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Ameliorative effects of pirfenidone in chronic kidney disease

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ABSTRACT

Renal fibrosis is the hallmark of advanced chronic kidney disease (CKD), which is characterized by excessive accumulation of extracellular matrix (ECM) proteins and plays a central role in the pathogenesis and progression of CKD to end-stage renal disease (ESRD). The molecular and cellular substances of kidney fibrosis include growth factors, such as fibroblast growth factor (FGF), transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF), alongside cytokines (like interleukin-1b) and metalloproteinases. Therefore, these factors can be evaluated as possible targets for anti-fibrotic agents. Among the mediators of fibrosis, TGF-β is the dominant facilitator of renal fibrosis that induces ECM construction and accumulation. Numerous studies have focused on the inhibition of TGF-β and its downstream targets for the treatment of renal disease. Abolition of TGF-β mRNA expression was found to be the mechanism of anti-fibrotic drug, pirfenidone, in the heart and kidneys of diabetic rats. Various investigations have shown the impact of pirfenidone in diminishing kidney fibrosis, with studies containing patients diagnosed with subtotal nephrectomy, diabetic kidney disease and unilateral ureteral obstruction (UUO), administered drugs such as cyclosporine, tacrolimus, doxorubicin and vanadate. Several therapeutic drugs for fibrosis reduce only one of the oxidative, inflammatory or profibrogenic markers, while pirfenidone targets all three of these markers and therefore, seems to be a particularly valuable drug.

Implication for health policy/practice/research/medical education:
Various studies have shown the impact of pirfenidone in diminishing kidney fibrosis in chronic kidney disease.
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Review

Introduction

Pirfenidone is a synthetic drug characterized by a small-molecular weight and simple chemical structure (5-methyl-1-phenyl-2(1H)-pyridone). It was primarily accepted as an anthelmintic and antipyretic drug; however, it also has anti-fibrotic and anti-inflammatory activities in a variety of *in vitro*, animal and cell-based models (lung, liver and kidney) (1). Pirfenidone was approved for treatment of idiopathic pulmonary fibrosis (IPF) in 2011 and was launched commercially by InterMune under the trade name Esbriet (2).

After oral administration, it is quickly absorbed by the gastrointestinal (GI) tract since it is highly hydrophilic and can move through cell membranes with relative ease and without requiring a receptor. After one to two hours, it reaches its maximum level in blood and is almost entirely excreted in urine within six hours. It has the advantage of possessing very low toxicity with minor side effects such as nausea, dizziness, headache, photosensitivity and gastrointestinal effects (3).

The anti-fibrotic effects of pirfenidone have also been demonstrated in other models of tissue fibrosis such

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as bleomycin-induced pulmonary fibrosis (4), multiple sclerosis (5) and liver fibrosis associated with chronic hepatitis C infection (6).

Renal fibrosis

Chronic kidney disease (CKD) heavily contributes to mortality and morbidity worldwide. Renal fibrosis is the hallmark of CKD progression, characterized by excessive accumulation of extracellular matrix (ECM) proteins, which plays a central role in the pathogenesis and progression of CKD to end-stage renal disease (ESRD) (1). CKD is often a comorbid condition in patients with IPF as up to 30% of IPF patients are also afflicted with underlying chronic renal failure (stages 3-5). Individuals with both conditions demonstrate worse prognosis, decreased survival, greater incidence of hypertension and ischemic heart disease, alongside lower lung diffusion capacity and exercise capacity than those who suffer from IPF without CKD (7).

Progression of fibrosis involves both cell-intrinsic/autonomous and ECM-driven mechanisms. Activated myofibroblasts are the main ECM component causing fibrosis. The cellular and molecular mediators of kidney fibrosis include growth factors, such as fibroblast growth factor (FGF), transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF), alongside cytokines (such as interleukin-1b), imbalances in metalloproteinases and their inhibitors, which may all act as suitable targets of antifibrotic drugs (8).

TGF-β-induced ECM production and accumulation is the central mediator of renal fibrosis, with numerous studies focusing on the inhibition of TGF-β and its downstream targets for the treatment of renal disease. Diabetic nephropathy is associated with increased TGF-β messenger RNA (mRNA) expression and induced progressive renal disease, which is characterized by thickening of the glomerular basement membrane, mesangial expansion, accumulation of matrix proteins and proteinuria. The abolition of TGF-β mRNA expression is allegedly the mechanism for the antifibrotic medications and the anti-fibrotic effect of pirfenidone in the hearts and kidneys of diabetic rats. Blocking TGF-β may have important hemodynamic effects relevant to diabetic complications. Additionally, a long-term and continuous total blockade of glomerular TGF-β may decrease proteinuria (9). However, inhibition of TGF-β reduces renal disease (10-14).

Mechanism of action of pirfenidone

In a study, mitogen activated protein kinase (MAPK) is activated in the obstructed kidney of rats with unilateral ureteral obstruction (UUO) and in TGF-β-treated renal tubular epithelial cells. Pirfenidone is able to inhibit tubular epithelial–mesenchymal transition (EMT) and renal fibrosis. Pirfenidone is also capable to reduce cellular proliferation *in vivo* and *in vitro* through downregulating the MAPK pathway (13-18). Chen et al showed that pirfenidone inhibits caspase-9 and caspase-3 cleavage in renal proximal tubular cells and inhibited apoptosis of epithelial tubular cells in a dosage-dependent fashion. Therefore, pirfenidone may also reduce oxidative stress by inhibiting the mitochondrial apoptotic-signaling pathway in renal tubular cells (19).

Pirfenidone at the concentration with having anti-fibrotic impacts is very toxic *in-vitro*. This effect could explain the inconsistencies between various studies on experimental models (20-25).

The renoprotective properties and mechanism of pirfenidone in a rat model with hypertension-induced renal injury was also investigated and pirfenidone was shown to prevent renal injury by its anti-fibrotic and anti-oxidative stress effects via the downregulation of TGF-β-Smad2/3signaling, improvement of MMP9/TIMP1 balance and suppression of fibroblast proliferation, without effect on the expression of tumor necrosis factor alpha protein, macrophage, T cell infiltration or plasma interleukin 1-beta levels (26).

Various therapeutic drugs for fibrosis reduction affect only one of the oxidative, inflammatory or a profibrogenic markers whereas pirfenidone targets all three markers, introducing it as a promising treatment. Hence, pirfenidone might be favorable not only in experimental studies, but also in human fibrotic disorders (3).

Pirfenidone in renal fibrosis

The TGF-β function is influenced by non-Smad and Smad signaling pathways in most cases. TGF-β/Smad signaling pathways often comprise effective therapeutic targets for treatment of renal fibrosis and inflammation. The targets, Smad2 and Smad3, are regulated by specific microRNAs, phosphorylation and nuclear translocation. Therefore, inhibition of Smad3 and up-regulation of Smad7, which improves the TGF-β /Smad signaling, may provide an effective strategy to prevent renal fibrosis and CKD progression (Figure 1) (10).

A study on animal models by Chen et al confirmed that treatment with an anti-TGF-β antibody in diabetic nephropathy models improved glomerular matrix expansion and renal function however it did not affect proteinuria and macromolecular permeability (11). Unfortunately, most of the completed clinical trials about anti-TGF-β therapy have small sample sizes and were provided by definitive results. The plasminogen activator inhibitor-1 (PAI-1) and PDGF were associated with TGF-β and renal fibrosis in the epithelial cells of proximal tubules in a rat model. Pirfenidone inhibits these fibrosis cascades, which results in similar antifibrotic effects in the kidney (12,25-28). Fibroblasts have been universally recognized in tubulointerstitial injury, where their presence is a marker of disease progression. Recently,

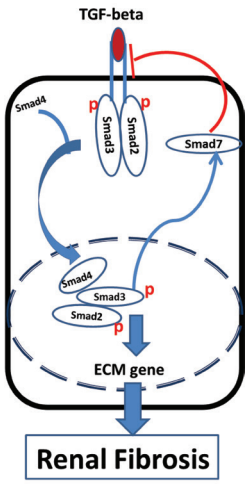

Figure 1. Various roles of Smads in renal fibrosis. P represents phosphorylated Smad. The phosphorylated Smad2 and Smad3 bind to Smad4 and form the Smad complex, which translocates into the nucleus and regulates the target gene transcription, including Smad7. Blue lines indicate pathogenic regulation pathways, while red arrows represent protective regulation pathways. Smad2 and Smad3 act as TGF-β/activin signaling and Smad 4 acts as transport of Smad2 and Smad3. Smad7 is an inhibitory Smad that functions to block Smad2/3 activation.

pirfenidone administrated in rats with UUO was shown to ameliorate progressive fibrosis and reduce established scarring, possibly acting as a novel anti-fibrotic agent. It has been shown that pirfenidone decreased spinal muscular atrophy and connective tissue growth factor protein expression. Effects of pirfenidone were independent of cell toxicity. Down-regulation of renal fibroblast activation and proliferation are mechanisms of action specific to pirfenidone (13).

Pirfenidone reduced glomerulosclerosis effectively in diabetic mice and in an animal model with subtotal nephrectomy by decreasing tubulointerstitial fibrosis. Moreover, it was shown in glomerular mesangial cells of mice that pirfenidone decreased TGF-β promoter activity, abolished TGF-β protein secretion, prevented Smad2-phosphorylation, and reduced reactive oxygen species (ROS) production induced by TGF-β (1-5).

In a study by Matsumoto et al, pirfenidone dramatically suppressed the progression to renal dysfunction in CKD patients with glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for six months or longer after starting treatment (14).

A study on hemodialysis patients with a history of sclerosing peritonitis demonstrated pirfenidone to be well tolerated even in ESRD patients without the need for dose reduction (15). An open-label, single-center, phase III pilot trial on 18 patients diagnosed with focal segmental glomerulosclerosis demonstrated treatment with pirfenidone slowed renal function decline rate by almost 25% (16). In a randomized, placebo-controlled phase II trial involving 77 individuals with diabetic nephropathy and albuminuria, the estimated GFR (eGFR) improved by 3.3 mL/min/1.73 m^2 in the group treated with 1200 mg of pirfenidone compared to 2.2 mL/min/1.73 m^2 in the placebo treated group at 54 weeks of treatment. However, no changes were observed in proteinuria or urinary TGF-β excretion (29). It should be noted that eGFR increased only in the lowest pirfenidone dosage group (1200 mg) and decreased in the higher dosage group (2400 mg), similar to the placebo group (17). Based on this study, it appears that pirfenidone may primarily exert its beneficial effects by reducing fibrosis in the tubulointerstitium instead of causing glomerular changes or affecting albuminuria and proteinuria.

Similarly, an open-label, nonrandomized pilot trial evaluated the safety of a new formulation of prolonged-release pirfenidone (2400 mg daily) in 18 patients with CKD, specifically with focal and segmental glomerular hyalinization (FSGH) over 60 months. This study found that the prolonged release pirfenidone slowed renal function decline significantly in CKD patients. While, eGFR, creatinine, cystatin C, urea, hemoglobin and hepatic transaminases levels was not changed in this study, however proteinuria was improved. This new pharmaceutical formulation of pirfenidone displayed minor side effects and increased tolerance compared to pirfenidone preparations used in previous studies. Prolonged release pirfenidone can safely be administered as an adjuvant therapy in patients with CKD (18).

The beneficial impact of pirfenidone in diminishing kidney fibrosis has been detected in various investigations, consisting of models of subtotal nephrectomy (19-22), diabetic nephropathy (14), cyclosporine (23), tacrolimus (24), doxorubicin (25) and vanadate (26) as explained in detail below.

A study by Takakura et al (20) detected that prophylactic therapy with pirfenidone diminished fibrosis by 80% with improvement of proteinuria as well as serum blood urea nitrogen and creatinine levels.

Shimizu et al (21) showed pirfenidone treatment inhibited 60% of collagen deposition after nephrectomy, associated with decreased presentation of collagen mRNAs and TGF-β in the subtotal 5/6 nephrectomy model, and was also associated with improved creatinine clearance.

UUO is a well-characterized model of experimental renal disease, which leads to tubulointerstitial fibrosis. The mRNA for collagen types IV and I, TGF-β and matrix metalloproteinase-2 (MMP-2) are upregulated in this model, while hydroxyproline content is increased in the post-obstructed kidney. After three days UUO onset, pirfenidone concentrations increased in cortical fibroblasts isolated from kidneys, causing a reduction in cell proliferation, smooth muscle actin, connective tissue growth factor presentation and hydroxyproline, without effects on collagen. Therefore, pirfenidone was shown to prevent renal damage, renal fibrosis, and irreversible renal failure in UUO models (22).

In isolated perfused kidneys of rats, streptozotocin treatment induced diabetes and temporarily decreased renal function and urine flow rates. Treatment with pirfenidone and spironolactone caused reversal of kidney and cardiac fibrosis and also weakened enhanced diastolic stiffness, which emphasizes the dynamic nature of the ECM. This study also showed high diabetes-induced cardiac stiffness to be lowered by pirfenidone (23).

Recent studies showed that combination treatment of pirfenidone with candesartan in rats with chronic anti-glomerular basement membrane glomerulonephritis demonstrated an additive effect compared to pirfenidone alone. Combination treatment improved absorption of droplets, reduction in proteinuria and decrease of cortical collagen I mRNA expression (28).

Pirfenidone also decreased sclerosis scores and proteinuria levels at three months using FGS/Kist mice as a model of spontaneous progressive glomerulosclerosis. However, this study showed no significant differences regarding effective therapy after the treatment period between the pirfenidone and control groups. It is suggested that longstanding administration of pirfenidone is required to reduce the development of kidney glomerulosclerosis and to ameliorate kidney activity in the FGS/Kist mice (29).

The antifibrotic effects of pirfenidone in a vanadate-induced renal fibrosis model in rats were also explored. Therapy with pirfenidone diminished vanadate-induced elevation of renal weight, collagen substance, RNA content and hydroxyproline concentrations. Morphological assessment disclosed that the intensity of the injury decreased to a mild degree after treatment with pirfenidone for 41 days, while it was of moderate to severe degree in the vanadate-treated group (26).

Chronic cyclosporine nephrotoxicity is characterized by tubulointerstitial fibrosis with increased TGF-β. Treatment with pirfenidone improved cyclosporine-induced fibrosis approximately 50%, decreased TGF-β expression about 80% and reduced the quantity of apoptosis-positive cells. Pirfenidone down-regulated mRNA expression of cyclosporine-induced p53, Fas-ligand and caspase 3 presentation especially in kidney epithelial cells (30). Reduction in apoptosis through apoptosis-regulatory genes acts as a mechanism underlying antifibrotic properties of pirfenidone (30).

Nephrotoxicity induced by tacrolimus modifies expression of mRNA for genes implicated in matrix metabolism and therefore father kidney transplantation dysfunction and subsequent renal failure. It is suggested that pirfenidone may decrease the fibrotic potential of tacrolimus, decreasing tissue inhibitors of metalloproteinases-1 (TIMP-1) mRNA and collagen III expression, which plays a crucial role in ECM composition (30).

More recent studies have shown pirfenidone to prevent acute renal damage induced by bilateral ischemia in rats. Pirfenidone is suggested to be a promising drug to reduce renal injury induced by ischemia and improve reperfusion by recovering nitric oxide production (31). The advantages of pirfenidone surpass its adverse events including dyspepsia, abdominal discomfort, sedation and fatigue.

Conclusion

Numerous investigations demonstrated the beneficial impact of pirfenidone in decreasing kidney fibrosis under various models such as UUO, diabetic kidney disease, subtotal nephrectomy, cyclosporine, tacrolimus and doxorubicin therapy as explored above. Several therapeutic drugs for fibrosis reduce only one of oxidative, inflammatory, or profibrogenic markers whereas pirfenidone targets all three markers and therefore, seems to be a particularly valuable drug. Various studies uncovered pirfenidone as a medication that can slow kidney insufficiency, and even recover kidney structure and function in individuals with diabetic kidney disease.

Authors' contribution

Primary draft by SG and AP. First edit by JB, YRH. Second edit by NA, AJ, FK and LM. All authors read and signed the final manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors.

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