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ORIGINAL ARTICLE

Daily Ciprofloxacin Treatment for Patients with Advanced Liver Disease Awaiting Liver Transplantation Reduces Hospitalizations

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Abstract
Background Progressive deterioration in liver function is a common cause of hepatic decompensation and indication for liver transplantation in patients with advanced liver disease. Previous studies in animal models of acute and chronic liver disease revealed that daily ciprofloxacin improves biochemical parameters of hepatic function.
Aims The primary objective of this study was to determine whether hepatic function improves in patients with advanced liver disease after 1 month of daily ciprofloxacin therapy. A secondary objective was to determine whether ciprofloxacin treatment for 1 or 3 months results in fewer hospitalizations for decompensated liver disease.
Methods Forty-four patients with advanced liver disease awaiting liver transplantation received oral ciprofloxacin (250 or 500 mg twice daily) or placebo for 1 ($n = 22$/group) or 3 ($n = 10$ ciprofloxacin, 14 placebo) months.
Results Compared to placebo recipients, ciprofloxacin-treated patients had mild improvements in serum albumin levels (+1.5 versus −3.4%, $p = 0.026$) while bilirubin and international normalized ratios (INR) of prothrombin times remained unchanged. Overall, fewer hospitalizations occurred in ciprofloxacin-treated patients (1/22, 5% versus 7/22, 32%, respectively, $p = 0.02$) during the study period. Treatment was well tolerated and no resistant infections occurred in either cohort.
Conclusions The results of this study suggest that daily ciprofloxacin may result in fewer hospitalizations for patients with advanced liver diseases awaiting liver transplantation but not by enhancing hepatic function.

Keywords Decompensated cirrhosis · Fluoroquinolones · Ciprofloxacin · Hepatic encephalopathy · Portal hypertension · Liver function

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Introduction

Advanced liver disease is the eighth most common cause of death from disease globally [1]. Although numerous therapeutic options have been developed for treating the complications of liver failure, these treatments have no effect on the underlying liver disease and have not been shown to favorably alter survival [2–4]. As a result, liver transplantation remains the only effective therapy for patients with end-stage liver disease. Unfortunately, donor organs are limited and deaths from liver failure in patients awaiting liver transplantation are common. Therapeutic agents that attenuate or stabilize the rate of hepatic dysfunction or perhaps improve the functional capacity of the liver would be expected to improve morbidity and mortality rates in transplant candidates and, ideally, obviate the need for transplantation in some individuals.

Our laboratory recently described the role of fluoroquinolone antibiotics as a treatment for various forms of liver failure. Results indicated that these agents (and ciprofloxacin in particular) are of therapeutic benefit in animal models of fulminant hepatic failure, acute and chronic liver disease, and cirrhosis [5–7]. While the mechanism(s) of

action has yet to be elucidated, data suggest that in the setting of advanced liver disease, fluoroquinolones stimulate hepatic regeneration, perhaps by interfering with gamma aminobutyric acid (GABA) receptor activity [8, 9]. Based on these findings, and the fact that ciprofloxacin is commercially available and often used as antimicrobial prophylaxis for patients with decompensated liver disease [10], we documented the outcome of daily treatment with oral ciprofloxacin for 1 or 3 months in patients being considered or listed for liver transplantation at our center.

Materials and Methods

This was a prospective, randomized, double-blind, placebo-controlled, single-center trial approved by the University of Manitoba Conjoint Ethics Committee for Human Experimentation.

Candidates were identified for the study as a result of their being followed in or referred to the Section of Hepatology's Outpatient Liver Transplant Evaluation Clinic at the Health Sciences Centre in Winnipeg, Canada. Inclusion criteria included: patients 18 years of age or older with clinical, biochemical and/or radiological evidence of decompensated liver disease (defined as persistent jaundice, ascites, history of portal hypertensive bleeding and/or hepatic encephalopathy), and at least two of the following laboratory abnormalities: serum bilirubin level greater than 50 μmol/l, albumin less than 30 gm/l or International Normalized Ratio (INR) of prothrombin times greater than or equal to 1.3. Patients were excluded if they were receiving at the time of evaluation or had received within the previous 6 weeks daily fluoroquinolone antibiotics, a history of allergy to fluoroquinolone antibiotics or seizure disorders, a sedative, hypnotic or centrally acting analgesic, a presentation in keeping with acute on chronic liver disease, fulminant hepatic failure, renal failure (serum creatine $>$ 300 μmol/l), or were unwilling to participate in the trial.

Estimates of the study population size were based on results of previous animal studies in which a 25–35% improvement in liver biochemistry and regenerative activity was achieved with fluoroquinolone treatment. Thus, assigning a P1 of 0.05, P2: 0.3, two-tailed alpha: 0.05, and beta $=$ 0.2, a sample size of 50 patients (25 per group) was estimated to address the principal outcome measure; changes in liver function at 1 month.

After obtaining informed, written consent, patients were randomized by sealed envelope to receive either 1 or 3 months of oral ciprofloxacin at a dose of 250 or 500 mg ($<$ or $>$75 kg weight, respectively) or placebo twice daily. The primary endpoint was differences in biochemical parameters of hepatic function (albumin, INR and bilirubin) at 1 month. The secondary endpoint was hospitalizations after 3 months of therapy. This end point was developed in order to determine whether changes in liver function tests resulted in altered clinical outcomes. Treatment was continued until the earlier of; 1 or 3 months of treatment as per randomization, liver transplantation, or death. Complications of liver failure such as hepatic encephalopathy, ascites, variceal bleeds, etc., were treated as required. Patients with documented or suspected sepsis and those hospitalized for portal hypertensive bleeding received non-fluoroquinolone antibiotics if antibiotics were deemed necessary. Decisions regarding hospitalizations were made by hospital-based emergency physicians not involved in the study.

Complete blood cell counts, liver enzyme and function tests, and number connection tests were obtained at the initial visit and monthly thereafter until the patient exited from the study. Serum hemoglobin levels were censored in patients with gastrointestinal bleeding that required blood transfusions. Number connection testing was performed as described previously [11]. All hematologic and biochemical testing was performed by standard laboratory techniques in the Clinical Hematology and Chemistry Laboratories at the Health Sciences Centre.

A Yates correction of the x-squared test was used to assess the distribution of discreet variables between the ciprofloxacin and placebo-treated study groups. Continuous variables were compared by independent *t* tests. The mean value of test results obtained 1 month prior to and on the first day of treatment were considered baseline values and expressed as 100%. All consecutive measurements were calculated as the percent change compared to the baseline value of 100%. Changes in laboratory values over time were compared using repeated measures ANOVA.

Results

Patient Randomization, Demographics, and Disease Profiles

Forty-nine patients were enrolled in the study. Five reversed their decision and withdrew prior to treatment. Two of the withdrawals had been assigned to receive ciprofloxacin and three placebo.

Of the remaining 44 patients, 20 (45%) were randomized to 1 month and 24 (55%) to 3 months of treatment. Among those randomized to 1 month of treatment, 12/20 (60%) were to receive ciprofloxacin and 8/20 (40%) placebo. Of those randomized to 3 months, 10/24 (42%) were to receive ciprofloxacin and 14/24 (58%) placebo. The mean (±SD) ages and gender distributions of the study cohorts are provided in Table 1.

Table 1 Demographic characteristics, underlying causes of liver disease, and Child-Pugh score of the patient population

	1 month		3 months		Totals	
	Ciprofloxacin ($n = 12$)	Placebo ($n = 8$)	Ciprofloxacin ($n = 10$)	Placebo ($n = 14$)	Ciprofloxacin ($n = 22$)	Placebo ($n = 22$)
Age (years) ± SD	47.6 ± 6.4	55.1 ± 10.0	56.9 ± 8.9	55.9 ± 18.3	51.8 ± 8.9	55.6 ± 15.6
Male/Female	9/3	6/2	4/6	10/4	13/9	16/6
Hepatitis C	6 (50%)	6 (75%)	5 (50%)	1 (7%)	11 (50%)	7 (32%)
Alcoholic cirrhosis	4 (33%)	1 (12.5%)	1 (10%)	2 (14%)	5 (23%)	3 (14%)
Cryptogenic cirrhosis	1 (8%)	0 (0%)	1 (10%)	3 (21%)	2 (9%)	3 (14%)
Other[a]	1 (8%)	1 (12.5%)	3 (30%)	8 (58%)	4 (18%)	9 (41%)
CPS-A	3 (25%)	4 (50%)	0 (0%)	1 (7%)	3 (14%)	5 (23%)
CPS-B	5 (42%)	2 (25%)	7 (70%)	8 (57%)	12 (55%)	10 (46%)
CPS-C	4 (33%)	2 (25%)	3 (30%)	5 (36%)	7 (32%)	7 (32%)

Abbreviations: *CPS*, Child-Pugh score

[a] Other conditions include primary biliary cirrhosis ($n = 4$), primary sclerosing cholangitis ($n = 4$), autoimmune hepatitis ($n = 2$), hepatitis B ($n = 2$), and nonalcoholic steatohepatitis ($n = 1$)

The underlying causes of liver disease are also shown in Table 1. Hepatitis C was the principal etiology in 41% of patients while alcohol-induced liver disease accounted for 18%, and cryptogenic cirrhosis 11%. Other disorders constituted less than 10% of the total. They included primary biliary cirrhosis ($n = 4$: 1 ciprofloxacin/3 placebo), primary sclerosing cholangitis ($n = 4$: 1 ciprofloxacin/3 placebo), autoimmune hepatitis ($n = 2$: 1 ciprofloxacin/1 placebo), hepatitis B ($n = 2$: 2 placebo) and nonalcoholic steatohepatitis ($n = 1$: 1 ciprofloxacin). The differences in distributions of liver disease between ciprofloxacin and placebo-treated groups were not significant.

Child-Pugh scores (CPS) at baseline were as follows: 8/44 (18%) CPS-A, 22/44 (50%) CPS-B and 14/44 (32%) CPS-C (Table 1). Once again, the distributions of CPS were similar for ciprofloxacin and placebo recipients.

Laboratory Results

One-Month Cohorts

Changes in liver function tests (albumin, INR, and bilirubin) after 1 month of treatment are shown in Table 2. Serum albumin levels increased by 1.5% in ciprofloxacin-treated patients while decreasing 3.4% in placebo recipients ($p = 0.032$). This difference could not be explained on the basis of exogenous albumin administered during large-volume paracentesis as only two patients from the ciprofloxacin and three from the placebo cohorts underwent such paracentesis during the 1-month period and similar amounts of albumin were administered (2.0 versus 2.2 units/patient, respectively). INR levels deteriorated to a lesser extent in ciprofloxacin-treated patients but the difference was not significant (ciprofloxacin: +0.8% versus placebo: +3.2%, $p = 0.213$). Also, not reaching statistical significance were serum bilirubin levels, which declined by 1.5% in ciprofloxacin and 3.4% in placebo recipients ($p = 0.762$).

As shown in Table 3, blood hemoglobin levels decreased by 0.2% in ciprofloxacin and 4.4% in placebo-treated patients ($p = 0.031$). Changes in white blood cell and platelet counts, liver enzymes, and creatinine levels were similar in the two groups. Although there was a trend towards higher serum AST values (+7.9 versus −6.6%) and lower creatinine levels (−1.2 versus +14.7%) in ciprofloxacin-treated patients, the differences did not reach statistical significance when compared to placebo recipients ($p = 0.18$ and 0.132, respectively).

Number connection test results improved by 8.6% in ciprofloxacin-treated patients while remaining essentially unaltered (+0.1%) in placebo recipients ($p = 0.329$).

Three-Month Cohorts

The improvement in serum albumin and the trend towards improved INR values seen after 1 month of treatment in ciprofloxacin recipients were maintained after 2 and 3 months of treatment (Fig. 1a, b). However, in the case of albumin, the differences were no longer significant at either subsequent time interval. Serum bilirubin levels continued to improve to a greater extent in placebo recipients, but again, the differences were not significant (Fig. 1c). It should be noted, however, that the number of subjects was small and the study not powered to document significant changes in liver function at these time intervals.

Changes in blood cell counts, liver enzymes, and creatinine levels were also similar at 2 and 3 months in the 3-month ciprofloxacin and placebo-treated cohorts (data

Table 2 Changes from baseline in liver function test results after 1 month of treatment with ciprofloxacin or placebo

	Ciprofloxacin ($n = 22$)			Placebo ($n = 22$)			p*
	Baseline	After 1 month of Tx		Baseline	After 1 month of Tx		
TEST	Mean ± SE	Mean ± SE	% change*	Mean ± SE	Mean ± SE	% change*	
Albumin	30.0 ± 1.2	30.5 ± 1.1	1.5	29.7 ± 1.4	28.7 ± 1.5	−3.4	0.032
INR	1.31 ± 0.05	1.32 ± 0.07	0.8	1.27 ± 0.07	1.31 ± 0.08	3.2	0.213
Bilirubin	46.1 ± 9.6	45.4 ± 12.3	−1.5	35.0 ± 7.1	33.8 ± 6.6	−3.4	0.762

* p value for the differences in the % change between ciprofloxacin vs. placebo-treated groups

Abbreviations: *n*, number of subjects; *SD*, standard deviation; *INR*, international normalized ratio of prothrombin times

Table 3 Changes from baseline in laboratory and NCT results after 1 month of treatment with ciprofloxacin or placebo

	Ciprofloxacin ($n = 22$)			Placebo ($n = 22$)			p*
	Baseline	After 1 month of Tx		Baseline	After 1 month of Tx		
TEST	Mean ± SE	Mean ± SE	% change*	Mean ± SE	Mean ± SE	% change*	
HGB*	128.3 ± 3.9	128.0 ± 3.7	−0.2	124.2 ± 4.8	118.7 ± 5.3	−4.4	0.031
WBC	4.61 ± 0.3	4.55 ± 0.3	−1.2	5.12 ± 0.4	4.77 ± 0.5	−6.8	0.247
Platelets	89.3 ± 10.0	86.0 ± 7.9	−3.7	117.5 ± 14.4	114.6 ± 16.9	−2.5	0.885
ALT	71.8 ± 15.7	69.1 ± 11.0	−3.7	47.3 ± 5.8	45.8 ± 4.0	−3.1	0.705
AST	89.0 ± 16.1	96.0 ± 13.8	7.9	65.7 ± 7.6	61.4 ± 8.6	−6.6	0.18
Alk. Phos.	176.9 ± 28.0	179.2 ± 30.3	1.3	188.3 ± 19.9	193.0 ± 21.7	2.5	0.613
GGT	84.4 ± 17.8	81.4 ± 15.5	−3.6	153.4 ± 50.0	149.7 ± 40.2	−2.4	0.454
Creatinine	64.9 ± 4.4	64.1 ± 6.8	−1.2	84.9 ± 8.3	97.4 ± 17.4	14.7	0.132
NCT	42.6 ± 4.5	38.9 ± 3.9	−8.6	50.0 ± 8.2	50.1 ± 6.6	0.1	0.329

* p value for the differences in the % change between ciprofloxacin vs. placebo-treated groups

Abbreviations: *n*, number of subjects; *SD*, standard deviation; *HGB*, hemoglobin; *WBC*, white blood cell count; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *Alk. Phos.*, alkaline phosphatase; *GGT*, gamma glutamyltransferase; *INR*, international normalized ratio of prothrombin times; *NCT*, number connection test

not shown). The trend towards improvement in the number connection test results observed in ciprofloxacin-treated patients at 1 month was more apparent at 3 months (ciprofloxacin: −15.8% versus placebo: −3.5%) but once again, failed to reach statistical significance ($p = 0.095$, Fig. 1d).

Hospitalizations

In patients randomized to 1 month of treatment, 1/12 (8%) receiving ciprofloxacin required hospitalization for complications of cirrhosis compared to 1/8 (13%) receiving placebo. In patients randomized to 3 months of treatment, 0/10 ciprofloxacin-treated patients required hospitalization compared to 6/14 (43%) who received placebo ($p = 0.023$). Thus, overall, 1/22 (5%) ciprofloxacin and 7/22 (32%) placebo required hospitalization for decompensated liver disease during the course of the study ($p = 0.02$).

The reasons for hospitalization are provided in Table 4. The one hospitalization in ciprofloxacin-treated patients was for hepatic failure while the majority of hospitalizations in placebo recipients (4/7) were for hepatic encephalopathy. In two of the four encephalopathic patients, the encephalopathy was thought to be precipitated by dehydration, while constipation and "spontaneous encephalopathy" were implicated in the remaining to subjects respectively.

There were no episodes of sepsis, new musculoskeletal complaints, liver transplantations, or deaths in either cohort during the subjects' 1 or 3 month study involvement.

Drug Tolerance

One patient randomized to 1 month of treatment with ciprofloxacin received twice daily treatment for 1 week, then reduced the dose to once daily for the remaining 3 weeks as a result of excessive nausea. Otherwise, no dose adjustments were required in the ciprofloxacin- or placebo-treated patients. Of note, there were no episodes of antibiotic-resistant infections or new musculoskeletal complaints in either cohort.

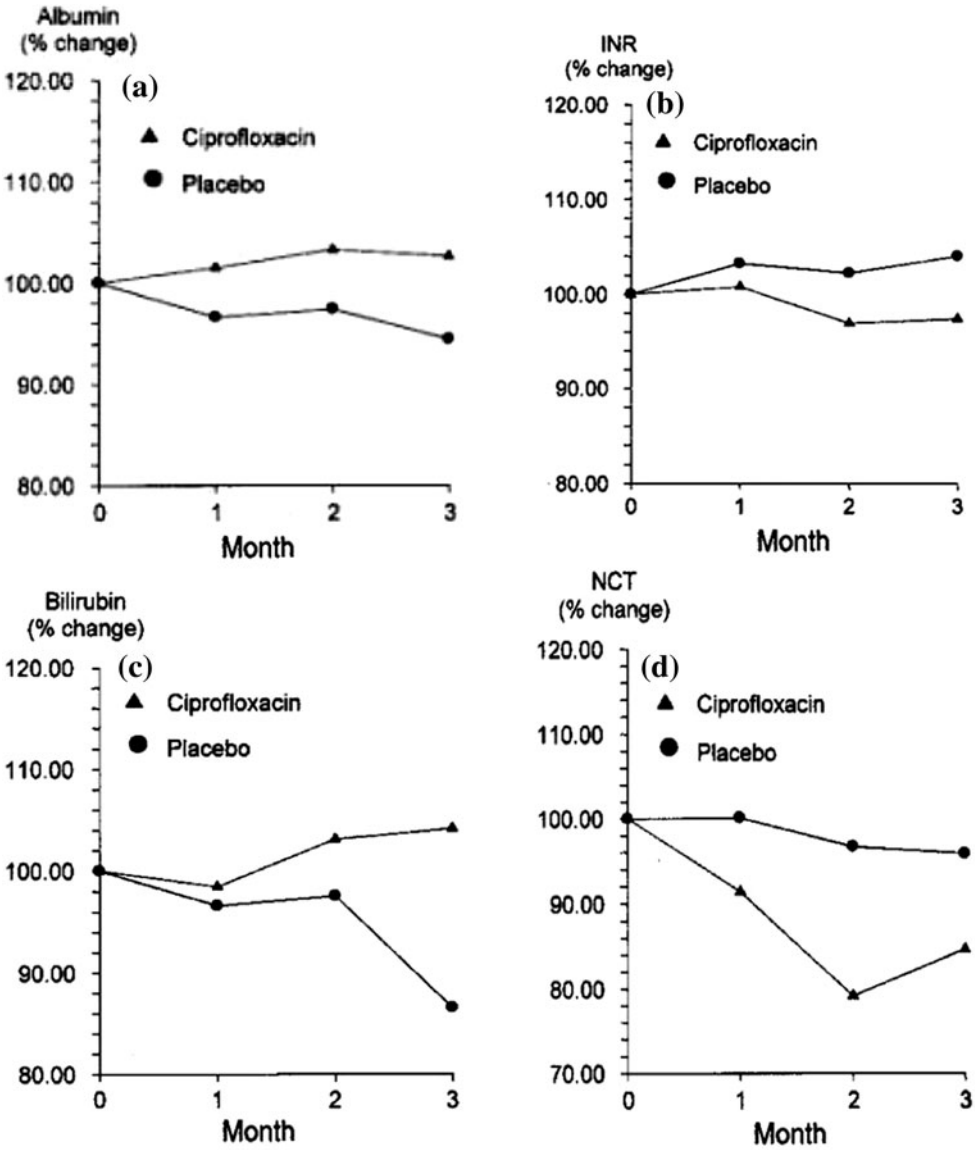

Fig. 1 Percent changes from baseline (T = 0) in serum levels of albumin (**a**), INR (**b**), bilirubin (**c**), and number connection test results (**d**) in patients randomized to 3 months of treatment with ciprofloxacin or placebo. The results provided represent findings in ten ciprofloxacin and 14 placebo recipients

Table 4 Indications for hospital admissions in patients randomized to receive 1 or 3 months of treatment with ciprofloxacin or placebo

Treatment	Indication for hospitalization	Age (years)	Sex	Diagnosis	CPS
1 month					
Ciprofloxacin	Jaundice, ascites, edema, encephalopathy	59	M	Alcohol	C
Placebo	Abdominal pain	54	M	HCV	A
3 months					
Placebo	Portal hypertensive bleed	27	M	PSC	B
Placebo	Portal hypertensive bleed	65	F	PBC	C
Placebo	Encephalopathy	70	M	Cryptogenic	C
Placebo	Encephalopathy	72	F	PBC	B
Placebo	Encephalopathy	75	M	PBC	C
Placebo	Encephalopathy	76	M	PSC	B

Abbreviations: *CPS*, Child-Pugh score; *HCV*, hepatitis C virus; *PSC*, primary sclerosing cholangitis; *PBC*, primary biliary cirrhosis

Discussion

In the absence of nutritional, gastrointestinal, renal and hematologic disorders, serum albumin, INR and bilirubin values serve as useful surrogate markers of hepatic function [12, 13]. In the present study, compared to placebo recipients, significant improvements in serum albumin levels were observed after 1 month in ciprofloxacin-treated patients but the improvements were limited (Δ 4.9%) and not accompanied by significant changes in INR or bilirubin levels. Thus, it is unlikely that daily ciprofloxacin therapy results in clinically relevant improvements in hepatic function in patients with advanced liver disease.

Why ciprofloxacin was less effective in humans than rodents with advanced liver disease remains to be determined. In our previous animal studies, enhanced hepatic regeneration was thought to be responsible for the beneficial effects on hepatic function [5–7]. Unfortunately, sensitive and specific non-invasive markers of hepatic regenerative activity are not presently available and percutaneous liver biopsies are generally contraindicated in patients with advanced liver disease with coagulopathies and/or tense ascites. Thus, whether hepatic regeneration was enhanced in the ciprofloxacin-treated patients enrolled in the present study remains unclear. Perhaps also relevant to the discrepancy in findings was the trend towards higher serum AST values in ciprofloxacin-treated patients (which may reflect increased hepatic oxidative stress with these agents) that was not reported in previous animal studies [14]. Also to be considered are data indicating that enteric flora produce cytokines and growth regulators that effect hepatic regeneration and function [15–17]. Whether ciprofloxacin alters rodent but not human enteric flora in a manner that results in improved hepatic function in one species but not the other requires further study. Finally, the previously studied animal models required ongoing inflammation of the liver to maintain the cirrhotic state whereas cirrhosis in humans tends to be more quiescent with thick fibrous septa that together, would render the liver less responsive to a regenerative stimulus.

Embedded within the primary study design was a pilot study wherein hospitalization rates for patients with decompensated liver disease were compared in ciprofloxacin and placebo recipients after 1 and 3 months of therapy. The results revealed significantly fewer hospitalizations in ciprofloxacin-treated patients overall and after 3 months, but not after 1 month of therapy. This delayed benefit would be in keeping with the time required for hepatic regeneration to occur. However, as discussed previously, if enhanced hepatic regeneration was achieved, it was clearly not associated with meaningful improvements in hepatic function. This raises the possibility of improvements in clinical outcomes that are independent of hepatic function. For example, fluoroquinolones possess anti-GABA receptor activity, which could contribute to fewer cases of hepatic encephalopathy and direct improvements in cognitive function as suggested by the results of number connection tests [18]. Recent data documenting fewer episodes of hepatic encephalopathy and hospitalizations for patients with advanced liver disease randomized to 6 months of Rifaximin (versus placebo) raises the possibility of altered bowel flora being responsible for the same beneficial outcomes identified in our study [19]. Antibiotics also possess procoagulant activities and have been reported to decrease portal hypertension in the setting of cirrhosis, which in addition to contributing to fewer hospitalizations for portal hypertensive bleeding, could also explain the significant improvement in blood hemoglobin levels documented in ciprofloxacin recipients [20, 21]. Finally, although spontaneous bacterial peritonitis and hepatorenal syndrome did not occur in either study cohort during the 3-month study period, primary prophylaxis with fluoroquinolones significantly decrease the incidence of these complications in patients with advanced liver disease [22].

The main concerns associated with long-term daily administration of fluoroquinolone antibiotics to patients with cirrhosis are drug toxicity associated with altered pharmacokinetics and antimicrobial resistance. Recent studies in cirrhotic patients indicate that the pharmacokinetics of ciprofloxacin are essentially unaltered in cirrhosis [23]. Regarding resistance, when used at the same dose and schedule for longer periods of time (6–12 months) as prophylaxis against urinary tract infections, fluoroquinolones were well tolerated and clinically relevant changes in bacterial sensitivities were not detected [24, 25]. Nonetheless, because no attempts were made to document antimicrobial resistance in the present study, and because fluoroquinolone use has recently been associated with the emergence of hyper virulent strains of *C. difficile* [26], it seems prudent to limit the duration of fluoroquinolones administration in this setting to 1–3 months.

There are a number of limitations to this study that warrant emphasis. First, the number of subjects studied was small, and therefore the possibility of a type 1 (or type 2) error is strong. Thus, the finding of reduced hospitalizations in ciprofloxacin-treated subjects must be interpreted with caution. Future studies involving larger numbers of patients are required to address this and other important end points. Second, as mentioned previously, non-invasive parameters of hepatic regenerative activity are lacking, hence the mechanism of ciprofloxacin's effect remains unclear. Third, although number connection test results were used to monitor changes in cognitive function (rather than for diagnosing hepatic encephalopathy), its value for this purpose has yet to be established. Finally, whether

antimicrobial resistance subsequently became a problem in ciprofloxacin recipients was not ascertained.

In conclusion, the results of this pilot study are sufficiently encouraging to warrant further studies involving larger numbers of patients, different doses of ciprofloxacin, and longer periods of treatment. If the results of these studies are supportive, then long-term ciprofloxacin administration may serve to stabilize patients with advanced liver disease awaiting liver transplantation.

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