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ORIGINAL ARTICLE

Evaluation of Safety of a Newly Formulated Pirfenidone in Chronic Kidney Disease: A Non-Randomized Pilot Study in Mexican Patients

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Abstract

The aim of this pilot clinical trial was to evaluate the safety of a new formulation of prolonged-release Pirfenidone (PR-PFD) in chronic kidney disease (CKD), specifically focal and segmental glomerular hyalinization (FSGH). Open-label, pilot, nonrandomized trial. Eighteen patients previously diagnosed with CKD stages 1– 5 according to "Kidney Disease: Improving Global Outcomes" were enrolled in the study. Target dosage of PFD was 1200 mg twice a day in the form of prolonged-release tablets to reach a full dosage of 2400 mg daily. Clinical trial was carried out for 60 months to evaluate the safety and efficacy of a newly formulated PR-PFD in patients with CKD. After the treatment for 60 months, it was found that PR-PFD kept renal function from declining significantly in CKD patients, as the glomerular filtration rate (GFR) showed only minimal variations throughout the study. Estimated glomerular filtration rate (eGFR) showed no differences at both baseline and the end points. Proteinuria improved, and creatinine, cystatin C, urea, hemoglobin and hepatic transaminases remained constant without any considerable changes across the study. Minor side effects were noticed when compared with those found in previous studies, indicating an increased tolerance to this pharmaceutical formulation of PFD. Prolonged-released PFD could be safely used as an adjuvant therapy in patients with CKD.
Registry number was obtained from ClinicalTrials.gov (NCT02408744).

Keywords: chronic kidney disease; glomerular filtration rate; prolonged-release pirfenidone

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Introduction

Chronic kidney disease (CKD) is a general term to classify a group of disorders affecting the structure and function of the kidney, present for >3 months, with implications for health. Recently, the "Kidney Disease: Improving Global Outcomes" (KDIGO) group defined CKD on the basis of

either evidence of kidney damage (proteinuria, hematuria, or anatomical abnormality) or the presence of kidney injury or substantially decreased glomerular filtration rate (GFR <60 mL/min per 1.73 m^2, stage 3a) for ≥3 months, regardless of cause. CKD has been classified into five stages based on the level of GFR (1–3) and based on the albuminuria category (A1–A3) (>30 mg/g or >3 mg/mmol, stage A2) (3).

In terms of epidemiology, CKD is a global public health issue, with an incidence of more than 200 cases per million per year in many countries, with a rising prevalence, poor outcomes, and high costs (4–6). CKD has a high global prevalence between 11 and 13%, with the majority being stage 3 (7). Unfortunately, mortality rates remain above 20% per year with the use of dialysis, reflecting the increased association between reduced GFR and increased risk of death, cardiovascular events, and hospitalization (8).

The causes leading to CKD are usually associated with old age, diabetes, hypertension, obesity, and cardiovascular disease (5, 7). In spite of the heterogeneity of the underlying disease, renal fibrosis (characterized by glomerulosclerosis and tubulointerstitial fibrosis) characterizes the final common manifestation of virtually all progressive renal diseases, chronic allograft nephropathy, and renal aging (9–11). Up till now, the standard of care for diabetic and nondiabetic nephropathies has been the use of inhibitors of the renin-angiotensin system (RAS) (12, 13). However, these inhibitors when used in maximum doses have severe side effects (hyperkalemia and decreased renal blood flow). Eventually, they might decrease the rate of disease progression, but they cannot improve renal fibrosis (14). Therefore, in recent years, the study of the roles of TGF-β1 and TNF-α, implicated in the activation of cellular pathways responsible for the development of renal diseases (15), has been instrumental in the development of new strategies to control fibrogenic activity of TGF-β1 as a promising approach (11).

Pirfenidone (PFD) is a pyridone derivative with wide anti-fibrotic and anti-inflammatory effects by modulation of diverse cytokines, such as TGF-β1, IL-1, IL-4, IL-6, IL-8, IL-13, IFN-γ, and TNF-α. Also, PFD reduces the expression of intracellular adhesion molecule-1 (ICAM-1) and enhances the expression of anti-inflammatory cytokines like IL-10 (16–18). Previous studies using PFD in animal models of renal damage have demonstrated encouraging results in tubulointerstitial fibrosis due to unilateral ureteral obstruction (UUO), diabetes (19), damage induced by cyclosporin, and in streptozotocin-induced diabetic rats (20–22). Besides, PFD is able to limit the fibrogenic potential of tacrolimus-induced nephrotoxicity (23), controls chronic anti-glomerular basement membrane glomerulonephritis (anti-GMB GN) (24). In clinical trials, standard-release pirfenidone has been used to treat CKD, and it has been tested in focal segmental glomerulosclerosis (25) and diabetic nephropathy with promising results (14, 26).

Sharma et al. confirmed a strong association between an increase of several protein biomarkers considered to be part of the inflammatory response (TNF, sTNF-R1, IFN-γ, and IL-1) and GFR decline, suggesting a relevant inverse relationship (14).

Lancaster et al. performed an integrated analysis of safety data from five clinical trials evaluating pirfenidone in patients with IPF. A total of 1299 patients were included in the analysis. The median duration of exposure was 1.7 years, and the mean daily dose was 2053.8 mg. They concluded that long-term treatment with regular PFD in patients with IPF is safe and generally well tolerated (27). However, there is a need for clinical studies demonstrating the safety of this new formulation of prolonged-release PFD administration in patients with CKD.

Thus, the aim of this pilot clinical trial was to evaluate the safety and preliminary evidence of efficacy of a new formulation of prolonged-released PFD in CKD, specifically focal and segmental glomerular hyalinization (FSGH). Our findings suggest that prolonged-release PFD could be used as an adjuvant therapy in patients with CKD.

Materials and Methods

Study design

This open-label, pilot, nonrandomized trial was originally designed for 12 months. As the study progressed, we decided to extend it up to 60-months' duration to evaluate long-term safety and preliminary outcomes in the efficacy of PFD [5-methyl-1-phenyl-2-(1H)-pyridone] taken orally daily as a potential adjuvant therapy in CKD. The target dosage of PFD was 1200 mg twice a day (b.i.d.) in the form of prolonged-release tablets (PR-PFD) according to the body surface area (m^2 BS) of each patient to reach a full dosage of 2400 mg daily. Therapy was initiated at 600 mg b.i.d. and escalated to the full dosage after 3 weeks when symptoms were controlled. PR-PFD was manufactured according to standard Good Manufacturing Practices (GMPs), Good Laboratory Practices (GLPs), and previously accepted sanitary regulations enforced by the Federal Commission for Protection against Sanitary Risks (COFEPRIS) (Mexican Minister of Health).

Regulatory authorities and ethics committees from the Centro de Estudios de Investigación Básica y Clínica S.C. and Hospital Real San José approved the conduction of this study (along with patient sheets and consent forms) with the registry number 2009-010. Furthermore, a registry number was obtained from ClinicalTrials.gov (NCT02408744).

The study group included patients previously diagnosed using renal biopsy with FSGH from Hospital Real San José and Dr. Ojeda-Duran's office. All participants received a major explication of the methodology to be used across the study and signed consent forms prior to the initiation of the protocol.

Method of recruitment, recruitment setting, settings and location where the data were collected

Given that this protocol was planned as a pilot, non-randomized study, we opted for a population of 30 subjects aged between 10 and 40 years, of both genders, who were scrutinized from July 2009 up to March 2010. The 18 patients who were finally included were recruited at Dr. Ojeda-Duran's office and Hospital San Jose at Guadalajara, Mexico, and followed up for 5 years. In addition, Case Report Forms (CRFs) were filled up accordingly and kept along with the medical files. All data were stored in an electronic data base.

Medication was supplied in the form of 600 mg tablets of PR-PFD packed in bottles of 120 tablets each. Adherence to the treatment was encouraged by the principal investigator with the help of a psychology counselor, and the records of medicine intake were scrutinized on a monthly basis. An accurate record of the shipment and delivery of the study medication was kept in a medication accounting book. Also, a precise record of the dates and amounts of the study medication given to each subject was available at all times for inspection.

Study group

Patients enrolled for treatment initially received 600 mg PR-PFD b.i.d. before the dosage being escalated after 3 weeks, once the symptoms permitted tolerance to full dosage (2400 mg/day), although all patients were instructed to take PR-PFD after meals to diminish gastrointestinal side effects for 60 months. Clinical evaluation was performed on a monthly basis, and laboratory tests were programmed at the time of enrollment and in months 2, 4, 6, 9, and 12, and then every 12 weeks until month 60. The baseline testing consisted of complete blood count, chemistry profile, including Cystatin c, hepatic panel, amylase, creatinine, and a 24 h urine collection to determine proteinuria.

Inclusion criteria used in this study were the following: (i) patients aged between 10 and 40 years with CKD; (ii) diagnosis of CKD stage 1–5 according to KDIGO definition and classification; (iii) no glucocorticoids, cyclophosphamide, mycophenolate, or other immunosuppressive drugs for at least 2 months before starting PR-PFD administration; and (iv) signing of consent forms.

Exclusion criteria were the following: (i) known intolerance to PR-PFD; (ii) CKD stage 5 according to KDIGO classification; (iii) posttransplant patients; (iv) history of peptic ulcer within 6 months of transplant; (v) history of cerebrovascular disease within 6 months of transplant; (vi) evidence of hepatic disease; (vii) pregnancy or breast feeding; and (viii) malignancy.

Eighteen out of 30 selected patients with evidence of kidney damage (proteinuria, hematuria) unabated for more than 3 months and diagnosed with CKD (FSGH) were included in the study according to the inclusion criteria. All patients continued their concomitant management based on a low protein, phosphate, and purine diet; restriction on the intake of sodium, potassium, and liquids per individual case; keto-analogues of essential amino acids; phosphate chelating agents (calcium acetate); and treatment with angiotensin-converting enzyme (ACE) inhibitors of angiotensin-receptor blockers (ARBs).

The primary outcome was to evaluate the use of PR-PDF in the rate of renal damage progression in patients with primary nephropathy (Stages 1–5 of the KDIGO classification) by determining GFR. The secondary outcomes were to measure renal function monitored by cystatin C, PR-PFD effect on proteinuria, and determination of adverse drug events in patients, determining the safety of the PR-PFD administration in this type of patients.

Statistical analysis

Data are presented as the mean±standard deviation (SD). Statistical significance was determined with one-way ANOVA and Bonferroni post-hoc test. Intention to treat analysis (ITT) was also performed. Statistical analysis was performed using Prism software (GraphPad Prism, CA, USA). Significance was defined as a P value < 0.05.

Results

Eighteen patients, comprising 10 women and eight men (mean age = 24.4 years old, SD ± 9.7), previously diagnosed with CKD (FSGH) were enrolled in the study (Figure 1). All

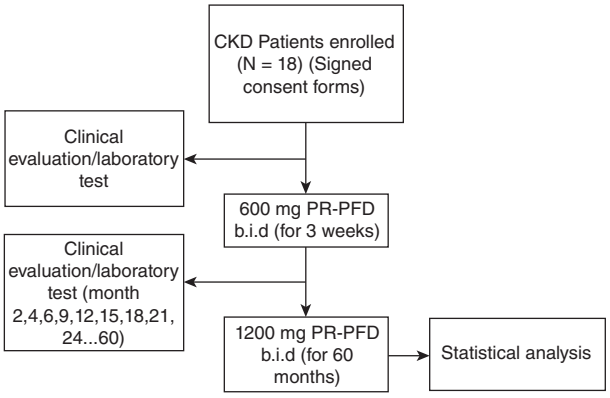

Figure 1. Study flowchart. Eighteen CKD patients were enrolled, 14 patients completed the 60-month treatment with prolonged-release Pirfenidone.
CKD: chronic kidney disease; PR-PFD: prolonged-release Pirfenidone.

patients tolerated fairly well a dose of 2400 mg/day of PR-PFD across the study. During this time, two patients decided to stop therapy after 27 months of treatment, one patient stopped therapy after 45 months since he became a transplant recipient, and one patient was excluded from the study after 54 months of treatment due to loss of adherence. Table 1 is a summary of the clinical characteristics of patients at baseline protocol. The intention to treat (ITT) analysis includes all the 18 patients with CKD (FSGH), and per-protocol (PP) analysis includes 77.7% of patients who completed the treatment originally (14 patients ended treatment after 60 months). The study group accounted for a mean time of CKD evolution of 52.4 months (SD ± 10.8) before enrollment in the study. The ITT was performed for biochemistry and clinical parameters (Table 2). None of the patients dropped out from the study due to severe side effects of PR-PFD.

The ITT for the 18 patients regarding laboratory measurements showed the next data.

GFR from baseline period to the end of study was evaluated. At the time of admission, the mean GFR was 52.8 mL/min/1.73 m^2, after 12 months was 61.2 mL/min/1.73 m^2, after 36 months' follow-up was 56.3 mL/min/1.73 m^2, and at the end of the study (60 months) was 57.0 mL/min/1.73 m^2, as reported in the laboratory tests. The mean difference between baseline to month 12 of treatment was +8.4 mL/min/1.73 m^2, between month 12 to month 36 was −4.8 mL/min/1.73 m^2, while from month 36 to month 60 was +0.7 mL/min/1.73 m^2, and the mean change between baseline to end of the study (month 60) was +4.2 mL/min/1.73 m^2. It is important to note that none of the patients included in the study showed a significant decline in GFR during the 60 months of study in spite of intrinsic kidney

Table 1. Patient characteristics at baseline.

Patient	Age (years)	Sex	Diagnostic	Diagnostic test	Biopsy results	CKD stage	Creatinine depuration mL/min	eGFR (mL/min/1.73 m^2)
1	15	F	SNS/PG	RB and RDU	FSGH	3b	38.17	40
2	31	F	SNS/PG	RB and RDU	FSGH	3a	46.69	46
3	18	F	SNS/PG	RB and RDU	FSGH	3b	40.81	31
4	20	M	SNS/PG	RB and RDU	FSGH	3b	62.43	43
5	14	M	SNS/PG	RB and RDU	FSGH	3a	54.5	55
6	18	F	SNS/PG	RB and RDU	FSGH	4	17.71	18
7	11	F	SNS/PG	RB and RDU	FSGH	1	96.45	153
8	17	M	SNS/PG	RB and RDU	FSGH	4	35.63	29
9	10	F	SNS/PG	RB and RDU	FSGH	1	114.22	156
10	24	M	SNS/PG	RB and RDU	FSGH	3b	55.76	37
11	38	M	SNS/PG	RB and RDU	FSGH	3b	47.93	32
12	10	M	SNS/PG	RB and RDU	FSGH	3a	23.89	59
13	12	F	SNS/PG	RB and RDU	FSGH	3a	28.76	52
14	43	M	SNS/PG	RB and RDU	FSGH	3b	41.23	32
15	34	F	SNS/PG	RB and RDU	FSGH	2	86.5	60
16	36	F	SNS/PG	RB and RDU	FSGH	4	29.82	28
17	21	M	SNS/PG	RB and RDU	FSGH	3a	48.35	45
18	19	F	SNS/PG	RB and RDU	FSGH	3b	53.24	31

SNS/PG: secondary nephrotic syndrome, primary glomerulopathy; RB: renal biopsy; RDU: Renal Doppler Ultrasound; FSGH: focal and segmental glomerular hyalinization; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; Creatinine depuration was calculated by COCKROFT-GAULT formula.

Table 2. ITT analysis of mean laboratory measurements throughout the study.

	Basal (SD)	Month 12 (SD)	Month 24 (SD)	Month 36 (SD)	Month 48 (SD)	Month 60 (SD)
GFR (mL/min/1.73 m^2)	52.8 (24.6)	61.2 (37.0)	57.4 (33.3)	56.3 (42.2)	53.0 (42.9)	57.0 (47.7)
Creatinine (mg/dL)	2.0 (0.8)	1.9 (0.9)	1.9 (0.8)	2.2 (1.0)	2.5 (1.3)	2.6 (1.5)
Cystatin C (mg/L)	1.7 (0.6)	1.6 (0.7)	1.7 (0.6)	1.6 (0.9)	2.0 (1.0)	1.8 (0.9)
Proteinuria (g/24 h)	3.3 (6.2)	1.7 (1.2)	2.3 (2.2)	2.3 (1.9)	2.6 (2.1)	3.3 (4.6)
Urea (mg/dL)	50.3 (18.3)	48.9 (20.9)	52.9 (18.8)	62.5 (28.4)	61.8 (27.6)	58.0 (26.9)
Hemoglobin (g/dL)	13.3 (1.9)	13.4 (1.6)	13.2 (1.6)	12.8 (1.7)	12.7 (2.0)	12.7 (1.8)

Laboratory measurements found in the study group from baseline to end of the study. Data shown are mean ± SD of all subjects (N = 18). For the intention to treat analysis (ITT), all patients as originally assigned to the study, including those who did not comply with the intervention protocol and those who had not completed the intervention, were included.

damage (Table 2). In addition, estimated glomerular filtration rate (eGFR) was calculated by the abbreviated Modification of Diet in Renal Disease (MDRD) equation: $186 \times (\text{Creatinine}/88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$, and no significant differences were found: median baseline values were 52 mL/min/1.73 m^2 as compared after 60 months (median 50 mL/min/1.73 m2) (Table 1 and Table 3).

ITT in creatinine values reported at the time of enrollment revealed a mean of 2.0 mg/dL, while at the end of the study creatinine was 2.6 mg/dL, which suggest that PFD treatment ensured steady levels of serum creatinine throughout the entire clinical trial (Table 2).

The ITT analysis of serum cystatin C, a small molecule used as a new endogenous filtration marker, revealed minimal variations along the study; patients' baseline was 1.7 mg/L and at the end of the study, the mean value was 1.8 mg/L (Table 2).

Other laboratory tests carried out were the 24 h protein urine test to assess proteinuria levels, which presented a slight but relevant reversal from baseline to the end of study. The ITT analysis showed the same value of 3.3 g/24 h at baseline and at the end of the study (Table 2), while PP analysis showed 4.03 g/24 h and 3.3 g/24 h from baseline to the end of the study, respectively (Table 4); this situation showed additional evidence that proteinuria levels can be maintained without changes using PR-PFD (Figure 2).

Urea levels remained with minor changes throughout the study. There were no significant variations in hemoglobin and/or hepatic transaminases, and all measurements remained within normal parameters (Tables 2 and 4).

Table 3. Patient characteristics at the end of protocol.

Patient	Age (years)	CKD stage	Creatinine depuration mL/min	eGFR (mL/min/1.73 m^2)
1	20	4	28.84	23
2	36	3a	54.67	47
3	23	5	16.28	11
5	19	3a	57.63	46
7	15	1	137.3	120
8	21	4	30.3	22
9	15	1	155.79	152
10	29	3b	49.15	38
11	43	4	35.63	24
12	14	4	21.46	21
13	17	3b	39.88	37
15	39	2	112.04	85
17	26	2	60.54	60
18	23	4	30.58	18

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; Creatinine depuration was calculated by COCKROFT-GAULT formula.

Adverse events

Only minor events were reported throughout the study, consisting of nausea 38.8% (7/18), vomit, 16.6% (3/18), dyspepsia or abdominal discomfort 11.1% (2/18), fatigue 11.1% (2/18), and headache 11.1% (2/18). Fatigue was mild and did not interfere with activities of daily living. Most of the side effects reported were transient or required only symptomatic management, and none of the events required treatment after the first 3 months. None of the adverse events described

required PR-PFD suspension or developed photosensitivity contrary to previously reported data (14, 26, 28–30).

It is also clear that the new formulation of prolonged-release pirfenidone tablets used in this study causes only minor secondary effects, which dissapeared after the first 3 months of treatment. Furthermore, when compared with previous studies, prolonged-release PFD induced less intense and less frequent secondary events than regular rapid-released PFD-capsules used in the studies of Cho and Sharma (14, 26). Taken all together, these studies suggest that PR-PFD used here is safe and well tolerated.

Discussion

In this study, both the ITT analysis and PP analysis showed that all patients enrolled in this pilot clinical trial were able to maintain their GFR with a slight improvement, although with minimal variation after 12 months (+8.4 and + 7.9 mL/min/1.73m^2 for ITT and PP analysis, respectively). Minimal changes were reported after 36 months, with an increase of +5.5 and +4.3 mL/min/1.73m^2 (ITT and PP analysis, respectively), compared with baseline; while at the end of 60 months' follow-up, no decline in GFR was reported (+4.2 and +4.7 mL/min/1.73m^2 from baseline in ITT and PP, respectively). Thus, the nondeclining evidence suggests good outcomes in our study group (Tables 2 and 4). It is important to keep in mind data shown by Cho et al. where patients without PFD treatment had a diminished GFR at a monthly median of −0.61 mL/min/1.73 m^2; however, once the same study group received rapid-released or regular PFD, monthly GFR declined at −0.45 mL/min/1.73 m^2 (26). Sharma et al. administrated pirfenidone in patients with diabetic nephropathy. Patients presented a baseline estimated GFR (eGFR) of 20 to 75 mL/min per 1.73 m^2. They were provided two doses of pirfenidone 1200 mg/day and 2400 mg/day. The mean eGFR increased in the 1200 mg/day group (+3.3 ± 8.5 mL/min/1.73 m^2), whereas the 2400 mg/day group presented a change in eGFR of −1.9 ± 6.7 mL/min/1.73 m^2 after 12 months of treatment (14). Noteworthy, regular standard-release PFD capsules were administrated in this study as opposed to our study where PR-PFD tablets were used. Our results are similar in the maintenance of renal function and additionally, most of the side effects reported with the PR-PFD tablets used in this study were milder, transient, or required only symptomatic management; none of the events required treatment after the first 3 months.

Noteworthy, recent studies with PFD in kidney disease have described no effect of PFD in proteinuria (14, 26), although in our study we showed that 24 h proteinuria rate slightly improved during PFD treatment, which avoids an increase in proteinuria that is seen at the end of follow-up.

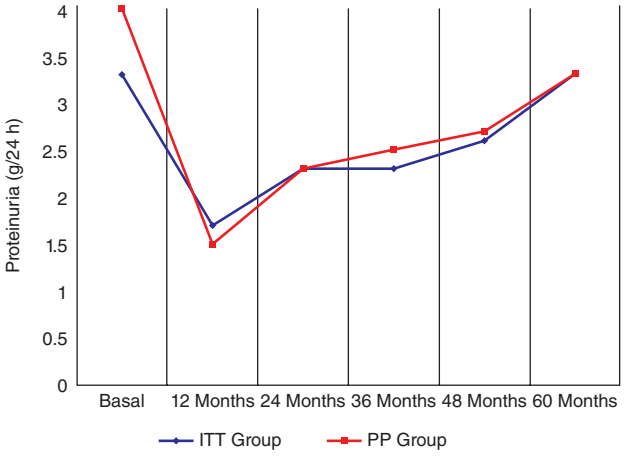

Figure 2. ITT and PP analysis for proteinuria levels. IIT, Intention to treat analysis; PP, per-protocol.

Table 4. PP analysis of average laboratory measurements throughout the study.

	Basal (SD)	Month 12 (SD)	Month 24 (SD)	Month 36 (SD)	Month 48 (SD)	Month 60 (SD)
GFR (mL/min/1.73 m^2)	54.2 (28.0)	62.1 (41.5)	60.2 (38.6)	58.5 (48.5)	54.1 (45.7)	58.9 (49.3)
Creatinine (mg/dL)	1.9 (0.9)	1.8 (0.9)	1.9 (0.9)	2.2 (1.1)	2.5 (1.2)	3.2 (1.6)
Cystatin C (mg/L)	1.5 (0.5)	1.5 (0.7)	1.6 (0.7)	1.5 (0.9)	1.9 (0.9)	2.0 (0.9)
Proteinuria (g/24 h)	4.0 (8.3)	1.5 (1.2)	2.3 (2.4)	2.5 (2.0)	2.7 (1.8)	3.3 (4.6)
Urea (mg/dL)	47.6 (20.0)	43.2 (17.2)	53.4 (19.6)	60.1 (22.4)	60.0 (22.2)	65.3 (28.5)
Hemoglobin (g/dL)	13.5 (1.5)	13.3 (1.3)	13.2 (1.4)	12.7 (1.2)	13.0 (2.0)	12.5 (1.9)

Laboratory measurements found in the study group from baseline to end of the study. Data shown are mean ± SD. For the per-protocol (PP) analysis, only subjects who complied with intervention protocols and completed the intervention were included (n = 14). GFR: glomerular filtration rate; SD: standard deviation.

Comparison between basal levels and after 12, 36, and 60 months shown in Tables 2 and 4 showed no decline, supporting the benefit of adding PR-PFD to improve proteinuria rate; this is a relevant finding due to the fact that proteinuria is an important indicator of adverse outcomes in CKD and its strong association with GFR and adverse clinical outcomes (31, 32). Measurement of creatinine, cystatin C, urea, and hemoglobin as visible in Tables 2 and 4 showed no considerable modifications across the study.

Also, in this study, we achieved a high adherence rate to treatment in comparison with other studies with PFD. Here, two patients decided to stop therapy after 27 months of treatment, one patient stopped therapy after 45 months since he became a transplant recipient, and one patient was excluded from the study after 54 months of treatment due to loss of adherence. High adherence to the medication results could be attributed to the use of a new pharmacological form of the compound (prolonged-released tablets), which diminished the rate and severity of side effects as published by Cho et al. (26), Gahl et al. (28), Bowen et al. (29), and Nagai et al. (30) where regular standard-release PFD capsules were used. Moreover, initiation of drug administration in an escalated manner was necessary to improve tolerance.

Shi et al. previously published PFD pharmacokinetics in healthy volunteers, describing a rapid absorption within 1–2 h after oral administration and cleared from plasma with a half-life of 2.1 ± 0.4 h, with a maximum plasma concentration occurring 0.33–1 h after administration. Mean $t_{1/2}$ ranged from 2 to 2.5 h in subjects with an oral CL/F of approximately 9.6 L/h (33). We have focused our research on PFD 600 mg prolonged-release tablets according to the pharmacokinetic studies carried out by our team (unpublished data) showing that PFD bioavailability levels (1.2 µg/mL) were raised after 1 h of intake, while a maximum plasma level of 2.4 µg/mL was found after 4 h of ingestion (Figure 3). According to these results, we can also conclude that this pharmaceutical presentation of 600 mg prolonged-release tablets has an improved and suitable bioavailability with a mean $t_{1/2}$ of 10.79 h. Thus, it does represent an adequate pharmacological presentation to maintain PFD plasma levels within therapeutic ranges improving outcomes, patient's adherence to treatment, and reducing incidence of side effects.

The standard-released PFD actually marketed as 257 mg capsules has been shown to cause intense gastrointestinal side effects in several clinical trials, resulting in a high dropout rate of patients (up to 42%) in different clinical trials, probably due to its high peak of fast absorption. Prolonged-released tablets (600 mg) were specifically designed to circumvent the high peak, maintaining total daily pharmaceutically stable levels. Figure 3 shows a dissimilar pharmacokinetics for the standard and prolonged-release formulations.

Therefore, data presented here suggest that CKD management with PR-PFD might be a suitable adjuvant therapy due to its mechanism of action, which inhibits activation of pro-inflammatory and pro-fibrogenic cytokines, and increases synthesis and activity of matrix metalloproteinases (MMPs) controlling the loss of renal parenchyma, characteristic in kidney damage and renal fibrosis.

Recently, Ikezoe et al. evaluated the relationship of CKD to clinical features and outcomes in patients with IPF. Some of the patients were treated with pirfenidone. In this case, the use of pirfenidone to treat IPF was not associated with survival. They concluded that a substantial percentage of IPF patients have CKD; that CKD with a low eGFR was associated with decreased survival in IPF; and that the impact on

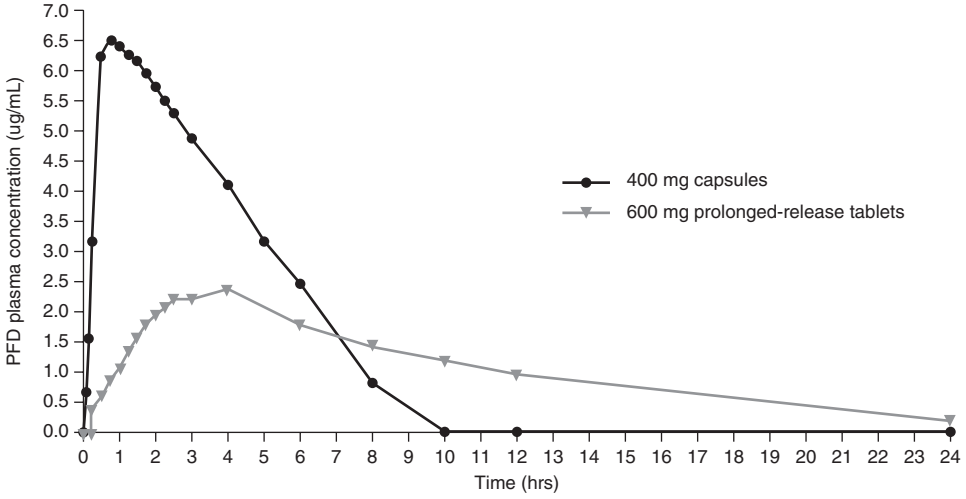

Figure 3. Mean plasma concentration-time profile of PFD 400 mg capsules versus 600 mg prolonged-release tablets.
PFD, Pirfenidone.

renal function and disease outcomes of pirfenidone should be elucidated in prospective clinical trials (34).

In summary, pharmacokinetic studies and pilot studies show that pirfenidone is safe in the CKD setting. One goal of this pilot protocol was to provide a basis for the safe use of a prolonged-release pirfenidone pharmaceutical-form to minimize the said effects of the standard formulation of pirfenidone in patients with CKD and enhance the treatment adherences. Kidney scarring is a dominant factor in the development of kidney disease (15). Hypothetically, pirfenidone administration at early times after patients are diagnosed with CKD will prevent the progression of renal tissue fibrosis and consequently improve renal function.

We are aware of the limitations of our work regarding the limited number of patients and the lack of a placebo-controlled group. However, the main strength of this study is the long term of 60 months of patient follow-up. As far as we know, there are no other protocols present in a clinical scheme similar to the one used here, which by itself is noteworthy.

In Mexico, as well as in many developing countries, there are no public health policies regarding the prophylactic and therapeutic approach for CKDs and, therefore, the economic burden of treating the devastating complications of this group of diseases have always taken their toll. Thus, new pharmacological approaches are required to decrease this pathologic condition.

Conclusion

In conclusion, long-term, prolonged-released PFD could be safely used as an adjuvant therapy in patients with CKD. We understand the limitations of our study in terms of controlling the protocol. Although promising, these results need to be endorsed under the perspective of a double-blind, placebo-controlled, clinical scenario.

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper. JAB is a consultant for Grupo Medifarma.

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