of encephalopathy during trial. Stratification was done to control effect modifiers like age, sex, range of MELD, and number of episodes of encephalopathy in the past. Chi-square test and t-test were applied where required to determine the significant difference between the two groups.

Safety data was summarized using descriptive statisitics. These included adverse events and deaths.

RESULTS

A total of 126 patients were randomly assigned to receive the study drug. Majority of patients had cirrhosis due to chronic hepatitis C. Baseline characteristics were similar. A greater number of patients fell in the age group of 41-69 years and gender distribution in both groups was similar. More patients had MELD score range of 11 - 20 in both groups (Table I).

All enrolled patients received at least one dose of study drug and underwent at least one safety assessment after enrollment. The study medicine was stopped at the time of first breakthrough episode of HE or if the patient developed an adverse event or died. All patients continued to use lactulose concomitantly with the study medicine. Patients were also allowed to use medicines such as Proton Pump Inhibitors, promotility agent, calcium and vitamin D preparations. Patients with cirrhosis are expected to commonly use these medicines. All except 3 patients in each group were not on diuretics due to absence of ascites. There were,

however, incidences of self-medication with metronidazole and ciprofloxacin/levofloxacin for uninvestigated episodes of either diarrhea, abdominal pain or cough productive of sputum by 4 patients in treatment group and 10 patients in Placebo group. All enrolled patients were compliant with the use of study drug and the follow-up visits to gastroenterology outdoor except for one patient in each group who was lost to follow-up. Breakthrough episodes were reported in 16 of 63 patients in treatment group and 14 of the 63 patients in placebo group. The difference turned out to be insignificant with a p-value of 0.203 (Table III).

Most common cause of HE in both groups was progression of disease (Table IV). These 6 patients in each group were investigated for all known precipitating causes of hepatic encephalopathy and none were found. An average rise of MELD score by 10 in Control group and 6 in Treatment group was noted when these patients presented with PSE during the study.

The incidence of adverse events reported during the study was similar in both groups. Study drug was discontinued once adverse events were reported. Most adverse events were either due to progression of disease or complications of cirrhosis and were managed along lines of prescribed standard of care (Table IV). The symptoms of nausea/vomiting, generalized weakness or sore throat and fatigue resolved once study drug was discontinued. The patient in Treatment group who developed abdominal pain was investigated for SBP and no such evidence was found on ascitic fluid analysis. Abdominal pain resolved on discontinuation of study

Table I: Basic demographics.

	Control group (n=63)	Treatment group (n=63)
Age (in years)		
< 65	48	53
≥ 65	15	10
mean ± sd	40.21 ± 2.33	42.87 ± 4.54
Gender		
Male	29 (46.03%)	31 (49.21%)
Female	34 (53.97%)	32 (50.79%)
Range of MELD score		
0-10	5 (7.94%)	2 (3.17%)
11-20	35 (55.55%)	34 (53.97%)
21-25	23 (36.51%)	27 (42.86%)
mean±sd	16.34 ± 2.87	15.45 ± 3.45
Number of episodes of encephalopathy in the past		
2 episodes	25 (39.68)	30 (47.62%)
> 2 episodes	38 (60.32%)	33 (52.38%)
Etiology of cirrhosis		
Hepatitis C	50 (79.37%)	54 (85.71%)
Hepatitis B	10 (15.87%)	6 (9.52%)
Ethanol	2 (3.17%)	2 (3.17%)
Others	1 (1.59%)	1 (1.59%)

MELD = Model for End stage Liver Disease.

Table II: Subgroup analysis of patients free of PSE during trial.

	Control group (40)	Treatment group (35)	p-value
Age (in years)			
< 65	32 (80%)	30 (85.71%)	0.514
≥ 65	8 (20%)	5 (14.29%)	
Gender			
Male	19 (47.5%)	19 (54.29%)	0.557
Female	21 (52.5%)	16 (45.71%)	
Range of MELD score			
0-10	5 (12.5%)	2 (5.71%)	0.389
11-20	33 (82.5%)	29 (82.86%)	
21-25	2 (5%)	4 (11.43%)	
Number of episodes of encephalopathy in the past			
2	17 (42.5%)	22 (62.86%)	0.078
> 2	23 (57.5%)	13 (37.14%)	

Table III:

SBP = Spontaneous Bacterial Peritonitis; HRS = Hepato Renal Syndrome; PSE = Portosystemic encephalopathy.

drug. The patient in Treatment group who died of acute on chronic hepatitis had a baseline bilirubin of 2.0 mg/dl which rose to 24 mg/dl and MELD rose from 17 to 35. He had alcohol related cirrhosis but had not been compliant with abstinence that was advised to him. The patient in Control group who developed acute on chronic hepatitis leading to PSE also had cirrhosis secondary to alcohol intake and the acute episode was precipitated by binge drinking. His bilirubin rose from 1.8 mg/dl to 20.0 mg/dl and MELD from 16 to 30. He was asked to discontinue the study medicine and was managed on lines of prescribed standard of care.

There were 14 deaths during the study. Seven patients died in Treatment group and 7 in Placebo group. Most of the deaths were related either to progression of disease or secondary to infection (Table IV). All patients had at baseline, apart from hepatic encephalopathy, one or more of an evidence of decompensated cirrhosis i.e. ascites, edema or history of variceal bleed.

DISCUSSION

The prevention of episodes of HE is an important goal in the management of decompensated cirrhosis since symptoms of HE are associated with decreased ability to take care of activities of daily living,[1] poor nutrition, frequent hospitalizations which put a financial burden on the family and a poor quality of life. This study showed that the use of Rifaximin failed to reduce the risk of a breakthrough episode of hepatic encephalopathy during a 6 months period among patients in remission who had a recent history of recurrent overt HE (≥ 2 episodes within previous 6 months) before enrollment. These findings are in contrast to the multicentre trial published by Bass *et al*. which showed a 58% relative reduction in risk of breakthrough HE.[7] This difference is due to a number of factors, one of which could be the etiology leading to cirrhosis. A greater number of patients in the trial mentioned above were suffering from alcohol induced cirrhosis, an etiology more common in the west than in our part of the world. Patients enrolled in this study had cirrhosis secondary to viral hepatitis mostly hepatitis C followed by hepatitis B as the next most common cause.

The current study also differs from previous randomized studies,[7,11,12] in that it was conducted on an equal number of men and women, all of whom belonged to the same ethnic background. Whereas in the trial conducted by Bass *et al*. not only were the patients predominantly male they were from diverse backgrounds including those in Russia, Canada as well as in the US and the trial was conducted at 70 investigative sites.[7] Thus, the difference in response could be because of the difference in the patients' population of gut microflora. The gut flora changes with genetic makeup, diet and environmental factors.[10] Hence, the composition of gut flora varies from one ethnic group to the other. It is a possibility that Rifaximin as an oral antimicrobial agent failed to act on the gut microflora in the study population. It has also been discovered that there was a trend towards greater treatment effect of Rifaximin with the highest dose of 2400 mg per day.[12] A higher dose of 1600 mg per day was required for treatment of small intestinal bacterial overgrowth.[13] It is a possibility that a higher dose would be more efficacious for this population. Further studies need to be carried out to define the gut flora in Pakistani population and to define the dose of Rifaximin that would act upon these.

In addition, poor immune response in cirrhotic patients combined with use of proton pump inhibitors either omeprazole or esomeprazole by all patients in the study lead to an increased susceptibility to sepsis from Secondary Bacterial Peritonitis, systemic infections like pneumonia and cellulitis. Sepsis is a known cause of HE and HE related mortality.[14-16] The development of infection precipitated HE, leading to death in some instances, and the role of Rifaximin was blunted.

In the study carried out by Bass *et al*.,[7] it has not been defined if patients with more severe disease, (higher MELD indicating more severe disease) had a higher incidence of development of HE while in this study it was shown that those patients who developed HE had higher MELD scores. In evaluating patients on Rifaximin maintenance therapy for HE, Neff *et al*. also found that Rifaximin is effective for the management of HE in patients with cirrhosis, particularly in populations with MELD scores ≤ 20.[17] The most common precipitating cause amongst patients in this study was progression of disease. Thus, Rifaximin failed to prevent HE in cirrhotics at high risk of its development. True, that several patients with treatable precipitating cause of HE in the past 6 months were enrolled at the beginning of the study, but they were enrolled only after these factors were corrected. This study clearly delineates the precipitating cause of HE while patients were on study medicine, such information is lacking in previously carried out randomized control trial.[7,8]

Lactulose has been found to be effective in the prevention of overt HE.[18] In this study by Sharma *et al*.[18] 125 patients were enrolled. Out of those 125 patients, 19% patients in lactulose group developed episodes of HE in comparison to 46.8% in placebo group over 14 months. Since concomitant use of lactulose was allowed in both groups of patients, it can be postulated that it was lactulose that was responsible for prevention of episodes in patients who remained free of HE. A meta-analysis by Jiang *et al*. and review by Zullo concluded that Rifaximin is not superior to lactulose in treatment of chronic HE.[19,20] The studies by Bass *et al*. and Sharma and colleagues, however, do point towards the concept that modulation of gut flora is of value in treatment of

recurrent HE.[7,18,21] The failure of prevention of HE in patients in our trial highlights the need to bring about additional therapies that would change the composition of gut flora and probiotics and prebiotics combined with probiotics are showing promise in this regard.[22]

Self medication with metronidazole, levofloxacin and ciprofloxacin in 10 patients in the Control group during trial could have led to the sterilization of the gut thus preventing an episode of overt HE since these drugs are proven for treatment of HE albeit for short term only owing to potential systemic side effects.[23]

The incidence of adverse events in general and adverse events consisting of infection in particular were similar in the Rifaximin group and the placebo group. The medicine was found to be relatively safe with side effects disappearing as soon as the medicine was withdrawn, a finding similar to other randomized control trials carried out.[7,20]

CONCLUSION

This study did not find a protective effect of Rifaximin against recurrent episodes of hepatic encephalopathy in patients with cirrhosis over a 6 months period.

REFERENCES

1. Bajaj JS, Wade Jb, Gibson DP, Heuman DM, Thaker LR, Sterling RK, *et al*. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. *Am J Gastroenterol* 2011; **106**:1646-53.
2. Oneykwere CA, Ogbera AO, Hameed L. Chronic liver disease and hepatic encephalopathy: clinical profile and outcomes. *Niger J Clin Pract* 2011; **14**:181-5.
3. Zakaria M, Hussain SR. Hepatic encephalopathy; precipitating factors in patients with cirrhosis. *Professional Med J* 2008; **15**: 375-9.
4. Romero-Gomez M, Jover M, Galan JJ, Ruiz A. Gut ammonia production and its modulation. *Metab Brain Dis* 2009; **24**: 147-57.
5. Mullen KD, Prakash RK. Management of covert encephalopathy. *Clin Liver Dis* 2012; **16**:91-3.
6. Phongsamran PV, Kim JW, Cupo Abbott J, Rosenblatt A. Pharmacotherapy for hepatic encephalopathy. *Drugs* 2010; **70**: 1131-48.
7. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010 25; **362**:1071-81.
8. Wiegannd J, Berg T. The etiology, diagnosis and prevention of liver cirrhosis. Part 1 of a case series on liver cirrhosis. *Dtsch Arztebl Int* 2013; **6**:85-91.
9. Almani SA, Memon AS, Memon AI, Shah I, Rahpoto Q, Solangi R. Cirrhosis of liver: etiological factors, complications and prognosis. *J Liaquat Uni Med Health Sci* 2008; **7**:61-6.
10. Marathe N, Shetty S, Lanjekar V, Ranade D, Shouche Y. Changes in human gut flora with age: an Indian familial study. *BMC Microbiol* 2012; **12**:222.
11. Festi D, Mazzella G, Orsini M, Sottili S, Sangermano A, LiBassi S. Rifaximin in the treatment of chronic hepatic encephalopathy; results of a multicenter study of efficacy and safety. *Curr Therapeut Res* 1993; **54**:598-609.
12. William R, James OF, Warnes TW, Morgan MY. Evaluation of the efficacy and safety of Rifaximin in the treatment of hepatic encephalopathy: a double blind, randomized, dose-finding multi centre study. *Eur J Gastroenterol Hepatol* 2000; **12**:203-8.
13. Scarpellini E, Gabrielli M, Lauritano CE, Lupascu A, Merra G, Cammarota G, *et al*. High dosage Rifaximin for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2007; **25**:781-6.
14. Shawcross DL, Sharifi Y, Canavan JB, Yeoman AD, Abeles RD, Taylor NJ. Infection and systemic inflammation, not ammonia, are associated with grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. *J Hepatol* 2011; **54**:640-9.
15. Cazzaniga M, Dionigi E, Gobbo G, Fioretti A, Monti V, Salerno F. The systemic inflammatory response syndrome in cirrhotic patients: relationship with their in-hospital outcome. *J Hepatol* 2009; **51**:475-82.
16. Mumtaz K, Ahmad US, Abid S, Baig N, Hamid S, Jafri W. Precipitating factors and the outcome of hepatic encephalopathy in liver cirrhosis. *J Coll Physicians Surg Pak* 2010; **20**:514-8.
17. Neff GW, Jones M, Broda T, Jonas M, Ravi R, Novick D, *et al*. Durability of Rifaximin response in hepatic encephalopathy. *J Clin Gastroenterol* 2012; **46**:168-71.
18. Sharma BC, Sharma P, Agrawal A, Sarin SK. Secondary prophylaxis of hepatic encephalopathy: an open label randomized controlled trial of lactulose versus placebo. *Gastroenterology* 2009; **137**:885-91.
19. Jiang Q, Jiang XH, Zheng MH, Jiang LM, Chen YP, Wang L. Rifaximin versus non absorbable disaccharides in the management of hepatic encephalopathy: a meta analysis. *Eur J Gastroenterol Hepatol* 20S08; **20**:1064-70.
20. Zullo A, Hassan C, Ridola L, Lorenzetti R, Salvatore MA, Riggio O. Rifaximin therapy and hepatic encephalopathy: Pros and cons. *World J Gastrointest Pharamcol Ther* 2012; **3**:62-7.
21. Stephen M, Riordan MD, Williams R. Gut flora and hepatic encephalopathy in patients with cirrhosis. *N Engl J Med* 2010; **362**:1140-2.
22. Malaguarnera M, Gargante MP, Malaguarnera G, Salmeri M, Mastrojeni S, Rampello L, *et al*. Bifidobacterium combined with fructo-oligosaccharide versus lactulose in the treatment of patients with hepatic encephalopathy. *Eur J Gastroenterol Hepatol* 2010; **22**:199-206.
23. Al Sibae MR, Mcguire BM. Current trends in the treatment of hepatic encephalopathy. *Ther Clin Risk Manag* 2009; **5**:617-26.