Treatment of Renal Fibrosis—Turning Challenges into Opportunities

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Current treatment modalities are not effective in halting the progression of most CKD. Renal fibrosis is a pathological process common to all CKD and thereby represents an excellent treatment target. A large number of molecular pathways involved in renal fibrosis were identified in preclinical studies, some of them being similar among different organs and some with available drugs in various phases of clinical testing. Yet only few clinical trials with antifibrotic drugs are being conducted in CKD patients. Here we review those clinical trials, focusing on agents with direct antifibrotic effects, with particular focus on pirfenidone and neutralizing antibodies directed against profibrotic growth factors and cell connection proteins. We discuss the potential reasons for the poor translation in treatment of renal fibrosis and propose possible approaches and future developments to improve it, eg, patient selection and companion diagnostics, specific and sensitive biomarkers as novel end points for clinical trials, and drug-targeting and theranostics.

Key Words: Chronic kidney disease, Growth factors, Antifibrotic therapy, Biomarker, Kidney imaging

INTRODUCTION

CKD affects more than 10% of the Western population and even higher proportions of populations in low- and middle-income countries with steadily increasing incidence and prevalence.[1-3] CKD is one of the major causes of death worldwide.[4]

The common pathologic finding in CKD is renal fibrosis, defined as excessive accumulation of extracellular matrix (ECM) deposited by activated and expanded ECM-producing cells. It affects all compartments of the kidney, termed glomerulosclerosis, tubulointerstitial fibrosis, and arterio- and arteriolosclerosis (Fig 1). In advanced disease, all compartments are affected but dependent on the underlying disease, one compartment can show more prominent fibrotic changes than the others.

Fibrosis is part of the evolutionary essential process of wound healing and is activated after any type of tissue injury. Based on the primary insult, the cells that initiate ECM overproduction are epithelial and endothelial cells, including podocytes, but perhaps also mesenchymal cells themselves like mesangial cells, fibroblasts, and pericytes. These injured cells start to produce a number of signaling molecules that act in a paracrine and possibly also autocrine manner and in a profibrotic way on the cells mainly depositing ECM, ie, mesangial cells but also parietal epithelial cells of the glomeruli, fibroblasts in the cortex, pericytes in the medulla, and vascular smooth muscle cells and perivascular fibroblasts in the vessels (Fig 1). Other kidney cells, eg, tubular epithelial cells and endothelial cells, can also produce increased amounts of ECM, but this is likely much less compared with mesenchymal cells, most likely confined to the basement membranes resulting in their thickening and is not per se termed fibrosis. As wound healing itself, fibrosis might have beneficial effects, eg, after pyelonephritis to maintain the integrity and functionality of the rest of the organ. However, the majority of kidney diseases diagnosed nowadays were unlikely to undergo any evolutionary selection, and fibrosis induced by such diseases is most likely pathological. In line with this, the vast majority of studies show that less fibrosis is accompanied by improved kidney function, and conversely, to the best of our knowledge, there are no studies showing that a reduction of fibrosis would lead to worsening of kidney function.

Once deposited and modified, eg, by cross-linking, ECM becomes resistant to degradation and thereby reduces chances for regeneration *ad integrum*. Fibrosis can also become self-sustained. For example, fibroblasts from fibrotic kidneys exhibit epigenetic alterations rendering them persistently active.[5] Although fibrosis is almost invariably associated with inflammation, fibrosis can also occur in the absence of inflammation.[6] Given its evolutionary importance, the process of fibrosis seems to be similar among various organs, involving similar and in their effects redundant molecular pathways.

Renal fibrosis is easily detectable and quantifiable in experimental models. Fibrosis is therefore often used as an end point of studies analyzing potential treatment targets, which are then often labeled "antifibrotic." However, only few of these molecules are truly antifibrotic, ie, directly reducing the activation, expansion, and ECM production of renal mesenchymal cells like fibroblasts or pericytes. Examples of directly profibrotic molecules include growth factors like transforming growth factor β (TGF-β) or connective tissue growth factor (CTGF).[7] These factors have considerable differences when it comes to their effects on other processes, such as inflammation or regeneration, which has to be taken into account when considering their antifibrotic therapeutic potential.

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Currently, the standard therapy to slow down the progression of CKD is blockade of the renin-angiotensin-aldosterone system (RAAS) using angiotensin-converting enzyme inhibitors, angiotensin II receptor type 1 (AT1) antagonists, or direct renin blockers. These drugs also have, mainly indirect, antifibrotic effects in experimental studies. In many cases, however, RAAS blockade is not sufficient to halt the progression of CKD let alone to reverse it.

At present, there are no drugs in clinical use that specifically target kidney cells or kidney fibrosis. Here we review clinical trials focusing on drugs that we believe are directly antifibrotic (Fig 1). We identified respective studies in CKD patients by searching the literature (Pubmed), Internet, and https://clinicaltrials.gov/ (Table 1). Most identified studies are in phase 2, and we have divided them based on molecular targets, ie, growth factors and cell connection proteins. We will not discuss potential targets that are not yet in clinical testing or are being tested only in other organs.[8,9] We do not focus on studies on agents tested in CKD patients that might have secondary antifibrotic effects, eg, anti-inflammatory agents, such as acthar gel (repository corticotropin for injection; NCT01129284, NCT01155141, NCT02006849, NCT02382523, NCT02633046, NCT02683889, NCT02399462), rituximab (anti-CD20 antibody; NCT00550342, NCT00981838, NCT00498368, NCT01268033, NCT01573533, NCT01164098), adalimumab (anti-tumor necrosis factor-α antibody; NCT00193648, NCT 00814255), C–C chemokine receptor type 2 (CCR2) antagonists PF-04634817 (NCT01712 061) and CCX140-B (NCT 01447147), or antihypertensives like, eg, Atrasentan (ET_A receptor antagonist; NCT00920764, NCT 01356849, NCT01399580, NCT 01424319, NCT01858532). Here, we mainly focus on pharmacologic inhibitors of fibrosis and, therefore, will not discuss cellular therapies, in particular with mesenchymal stem cells (MSC), which were shown to have antifibrotic effects in preclinical studies,[10,11] but these seem to be mainly because of their production of anti-inflammatory and pro-angiogenic molecules. There are three clinical trials recruiting patients with transplant rejection (NCT02057965, phase 2) or focal segmental glomerulosclerosis (FSGS; NCT02693366, NCT02382874, both phase 1) to test the direct antifibrotic potential of MSC therapy. Additionally, although preclinical studies describe impressive benefits of MSC in renal fibrosis, the safety of stem cell therapy in CKD cannot yet be taken for granted because studies have shown that uremia may induce senescence or maldifferentiation of MSC.[12,13] Finally, we discuss potential pitfalls and shortcomings in translational research in renal fibrosis and propose some potential solutions for future research and development.

CLINICAL SUMMARY

- There are currently no drugs for CKD and fibrosis in clinical use that would specifically target the kidney.
- Despite a number of potential anti-fibrotic treatment targets identified in preclinical studies, translation to clinical trials has remained remarkably poor.
- Poor translation is due to several challenges in performing clinical trials in CKD and renal fibrosis, particularly due to the lack of short-term fibrosis-specific surrogate endpoints for clinical trials, insufficient patient selection or lack of companion diagnostics.
- Given the world-wide burden of CKD, overcoming these translational challenges and improving drug development should be one of the research priorities for the future.

CLINICAL TRIALS WITH DIRECT ANTIFIBROTIC AGENTS

Growth Factors

Growth factor signaling is the best described stimulus for activation and ECM production of mesenchymal cells and an important factor in the early and active stages of fibrogenesis (Fig 1).

One of the best-characterized profibrotic growth factors is TGF-β. A large number of animal studies have confirmed a reduction of fibrosis and an improved kidney function after inhibition of the TGF-β pathway by neutralizing antibodies, antisense oligodeoxynucleotides, soluble receptors, or specific inhibitors of TGF-β kinases.[9,14,15] Neutralizing anti-TGF-β antibodies were also tested in clinical studies. A phase 1 trial tested fresolimumab (human monoclonal antibody against TGF-β) in FSGS (NCT00464321),[16] but the following phase 2 study failed to show significant renoprotective effects in steroid-resistant FSGS patients (NCT01665391). In the latter trial, patients received monthly intravenous injections of either 1 or 4 mg fresolimumab per kilogram total body weight for 9 months. Compared with placebo, neither fresolimumab group showed a benefit on the primary outcome (partial or complete remission assessed by urinary protein/creatinine ratio) and also not a reduction of adverse events. However, fresolimumab-treated patients did experience a stabilized course of estimated glomerular filtration rate (eGFR), whereas in placebo-treated patients the eGFR steadily decreased.[17] This example shows one of the potential pitfalls in study design, particularly study duration and selection of the primary end point (see subsequently).

In another phase 2 study, patients with diabetic nephropathy received a different TGF-β antibody, LY2382770, subcutaneously (2, 10 or 50 mg monthly) for 12 months with the primary outcome of change in serum creatinine from baseline to 12 months (NCT01113801). No outcomes have been published yet, but the study was terminated prematurely in 2015 because of lack of efficacy.

Pirfenidone, a small synthetic molecule, was shown to reduce renal fibrosis in preclinical models, most likely via blocking the TGF-β promotor.[18] In a phase 2 study in patients with FSGS (NCT00001959), treatment with pirfenidone had no effect on blood pressure or proteinuria, but GFR decline was reduced by 25%.[19] However, in placebo-controlled phase 1 and 2 studies in diabetic patients, pirfenidone did not significantly affect GFR loss (NCT00063583).[20] An ongoing phase 3 placebo-controlled trial to study the "effect of pirfenidone on