Do We Have a Pill for Renal Fibrosis?

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Renal fibrosis, characterized by glomerulosclerosis and tubulointerstitial fibrosis, is the final common pathway of a wide variety of chronic kidney diseases (CKD). Regardless of the underlying disorder and whether the injury is sustained, the kidney will follow a doomsday path of fibrogenesis, a condition characterized by excessive extracellular matrix accumulation. Can we do anything to slow the rate of functional decline associated with fibrotic renal diseases? This major challenge requires an understanding of the mechanisms involved in the pathogenesis of renal fibrosis. Doing so may allow us to develop new therapeutic targets to ameliorate disease directly and to identify those who are at risk for future disease.

It should be stressed that renal fibrosis is a dynamic process in which many cellular events occur simultaneously, often in a mutually stimulating manner. These events include increased matrix production, inhibition of matrix degradation, modulation of matrix receptors to facilitate cell–matrix interactions, mesangial and fibroblast activation, tubular epithelial-to-mesenchymal transition, monocyteic and lymphocytic cell infiltration, and cell apoptosis. It is also widely accepted that TGF-β and its downstream Smad signaling play an essential role in tissue fibrosis in general and in renal fibrosis in particular. Therefore, therapeutic targeting of TGF-β is seemingly critical and attractive and holds much hope for slowing or halting fibrosis.

Attempts to block renal fibrosis have been successful in laboratory settings but have fallen short of the goal in clinical practice. The approach of limiting fibrosis through angiotensin II inhibition or antagonism has been exploited clinically, but the success has been limited. In the laboratory setting, some of the TGF-β-targeted therapies have included neutralizing antibodies, antisense oligonucleotides, and natural inhibitors such as the hormone relaxin and the proteoglycan decorin. However, these experimental interventions proved to be difficult to carry to the real world. It is for this reason that a great deal of interest has emerged when a relatively novel antifibrotic molecule, pirfenidone, was introduced (1). To make things better, it is a pill!

Pirfenidone (5-methyl-N-phenyl-2-(1H)-pyridone) is a small, nonpeptide, orally available molecule that has been shown to prevent or even reverse excess matrix accumulation in experimental models, including pulmonary fibrosis (2), peritoneal sclerosis (3), cardiac fibrosis (4), and progressive renal diseases (5–8). The antifibrotic properties of pirfenidone are poorly understood. Pirfenidone has been shown to decrease TGF-β1 production and actions on matrix synthesis, to antagonize TNF-α, and to be a scavenger of reactive oxygen species. Moreover, pirfenidone may reduce the availability of hydroxyproline required for collagen synthesis and was shown to reduce fibroblast proliferation and macrophage infiltration. In a rat model of chronic cyclosporine nephrotoxicity, pirfenidone ameliorated interstitial fibrosis by approximately 50% and reduced TGF-β1 mRNA and protein expression in addition to decreasing plasminogen activator inhibitor-1 and other extracellular matrix proteins (5). It also affected the balance of apoptotic genes in a manner that favored antiapoptosis, resulting in downregulation of caspase activity (6). Similar results were previously observed in other progressive renal disease models, including the remnant kidney model (7), and in unilateral ureteral obstruction (8), a well-characterized model of tubulointerstitial fibrosis.

The first clinical use of pirfenidone was in the setting of idiopathic pulmonary fibrosis (IPF). Two uncontrolled, open-label studies of oral pirfenidone have been published. Raghu et al. (9) studied the drug in 54 patients with IPF and suggested that it may help to stabilize lung function. Nagai et al. (10) studied eight patients with IPF and noticed no deterioration in the chest radiographic scores and arterial oxygen pressure. Pirfenidone was also shown to slow the progression of lung impairment in a small group of patients with pulmonary fibrosis as a result of Hermansky-Pudlak syndrome (11). A recent randomized phase II trial in IPF showed a significant improvement in exercise-induced hypoxemia in pirfenidone-treated patients, but the study was aborted early because of an increase in acute exacerbations in the placebo group (12). Conversely, the results were discouraging in pilot studies involving patients with myelofibrosis (13) and in primary sclerosing cholangitis (14), whereas they were inconclusive in familial adenomatous polyposis (15). More recently, pirfenidone proved to be useful in a small group of patients with advanced liver fibrosis (16), in patients with secondary progressive multiple sclerosis (17), and in patients with neurofibromatosis type 1 (18). In addition, pirfenidone ameliorated radiation-induced fibrosis in seven patients who had undergone regional radiation therapy (19). In all of those studies, adverse effects that were attributable to the drug were relatively minimal and were mostly gastrointestinal (e.g., dyspepsia, nausea), sedation or fatigue, and a photosensitivity dermatitis.

This issue of CJASN offers the first glimpse on the clinical
safety and efficacy of pirfenidone in kidney disease. The study by Cho et al. (20) presented the results of a relatively small open-label trial in idiopathic and postadaptive FSGS. In the period before starting pirfenidone, all patients had a well-controlled BP, and most of them received an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. Of the 21 patients enrolled, 18 completed a median of 13.4 mo of therapy. These were patients with advanced CKD, because the median baseline GFR was 27 ml/min per 1.73 m². The monthly rate of decline in GFR improved from −0.61 during the baseline period to −0.45 ml/min per 1.73 m² during the treatment period. These changes are seemingly small but were statistically significant. A notable finding was also that pirfenidone had no effect on BP or proteinuria.

In addition to the number of patients being small, the authors acknowledged that their study had serious limitations, namely that it lacked a placebo control; that all of their patients had moderate to severe CKD, which may not apply to all patients with FSGS; and that serial biopsies were not performed to assess regression of fibrosis. Another important limitation is that FSGS is a heterogeneous group of disorders; therefore, we may be dealing with different disease entities. One would argue that it should not matter, because the benefit of pirfenidone is likely due to its effect on TGF-β and that TGF-β represents the final common pathway for a number of fibrotic renal diseases. However, TGF-β is upregulated as a result of tissue injury, and its expression is related to whether the tissue injury is sustained and to the type and severity of the injury. In addition, TGF-β has known immunosuppressive qualities and may play a beneficial role in certain inflammatory states. As a result, a study that targets TGF-β actions would benefit from measurement of TGF-β in the kidney, the blood, or the urine. What strengthens that argument is the need to determine the direct impact of TGF-β inhibition on actual fibrosis, especially because proteinuria was not affected in this study. Although the authors have offered some reasonable explanations, these remain unsatisfying to explain the benefit of therapy in a glomerular disease in which proteinuria is a major manifestation. After all, most of the clinical studies that examine the renoprotective effect of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in glomerular diseases showed an associated reduction in proteinuria.

We will be able to obtain some of this information soon from a phase II study with pirfenidone that is under way in patients with diabetic nephropathy, a more homogeneous type of kidney disease. This randomized, placebo-controlled, dosage-ranging trial has completed enrollment, and the results should be forthcoming. Although the primary end point is change in renal function, the other, secondary end points are changes in urinary albumin excretion and, importantly, in levels of plasma and urinary TGF-β in addition to examining retinopathy. Nevertheless, at a time when the armamentarium to treat CKD is very limited, having a new therapy on hand is very exciting. However, before any foregone conclusions are made regarding the safety and efficacy of pirfenidone, there is a need to conduct large-scale, well-controlled studies in different types of kidney disease. Maybe there is hope on the horizon!

Disclosures
None.

References
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See the related article, “Pirfenidone Slows Renal Function Decline in Patients with Focal Segmental Glomerulosclerosis,” on pages 906–913.