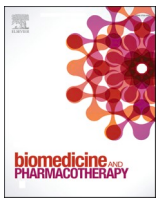
Biomedicine & Pharmacotherapy 168 (2023) 115712

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



Prolonged release pirfenidone pharmacokinetics is modified in cirrhosis GENESIS study

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ARTICLE INFO

Keywords:
Child-Pugh A and B cirrhosis
Pharmacokinetics
Prolonged-release pirfenidone
Antifibrotic
Liver fibrosis

ABSTRACT

Background: In both clinical and experimental trials, pirfenidone (PFD) showed anti-inflammatory and anti-fibrogenic effects. Considering the wide variation in hepatic functional reserve in patients with cirrhosis, we decided to learn more about the pharmacokinetics of a new formulation of prolonged release PFD in this population (PR-PFD), focusing on assessing changes on $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}.

Methods: In this study, 24 subjects with cirrhosis were included: eight subjects with mild liver impairment (Child–Pugh A) and eight with moderate liver impairment (Child–Pugh B), and a third group of eight age-matched subjects without fibrosis. All participants were under fasting conditions before receiving orally two 600-mg tablets of a prolonged-release formulation of pirfenidone (PR-PFD) and remained in the clinical unit for 36 h after PR-PFD administration. Serial blood samples were collected after dosing (0.5-36 h). A validated high-performance liquid chromatography–mass spectrometry method was used to determine PFD plasma concentrations.

Results: The exposure to PR-PFD was 3.6- and 4.4-fold greater in subjects with Child–Pugh A and Child–Pugh B than in subjects without cirrhosis, and Cmax was 1.6- and 1.8-fold greater in subjects with Child–Pugh B and Child–Pugh-A than in patients without cirrhosis, without significant differences between the two cirrhotic groups. PFD was well tolerated.

Conclusion: The pharmacokinetic parameters of PR-PFD are significantly modified in patients with cirrhosis compared with those in controls, indicating that liver impairment should be considered in clinical practice.

1. Introduction

Pirfenidone (PFD, 5-methyl-1-phenyl-2(1 H)-pyridone) is a small molecule, initially developed as an antihelminthic and antipyretic agent [1]. Presently, it is considered as standard of care for Idiopathic Pulmonary Fibrosis (IPF) treatment [2]. Organs on which PFD has been tested as an antifibrotic drug with promising results include the liver, heart, kidney, eyes, and skin, and it has been tested for the prevention and treatment of complex diseases and intestinal adhesion formation [3–6].

Abbreviations: ALD, alcoholic liver disease; AUC, area under the curve; FDA, food and drug administration; HCV, Hepatitis C virus; INR, international normalized ratio; IPF, idiopathic pulmonary fibrosis; IS, internal standard; LLOQ, lower limit of quantification; MS, mass spectrometer, PFD, pirfenidone, PR-PFD, prolonged release pirfenidone.

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https://doi.org/10.1016/j.biopha.2023.115712
Received 18 August 2023; Received in revised form 5 October 2023; Accepted 11 October 2023
Available online 21 October 2023

At a dose of 2400 mg/day, most studies have not reported significant toxicity attributable to the drug, confirming a good safety profile; nausea, photosensitivity and gastrointestinal problems are some of the side effects observed [7,8]. However, the US Food and Drug Administration (FDA) has expressed concerns about the use of PFD in patients with liver disease, particularly those with severe hepatic impairment (Child-Pugh class C) [9,10].

The metabolism of PFD involves several steps in the liver.[11] First, PFD is rapidly absorbed from the gastrointestinal tract after oral administration, and it undergoes extensive first-pass metabolism in the liver. It is primarily metabolized by cytochrome P450 (CYP) enzymes, particularly CYP1A2 and CYP2C9, to form several metabolites, including 5-carboxy-pirfenidone (5-CP), an inactive metabolite [11].

The metabolites of PFD are primarily eliminated in the urine, with only a small fraction eliminated in the feces [12]. The half-life of standard release PFD in the plasma is approximately 3–5 h, whereas that of 5-CP is longer, at approximately 11–13 h.[14,15] Several factors, such as age, sex, and genetic variations in CYP enzymes, can affect the metabolism of PFD. For example, it has been shown that CYP1A2 activity is lower in elderly individuals, which may lead to slower metabolism of PFD and a higher risk of adverse effects. Furthermore, CYP mediates major drug-metabolizing enzyme activity in the liver, and this activity is reduced in individuals with hepatic fibrosis [11].

In Mexico, PFD has been developed and introduced to the Mexican market as a prolonged-release formulation (PR-PFD) allowing administration every 12 h instead of the usual 8 h administration dosage for standard release-PFD.[16] However, presently, data on the pharmacokinetics of PR-PFD in patients with liver cirrhosis, a population showing extensive fibrotic damage to the liver, are nonexistent. Therefore, this study aimed to describe how the degree of liver function may affect the area under the curve (AUC) derived from the plasma concentration-time profile of the drug, comparing age- and sex-matched subjects without cirrhosis with patients with cirrhosis with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairments.

2. Methods

This was a study to evaluate the pharmacokinetics of PR-PFD of adult patients with chronic liver disease with confirmed advanced liver fibrosis (F4) of two degrees of liver function, either Child–Pugh A or B status, compared with those of healthy age-matched subjects without liver fibrosis according to noninvasive methods.

2.1. Patient selection

Forty-three adult patients were identified from the outpatient list of Clinica REMEDHE, an ambulatory liver clinic located in Mexico City, for study participation. The inclusion criteria were as follows: patients who had stable liver cirrhosis confirmed by fibrotest, a noninvasive method; those with liver function grade A (n = 15) or B (n = 14) according to the Child–Pugh classification; and those who could abstain from the use of proton pump inhibitors, antibiotics, tobacco, alcohol, caffeine, xanthine, theobromine, grape, grapefruit, and hisbiscus juices at least 48 h before and during the pharmacokinetic confinement evaluation. Fourteen subjects without liver disease with F0 according to fibrotest evaluation, matched in age and sex to the cirrhotic population, were also included. Patients with the following conditions were excluded: allergy to the study medication; use of nonsteroidal anti-inflammatory drugs, colchicine, silymarin, and known hepatotoxic drugs; Child–Pugh class C; active variceal hemorrhage; uncontrolled ascites; human immunodeficiency virus; malignancy; active sepsis; heart, lung, or kidney impairment; pregnancy; and alcohol or drug abuse in the past year. Stable-dose medications prescribed for chronic use in patients with cirrhosis, such as propranolol, adhesive gastric protection with sucralfate, drugs for hypertension, diabetes mellitus, or hypothyroidism; low-dose steroids (prednisone <10 mg/day); diuretics (e.g., spironolactone and furosemide); and vitamin and mineral intake were allowed until 12 h before pharmacokinetic confinement and reinstalled 8 h after study drug intake, as needed.

2.2. Study design and treatment regimens

This was a single-dose, open-label, three-group parallel design pharmacokinetic study conducted in compliance with the international standards of good clinical practices and procedures and the principles of the Declaration of Helsinki. The protocol and informed consent form were approved by the Institutional Review Board of the Hospital General of Pachuca City (No. EI/064, on April 28, 2015) and approved and registered by the Mexico Ministry of Health Drugs Agency (COFEPRIS, No. 153300CT190290/2015, on May 2015). The clinical phase of the study was conducted from August to November, 2015. All participants were admitted to the AMIC Research Unit in Pachuca City the day before (18 h) this pharmacokinetic study was started.

The medication under study consisted of two 600-mg tablets of PR-PFD, (Kitoscell LP® in Mexico) administered orally, with 250 mL of water, and under direct supervision of the nursing staff. All participants underwent a 10-h overnight faste before administration.

Blood samples (6 mL) were drawn and collected into 6-mL heparinized tubes at 0 (predose) and 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 30 and 36 h after study medication administration.

2.2.1. Blood sampling preparation

Plasma was obtained by centrifugation (2000 ± 200 rpm for 10 min at room temperature [25 °C]); 1 mL of aliquots was separated and stored frozen at − 70 °C ± 10 °C until analyzed.

2.3. Study end points

The primary end point was the ratio of geometric means for the area under the curve (AUC0-last and AUC0-α) and maximal concentration (Cmax) between the cirrhotic and noncirrhotic groups. The secondary study objectives were differences in other pharmacokinetic parameters (i.e., T_{max}, and $t_{1/2}$).

2.4. Evaluation of safety profile

Monitoring for safety was performed throughout the study. The subjects were instructed to report any adverse effects at any time over the entire duration of the study. Changes in the laboratory test values were also under medical surveillance.

2.5. Clinical and laboratory evaluation

The following studies were conducted: liver function tests (i.e., bilirubin, albumin, prothrombin time expressed as INR, and serum transaminases), blood count, glucose, and creatinine, at baseline and at the end of the study. Patients' somatometric measurements (i.e., height, body weight, and body mass index) and vital signs were recorded.

2.5.1. Fibro Test®

For the Fibro Test evaluation (BioPredictive, Paris France), fresh serum was used, according to the recommended preanalytical and analytical methods [13]. This test is recognized for having a high sensitivity for predicting advanced fibrosis (F4) in patients with liver damage [14,15].

2.5.2. Determination of PFD plasma concentrations

The PFD reference standard was obtained from Tecsiquim (lot: TEC-407-LK) (Tecsiquim, Toluca, México), and that for glibenclamide was obtained from USP (Maryland, USA). The solvents acetonitrile and methanol were LC-mass spectrometer (MS) grade (Tedia High Purity Solvents, Fairfield, USA); ammonium formate and formic acid were

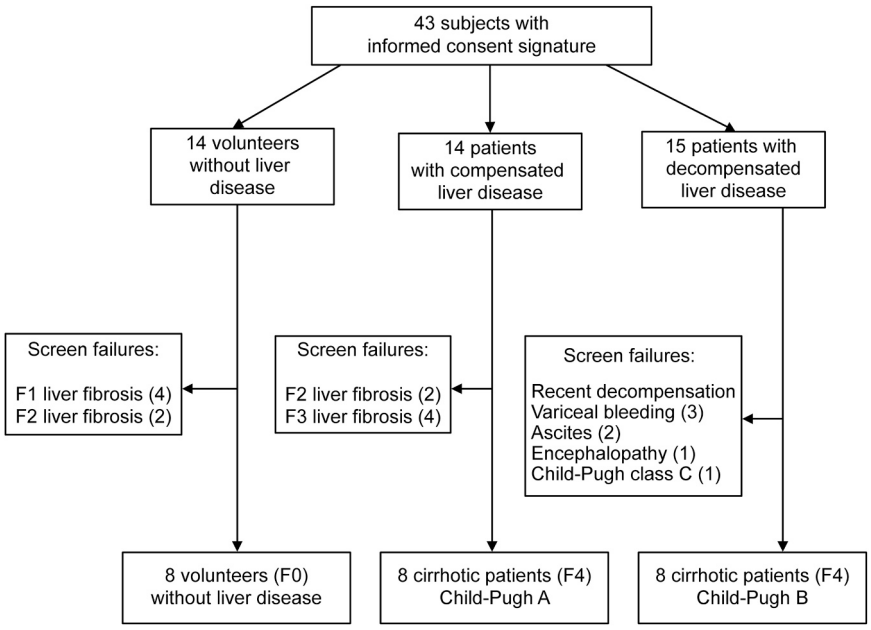

Fig. 1. GENESIS patient selection flowchart.

analytical grade (Sigma-Aldrich, Inc. Missouri, USA). PFD plasma concentrations were quantified using an HPLC method coupled with a MS; this method was developed and validated by personnel of IPHARMA, S. A de C. V (Monterrey, Nuevo León, Mexico). The validation was conducted according to Mexican guidelines (NOM-177-SSA1–2013).

2.5.3. Analytical method conditions

The column (4.6 × 150 mm) was a Zorbax® Eclipse XDB-C18 with a particle size of 5 μm (Agilent Technologies, Santa Clara, USA). PFD and glibenclamide used as internal standard (IS) were eluted with a mobile phase consisting of a mixture of acetonitrile, ammonium formate (5 mM) with 0.1% of formic acid with a volume proportion of 60:40. The column temperature was 40 °C and the flow of the mobile phase was 0.9 mL/min, in HPLC (Agilent Technologies model 1200), and both analytes were detected using a spectrometer (MS/MS) (Agilent Technologies, model G6410B). The spectrometric (MS/MS) analysis was performed by monitoring the transition from 186 to 92 *m/z* for PFD and from 492 to 369 *m/z* for the IS. The typical retention times for PFD and IS were 1.45 and 3.1 min, respectively. The peak areas were measured to calculate the peak area ratio of PFD with respect to that of the IS, and from this ratio, the concentration was calculated. The calibration curve had the following PFD concentrations: 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, and 20 μg/mL. Hence, the Lower Limit of Quantification (LLOQ) was 0.1 μg/mL. Quality control was conducted using four PFD concentration levels (i.e., 0.25, 1.75, 7.0, and 15.0 μg/mL). The intra and interassay %CV were < 5 and < 6 respectively; the accuracy (relative error) of pirfenidone was $< 7\%$.

2.6. Pharmacokinetic parameters

Plasma concentration–time curves were obtained using a non-compartmental method. The C_{max} and time to peak plasma concentration (T_{max}) were estimated from these curves. The elimination rate constant (ke) was estimated from the terminal log-decay phase using linear regression, and the elimination half-life ($t_{½}$) was estimated with the following equation:

$t½ = \ln(2)/ke$, where ln is the natural logarithm. The AUC from time 0 to the last measurable concentration (AUC_{0-t}) for PFD was determined using the line-log trapezoidal rule; and $AUC_{0-\infty}$ is the AUC from time 0 extrapolated to infinite time and calculated as follows: $AUC_{0-\infty} = AUC_{0-t} + C_{last}/ke$, in which C_{last} is the last measurable concentration. Other pharmacokinetic variables were estimated: $t_{1/2}$, and time to C_{max} (T_{max}). The pharmacokinetic analysis was performed using Phoenix WinNonlin (version 8.3; Certara LP., Princeton, New Jersey).

2.7. Statistical analysis

There were eight subjects in each of the three groups ($n = 24$). Sample size was not calculated in advance because it was a pilot study. All data coming from the 24 subjects were used for the statistical analysis. Descriptive statistics (mean and standard deviation) were reported for the demographic and laboratory tests.

For the pharmacokinetic parameters AUC_{0-t}, and $AUC_{0-\infty}$, the mean and standard deviation are reported, whereas, for $t_{1/2}$, and T_{max}, the median and range are reported.

The C_{max} and AUCs (AUC_{0-t} and $AUC_{0-\infty}$) of PFD were considered the primary end points (variables); other pharmacokinetic parameters were regarded as the secondary outcomes.

Analysis of variance was performed on the log-transformed values of C_{max} and AUCs, whereas the nonparametric Kruskal–Wallis analysis of variance followed by Dunn's test on the untransformed values of T_{max} and $t_{1/2}$. Comparisons among the three groups were Bonferroni-adjusted for multiple comparisons. Significance level was fixed at 5% ($\alpha = 0.05$).

Additionally, for the primary end points, geometric means ratios were estimated with their associated classical confidence intervals (CIs) (90%), along with their corresponding Bonferroni-adjusted intervals. All statistical analyses were performed using Phoenix WinNonlin 8.3 (Certara LP, New Jersey) and Stata/IC 15.1 (StataCorp LLC, Texas).

3. Results

Fig. 1 describes the causes of screening failure in the three study groups and the final selected population, including eight healthy subjects with cirrhosis, eight patients with Child–Pugh A liver impairment, and eight patients with Child–Pugh B liver impairment. Cirrhosis etiology was alcoholic liver disease (ALD) in four patients (25%), hepatitis C virus (HCV) in four patients (25%), autoimmune hepatitis (AIH) in two patients (12.5%), and nonalcoholic fatty liver disease in six patients (37.5%).

The demographic, somathometric, and biochemical characteristics

Table 1
Demographics and laboratory test results of the patients (N = 24).

Characteristic	Noncirrhotic group (n = 8)	Cirrhotic Child–Pugh A (n = 8)	Cirrhotic Child–Pugh B (n = 8)
Demographics			
Female, sex, no.	4	5	5
Age, years	56 (4)	61 (9)	56 (13)
Weight, kg	71 (10)	66 (9)	71 (14)
Height, m	1.65 (0.07)	1.59 (0.04)	1.56 (0.12)
BMI, kg/m^2	25.8 (2.0)	26.6 (4.7)	28.9 (2.1)
Vital signs			
Basal SBP, mmHg	106 (11)	115 (16)	114 (20)
Final SPB, mmHg	101 (10)	114 (12)	123 (17)
Basal DBP, mmHg	71 (6)	73 (9)	76 (12)
Final DPB, mmHg	70 (9)	73 (7)	76 (7)
Basal heart rate, bpm	65 (3)	66 (4)	66 (4)
Final heart rate, bpm	64 (6)	66 (4)	68 (8)
Blood biometry			
Basal hemoglobin, g/dL	15.3 (1.4)	13.9 (2.0)	13.6 (1.7)
Final hemoglobin, g/dL	14.9 (1.4)	14.6 (1.6)	13.5 (1.3)
Basal WBC, 10^3/μL	5.5 (1.4)	5.4 (1.7)	4.6 (1.1)
Final WBC, 10^3/μL	5.0 (1.5)	4.8 (1.5)	4.3 (1.4)
Basal platelet count, 10^3/μL	246 (70)	112 (58)	82 (36)
Final platelet count, 10^3/μL	241 (82)	113 (65)	76 (31)
Blood chemistry			
Basal glucose, mg/dL	89 (6)	95 (12)	104 (22)
Final glucose, mg/dL	86 (9)	92 (12)	104 (20)
Basal creatinine, mg/dL	0.9 (0.2)	0.7 (0.2)	0.8 (0.3)
Final creatinine, mg/dL	0.9 (0.1)	0.8 (0.1)	0.9 (0.4)
Basal BUN, mg/dL	12 (3)	12 (3)	14 (5)
Final BUN, mg/dL	16 (3)	13 (3)	18 (8)
Liver function Child Pugh score	NA	5.5 (0.5)	7.6 (0.7)
Basal total bilirubin, mg/dL	0.57 (0.12)	1.25 (0.44)	1.55 (0.90)
Final total bilirubin, mg/dL	0.55 (0.13)	1.07 (0.37)	1.33 (0.48)
Basal direct bilirubin, mg/dL	0.12 (0.03)	0.51 (0.38)	0.59 (0.34)
Final direct bilirubin, mg/dL	0.10 (0.02)	0.41 (0.30)	0.52 (0.24)
Basal albumin, g/dL	3.99 (0.02)	3.52 (0.39)	2.94 (0.40)
Final albumin, g/dL	3.94 (0.19)	3.55 (0.39)	2.86 (0.50)
Basal PT as INR	1.12 (0.05)	1.30 (0.13)	1.39 (0.14)
Final PT as INR	1.09 (0.05)	1.29 (0.16)	1.33 (0.14)
Liver enzymes			
Basal ALT, U/L	31 (10)	74 (36)	77 (44)
Final ALT, U/L	26 (6)	69 (38)	76 (38)
Basal AST, U/L	20 (3)	69 (36)	92 (79)
Final AST, U/L	19 (3)	72 (35)	78 (38)
Basal ALP, U/L	97 (32)	241 (230)	248 (87)
Final ALP, U/L	90 (30)	203 (134)	252 (148)
Basal GGT, U/L	27 (15)	210 (144)	215 (232)
Final GGT, U/L	27 (13)	181 (70)	254 (350)

Values are given as mean (standard deviation); NA, not applicable
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure
WBC, white blood cell count; BUN, blood urea nitrogen; PT, prothrombin time
INR, international normalized index; AST, aspartate aminotransferase;
ALT, alanine aminotransferase; ALP, alkaline phosphatase;
GGT, gamma-glutamyl transferase

of the study participants are presented in Table 1. Ages ranged between 30 and 74 years in patients with cirrhosis and between 45 and 79 years in individuals without cirrhosis. All study subjects had a complete medical history, lab results, and fibrotest at baseline confirming the absence or presence of hepatocellular damage. As expected, patients with cirrhosis had lower hemoglobin levels, platelet count, and serum albumin levels and higher levels of glucose, bilirubin, prothrombin time (as international normalized ratio [INR]), and liver enzymes than the noncirrhotic group. Patients with cirrhosis were negative for hepatocellular carcinoma. Concomitant diseases were detected in 10 patients with cirrhosis (65.5%), including diabetes mellitus (n = 6), systemic hypertension (n = 2), mild acidopeptic disease (n = 2), primary hypothyroidism (n = 1), and primary epilepsy (n = 1).

Nine (56.2%) of the 16 patients with cirrhosis were compensated, and seven were decompensated (six with ascites, four with previous esophageal variceal bleeding, and one with previous portosystemic encephalopathy). All decompensated patients were kept stable with diuretics and on secondary prophylaxis with betablockers, and one patient was treated with lactulose and neomycin. Propranolol was prescribed in patients with a history of variceal bleeding, and they were required to complete an eradication program by variceal ligation. Three additional patients with large varices without prior bleeding received betablockers and/or variceal ligation as primary prophylaxis. During the PK confinement study, none had overt portal systemic encephalopathy or digestive hemorrhage in the previous 6 months. None suffered previous gastric variceal bleeding.

The 24 participant subjects completed the study without any deviation from the protocol. The demographic characteristics and vital signs for the three study groups were similar, based on their averages and standard deviations reported in Table 1, which also includes the laboratory test values.

Expected differences between subjects with cirrhosis with mild to moderate hepatic impairment (Child–Pugh A and B, respectively) and subjects without cirrhosis were observed. In subjects with cirrhosis, platelet counts and albumin levels were lower and the levels of glucose, bilirubin (total and direct), INR, aminotransferases, and alkaline phosphatase were higher.

For the three study groups, changes in vital signs and laboratory testing values from baseline conditions to the final conditions were small and did not reach clinical significance. Fig. 2 shows the pharmacokinetic profiles for the three study groups, with notable differences in AUCs and C_{max} between the cirrhotic groups and the noncirrhotic group.

Table 2 presents the estimated pharmacokinetic parameters (mean and standard deviation). The values of AUCs, C_{max}, and $t_{1/2}$ were significantly higher in the cirrhotic groups than in the noncirrhotic group. No significant difference in Tmax was observed among the three groups.

Table 3 presents the geometric mean ratios expressed as percentages (GMR%) of the primary end points (AUCs and C_{max}), their associated classical CIs (90%), the corresponding Bonferoni adjusted intervals, and p-values. The GMR% for the comparisons of the AUCs of the cirrhotic groups with respect to the non-cirrhotic group was significantly higher, indicating that the AUCs for the cirrhotic groups, considering $AUC_{0-\infty}$, are approximately 3.6-fold (Child Pugh A) and 4.4-fold (Child Pugh B) greater than those obtained for the non-cirrhotic group. Similarly, the GMR% for the comparisons of C_{max} for the cirrhotic groups was approximately 1.8-fold (Child Pugh A) and 1.6-fold (Child Pugh B) greater than for the non-cirrhotic group, suggesting a larger PFD exposure for subjects with cirrhosis. No significant differences in the GMR% comparisons (AUCs and C_{max}) were observed between the two cirrhotic groups.

Nine of the 24 subjects reported 13 AEs, five subjects belonging to the Child Pugh A group, three subjects belonging to the Child Pugh B group and one subject belonging to the non-cirrhotic group. The AEs were nausea 5 (Child-Pugh A = 3, Child Pugh B = 2), vomiting 3 (Child Pugh A = 1, Child Pugh B = 2), urinary tract infections 2 (non-cirrhotics

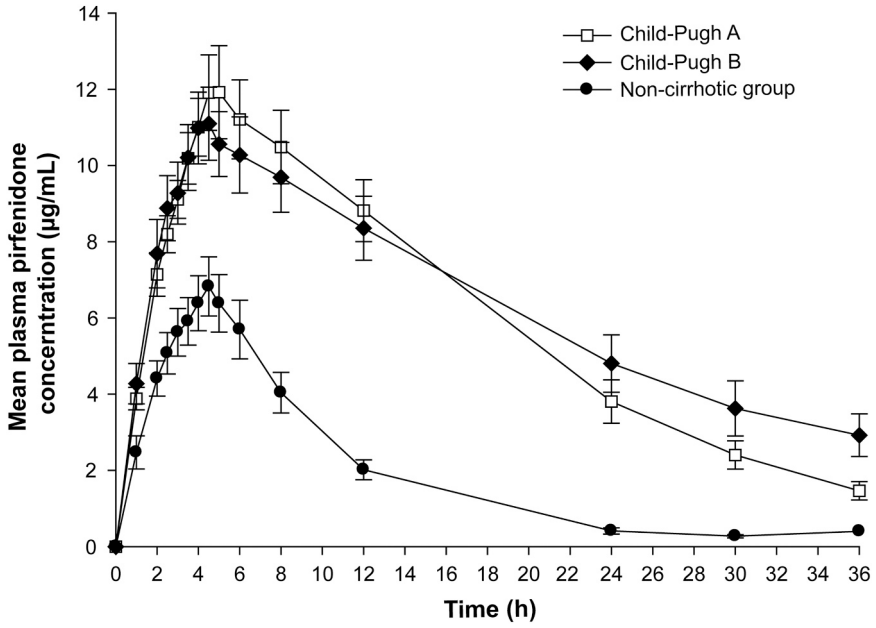

Fig. 2. Mean plasma concentration–time curves (mean ± SE) after a single administration of 1200 mg of pirfenidone. Solid circle symbols represent the non-cirrhotic group (n = 8), open-square symbols represent the Child–Pugh A group (n = 8), and solid diamond symbols represent the Child Pugh–B group (n = 8).

Table 2
Summary of the pharmacokinetic parameters evaluated (N = 24). Values are presented as the arithmetic mean (SD) or median [minimum, maximum].

Parameter	Noncirrhotic group (C) (n = 8)	Cirrhotic Child–Pugh A (n = 8)	Cirrhotic Child–Pugh B (n = 8)	*P**
AUC_{0-t} (µg/mL*h)	61.33 (19.65)	210.02 (52.18)	223.57 (57.57)	A–C < 0.001 B–C < 0.001 B–A = 1.000
$AUC_{0-\infty}$ (µg/mL*h)	64.34 (19.22)	229.25 (59.25)	294.95 (123.35)	A–C < 0.001 B–C < 0.001 B–A = 0.801
C_{max} (µg/mL)	7.07 (2.14)	12.38 (3.33)	11.44 (2.79)	A–C = 0.001 B–C = 0.005 B–A = 1.000
$t_{1/2}$ (h)	4.91 [3.27, 7.06]	8.54 [6.00, 11.10]	12.51 [4.13, 34.00]	A–C = 0.011 B–C = 0.002 B–A = 0.857
T_{max} (h)	4.50 [3.00, 5.00]	4.75 [4.50, 6.00]	4.50 [3.50, 5.00]	A–C = 0.064 B–C = 1.000 B–A = 0.085

* P-values are Bonferroni-adjusted and are associated with the mean differences in the log-transformed values of AUCs, and Cmax, whereas the P-values for the time-related parameters (i.e., t1/2, and Tmax) are associated with the median differences in the untransformed values, and they include the Bonferroni-adjusted values as well.

= 1, Child Pugh A = 1), transient hypertension 1 (Child Pugh B), transient ALT elevation 1 (Child Pugh A), and transient azotemia 1 (Child Pugh B).

4. Discussion

To the best of our knowledge, this is the first published study to evaluate PFD pharmacokinetics in subjects with cirrhosis. For the pharmacokinetics of most drugs, good liver function is considered essential [16].

Some consequences of reduced liver function include the following: (a) reduced processing of drugs for elimination via the bile or urinary tract; (b) low production of albumin, affecting plasma protein binding, distribution processes, and elimination; and (c) the presence of porto-systemic shunts, which can affect the first-pass effect of highly extracted drugs after oral administration [17]. In the presence of cirrhosis, reduction in the activity of various system enzymes stands out, particularly CYP. Additionally, in the case of hepatorenal syndrome, adjusting the dose of drugs excreted through the urine may be necessary [18].

To provide specific dosing recommendations in patients with hepatic dysfunction, both the FDA and European Medicines Agency recommend conducting pharmacokinetic studies of drugs metabolized by the liver in various populations, including patients with liver cirrhosis [19]. This study finds that the level of exposure to PFD, as measured by the AUCs, particularly $AUC_{0-\infty}$, is significantly enhanced to approximately 3.6-fold (Child–Pugh A) and 4.4-fold (Child–Pugh B) for patients belonging to both cirrhotic groups as compared to patients without cirrhosis. This result along with the other pharmacokinetical findings (significantly higher C_{max} and $t_{1/2}$ values) indicates that the metabolism of PFD is affected in patients with cirrhosis, which could be attributed to the aforementioned factors, such as low activity of CYPs and reduced blood flow across the liver. Therefore, having cirrhosis is important and should be considered when deciding the daily dose to be administered in clinical practice. Notably, we did not find significant differences between patients with cirrhosis with mild liver damage and those with moderate liver damage, suggesting that the medication could be well tolerated in these clinical conditions. However, we cannot extrapolate our findings to patients with severe liver damage (Child–Pugh C).

Although these data may indicate the need for a dose reduction,

Table 3
Geometric mean comparisons of AUCs and C_{max} (N = 24).

Pharmacokinetic parameter	Comparison	GMR (%)	Classical 90% CI	Bonferroni CI	P*
AUC_{0-t} (μg/mL*h)	A/B	94.34	73.44, 121.19	67.53, 131.80	1.000
$AUC_{0-\infty}$ (μg/mL*h)		81.80	58.71, 113.96	54.76, 122.17	0.801
C_{max} (μg/mL)		108.10	86.09, 135.73	79.31, 147.34	1.000
AUC_{0-t} (μg/mL*h)	A/C	346.87	268.10, 448.78	248.28, 484.61	< 0.001
$AUC_{0-\infty}$ (μg/mL*h)		358.57	277.94, 462.60	240.07, 535.59	< 0.001
C_{max} (μg/mL)		176.88	138.49, 225.92	129.77, 241.10	0.001
AUC_{0-t} (μg/mL*h)	B/C	367.67	281.39, 480.41	263.17, 513.66	< 0.001
$AUC_{0-\infty}$ (μg/mL*h)		438.37	312.78, 614.40	293.50, 654.78	< 0.001
C_{max} (μg/mL)		163.63	127.97, 209.22	120.05, 223.04	0.005

GMR, estimated geometric mean ratio expressed as % coming from log-transformed data of AUCs and C_{max}. A = Cirrhosis Child–Pugh A; B = Cirrhosis Child–Pugh B; and C = noncirrhotic group.
* P-values were Bonferroni-adjusted.

recently, we have published our experience prescribing a daily dose of 1200 mg, administered as 600-mg tablets bid, after meals, for 12 months, in an open real-life trial involving patients with advanced liver fibrosis (F3–F4), showing good tolerance and potential benefits of reducing liver stiffness, a finding that needs confirmation in a placebo-controlled clinical trial [20].

The gastrointestinal adverse events detected in our study have already been a matter of concern in other studies [21,22]. These adverse events may have occurred because we used a high single dose (1200 mg) in patients with cirrhosis under fasting conditions. Administration with food has been reported to reduce side effects and lower PFD peak concentrations, which may improve tolerability [26].

We are aware of some limitations of our study due to its small sample size. Another limitation of this study is its design, where the patients were evaluated under fasting conditions only. Furthermore, the age range in this study was limited, and this study only included individuals without obesity. Decompensated cirrhosis or other concomitant conditions (e.g., cancer) were not considered. 5-CP, despite being considered an inactive metabolite, was not measured; however, in future studies, a reduced concentration might confirm our hypothesis that in cirrhosis, CYP activity is low.

Recommendations and issues raised by the investigation include the need of future pharmacokinetic studies involving patients with cirrhosis, mainly regarding the high level of exposure to PFD (>two times) in cirrhotic groups, strongly suggesting the possibility of drug reduction. Therefore, we recommend conducting additional pharmacokinetic studies in the cirrhotic population with single and multiple reduced doses, under fed and fasting conditions, including the determination of 5-CP to eventually determine the bioavailability of lower doses.

In the mean time, based on the results of our study, we suggest that the daily PFD dose should not be greater than 1200 mg to prevent unnecessary adverse events.

5. Conclusion

In conclusion, this study showed a clear pharmacokinetic difference between patients with cirrhosis and non-cirrhotic subjects. In particular, the results suggest that the metabolism of PR-PFD was affected by the reduction in liver function. Therefore, additional pharmakokinetic studies are required to determine the best dosage regime of PR-PFD to be used as an antifibrotic agent in the cirrhotic population.

Funding

This project was sponsored by Grupo Medifarma.

CRediT authorship contribution statement

JRA, RB, RA, were involved in population recruitment, and ambulatory care of the patients. LH and FG were involved in ambulatory nutritional care and carried out the capturing and integration of a data base with all demographic, clinical and biochemical data; EP, MG carried out the PFD pharmacokinetic measurements and wrote the specific methodology section. MGP performed statistical analysis and wrote the corresponding section. PP and NH collaborated in protocol writing and methodology planning. GT participated in protocol planning and reviewing biostatistical analysis. MGP reviewed pharmacokinetics results, carried out the biostatistical analysis, and was fully involved in manuscript writing. LM collaborated in protocol writing and methodology planning and made style and syntax changes to the manuscript. JLP led the multicenter group working with PR-PFD, was involved in recruitment and ambulatory care, and oversaw the manuscript writing and style. All authors read and approved the final manuscript.

Declaration of Generative AI and AI-assisted technologies in the writing process

Authors declare that AI or AI-assisted technologies were not used in writing process.

Declaration of Competing Interest

JLP, JRA, RB, RA, FG, LH, EP, MG, MEG, MGP, GT, LEMP declare no conflicts of interest. PP and NH work for Grupo Medifarma.

Acknowledgements

We acknowledge Erin Ferris and Mark Sander for improving the English language.

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