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Making Progress on Chronic Kidney Disease Treatments

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Dedication : This paper is dedicated to my uncle Late Ganesh Chandra Dahal.

ABSTRACT

The impact of chronic kidney disease (CKD) on society is deadly and rising quickly. In spite of this, there aren't many therapies being developed to treat CKD. The interest in investing in pharmaceuticals has decreased as a result of several recent expensive phase 3 trials that failed to deliver improved kidney results. Furthermore, sluggish trial recruitment and successful implementation of these studies have been attributed to limited patient, physician, and payer knowledge of CKD as a diagnosis. Nevertheless, a number of therapies, such as anti-oxidant medications, sodium/glucose cotransporter 2 inhibitors, mineralocorticoid-receptor antagonists, and anti-inflammatory medications, are still being researched and developed for the treatment of CKD. Future CKD therapy trials' success will depend not only on increased knowledge of the disease's aetiology but also on higher trial enrollment rates brought about by greater public, governmental, and medical community understanding of this condition.

KEYWORDS : Diabetic nephropathy, SGTL2, Angiotensin, Inflammation, Renal outcomes

INTRODUCTION

One of the most lethal and expensive diseases for both patients and modern society is kidney failure. In the United States, more than 100,000 new patients begin dialysis each year, while roughly the same number pass away. 1 End-stage renal disease (ESRD) has a worse prognosis than most malignancies since more than 20% of patients who begin dialysis die within the first year2 and more than 70% of diabetic patients who begin dialysis die within five years3. Less than ten percent of patients are even aware that they have early chronic kidney disease (CKD), and a comparable amount of doctors neglect to diagnose CKD when it is present.4 . Although the care of individuals with kidney disease in USA cost more than $50 billion in 2013, accounting for 20% of all Medicare spending on patients over 65, society is still unaware of the rise of renal failure as a significant health and financial burden. An additional $31 billion was spent on dialysis patient care in 2013. 1 Around 500 million persons are thought to have chronic renal disease worldwide. 5 In contrast to practically every other medical field, there are less interventional studies being conducted to create medicines that can stop the progression of renal disease. 6,7. One of the main challenges preventing the development of drugs for CKD is the slow patient enrolment (partly due to low disease awareness), regulatory requirements for strict patient outcomes for medication registration, and limited payer engagement. 6,8–10 Some pharmaceutical companies have continued to be drawn to the development of medications for this use only because of the unmet medical need.

The main cause of renal failure in developed countries is diabetic nephropathy (DN), and the burden of end-stage renal disease (ESRD) caused by type 2 diabetes mellitus (T2DM) is predicted to increase by four times in the coming decades11,12, in part because T2DM is more common in younger populations. 13 Even though nephropathy only affects a small percentage of diabetic individuals, the 10 to 30 % who do develop end-stage renal disease (ESRD) constitute an unsustainable burden on society. 14,15 Genetic studies have not provided conclusive information, thus it is still unclear why some diabetic patients experience nephropathy while others do not. 16–19 . However, many therapeutic development programmes have concentrated on DN as an indication due to its prevalence in comparison to other causes of ESRD and the substantial unmet need for the medicines to stop or reduce the development of kidney failure.

Nephropathy's pathogenesis in diabetic patients who go on to develop it is still unknown. Although mesangial, podocyte, and endothelial glycocaylx23,24 dysfunction have all been implicated, it is still unclear which cellular and molecular abnormalities are responsible for the disease. Since only around 40% of individuals with type 2 diabetes

mellitus demonstrate evidence of classic DN lesions, the variability of biopsy findings further complicates our knowledge of the pathophysiology of nephropathy in this condition. 25–27 A growing body of research suggests that inflammation may also play a role in the treatment of patients with classic histopathologic signs of DN, including glomerular hyperfiltration28, albuminuria29, and glomerular hyperfiltration. 32-34 . It is significant that the severity of the glomerular lesions correlates less strongly than the tubulointerstitial inflammation with poor renal outcomes35, and anti-inflammatory medicines may play a role in this relationship. 36 However, many T2DM patients who have had a biopsy also have acute tubular necrosis, focal segmental glomerulosclerosis, or hypertensive nephropathy, which makes it more difficult to identify the best treatments to halt the progression of the illness in a particular patient.

CHRONIC KIDNEY DISEASE CURRENTLY UNDERGOING THERAPY

For the treatment of diabetic nephropathy and many other types of CKD, angiotensin-converting enzyme inhibitors (ACEis) or angiotensin-receptor blockers (ARBs) are currently the gold standard of therapy. 38,39 In addition to lowering proteinuria (and albuminuria), ACEi/ARB medication also lowers the number of diabetic individuals who eventually need dialysis each year. 40–42 The ability of this family of medications to regulate glomerular hyperfiltration in the diabetic kidney has been linked to the renoprotective effect. 43,44 Reduced hyperfiltration is in line with the clinical finding that starting ACEi/ARB medication is linked to an immediate drop in estimated glomerular filtration rate (eGFR) and that larger eGFR drops were linked to less long-term loss of renal function. 45. Although ACEi/ARB medication decreases renal functional loss in DN, neither remission nor even a halt in the progression to ESRD are guaranteed by it. Recent efforts to increase renal protection have concentrated on further inhibiting the renin-angiotensin system, however combinations of ACEi plus ARB or renin blockage with ACEi or ARB have failed to deliver the desired results. 46,47 The combination therapies of both strategies were linked to increased hyperkalemia, hypotension, and acute renal injury, which led to the early discontinuation of the trials. Combination techniques are troublesome since both hypotension and hyperkalemia are likely pathways linked to negative effects. Spironolactone and epleronone are examples of mineralocorticoid-receptor antagonists that lower blood pressure, eGFR, and albuminuria in diabetic nephropathy but are linked to hyperkalemia. 48–50 Several businesses, notably Finerenone (Bayer),51 CS-3150 (Diachii Sankyo), and MT-3995, are now developing trials combining ACEi and ARB with new mineralocorticoid-receptor antagonists to lower the risk of hyperkalemia in diabetic nephropathy (Mitsubishi). 51 Positive findings from a phase 2 trial of Finerenone in individuals with T2DM and nephropathy showed a dose-dependent decrease in the urine albumin to creatinine ratio of between 21 and 38 percent. 51 It is unclear if the increased risk of hyperkalemia associated with these novel mineralocorticoid receptors will make them more popular among patients with kidney disease than spironolactone or eplerenone.

The development of innovative treatments depends on the discovery of new targets for CKD and diabetic nephropathy due to the lack of clinically proven targets outside of the renin-angiotensin system. Patients with diabetic nephropathy have recently been explored for the treatment of T2DM through inhibition of the sodium/glucose cotransporter 2 (SGLT2). SGLT2 inhibition by either empagliflozin or canagliflozin is linked to further acute albuminuria reduction and a slight acute drop in eGFR when used in combination with ACEi or ARB in DN. 52,53 Because a decrease in albuminuria is closely linked to better renal outcomes,54 it is anticipated that this class will lower the incidence of ESRD. Notably, empagliflozin therapy has recently been demonstrated to significantly improve cardiovascular outcomes in a high-risk diabetic population,55 providing additional support for the likelihood that SGLT2 inhibition may improve renal outcomes in proteinuric individuals with T2DM and nephropathy. It is appealing that empagliflozin medication, in contrast to ACEi/ARB, does not appear to be related with hyperkalemia, suggesting that adding it to ACEi or ARB may not be constrained by this safety risk. 56 Similar to ACEi/ARB, it has been suggested that decreased glomerular hyperfiltration is the mechanism underlying this family of medications' potential benefit in diabetic nephropathy. 28 In addition to lowering hyperglycemia in people with type 2 diabetes, SGLT2 inhibitors also significantly lower glomerular hyperfiltration in people with type 1 diabetes who are glucose-clamped euglycemic. 28 These findings are in accordance with the hypothesis that the drug class increases NaCl transport to the macula densa, stimulating tubuloglomerular feedback and afferent arteriolar constriction in the process. 57,58 Canagliflozin's benefits for individuals with diabetic nephropathy will be fully tested in the CREDENCE study, which is now enrolling 4200 participants at 675 locations throughout the world. 59 SGLT2 inhibitor use is currently not advised in patients with low eGFR and is contraindicated in patients with severe renal impairment. The CREDENCE trial's requirement that patients have an eGFR of greater than 30 mL/min/1.73 m2 is consistent with this, raising questions about the usefulness of this class of medications in stages 4 or 5 of CKD.

EMERGING THERAPIES FOR CHRONIC KIDNEY DISEASE

A phase 3 renal outcomes trial is testing the endothelin receptor type A antagonist (ETRA), atrasentan, on individuals with diabetic nephropathy. 60 In patients with diabetic nephropathy taking ACEi/ARB, it has been demonstrated that treatment with ETRA-receptor antagonists causes an immediate decrease in albuminuria. However, stopping treatment causes an equally immediate return to the higher baseline values. 61,62 These alterations are in line with the systemic arterial blood pressure drop that was seen after ETRA blocking, which is thought to have decreased albuminuria. 61,62 Despite not being linked to hyperkalemia, this family of medications is linked to edoema and conceivably congestive heart failure. 63. This is why patients with severe peripheral edoema, facial edoema requiring diuretics, prior history of heart failure, or increased brain natriuretic peptide greater than 200 pg/mL are not allowed to participate in Study Of Diabetic Nephropathy With Atrasentan, a phase 3 trial of atrasentan in patients with diabetic nephropathy60. Although these exclusion criteria should reduce safety issues, they will greatly restrict recruitment and prevent more widespread use of this class of medication in patients with diabetic nephropathy given the high frequency of heart failure in patients with CKD. It's also noteworthy that atrasentan is linked to an abrupt drop in eGFR, just like ACEi/ARB and SGLT2 inhibitors are. 62. Atrasentan, SGLT2 inhibitors, and ACEi/ARB all have the tendency to acutely lower eGFR, which begs the issue of whether future studies combining these medications may see an increase in acute renal failure, perhaps as a result of decreased renal blood flow, as was seen in ACEi plus ARB trials. It is unclear if the previously mentioned trinity of blood pressure reduction, acute drop in eGFR, and albuminuria can be separated from good renal outcomes from a treatment. A decrease in proteinuria frequently occurs in conjunction with the aforementioned benefits (or albuminuria). Clinical trials have been conducted on a number of medicines that do not immediately lower eGFR or proteinuria, but none of these have been able to successfully improve renal outcomes.

These include sulodexide, which had no effect on blood pressure or serum creatinine levels65, the proposed Nrf2 activator bardoxolone, which was linked to an increase in cardiovascular events and actually increased eGFR and albuminuria64, and a monoclonal antibody to transforming growth factor 1, which had no discernible effect on any of these parameters. It is still debatable whether a medication that lowers proteinuria through any mechanism alone would have a positive effect on the kidneys67,68 or whether lowering proteinuria alone is sufficient to lower blood pressure and eGFR. Nonsteroidal anti-inflammatory medicines, for example, can briefly lower proteinuria and glomerular hyperfiltration,69 but they also raise blood pressure and are linked to a higher risk of cardiovascular death and renal events, 70 to 73 raising doubts about their effectiveness in treating CKD. Two recent phase 2 diabetic nephropathy trials of a NOX1/4 inhibitor, GKT137831, and a phosphodiesterase inhibitor, CTP-499, failed to observe any detectable effect on any of these parameters (Table 1). These costly failures have discouraged pharmaceutical investment in chronic kidney disease. Despite the foregoing observations, a number of businesses are developing drugs for the treatment of chronic renal disease in phase 2 but they do not exhibit all (or any) of the previously mentioned functional properties. A lot of these medications work by inhibiting inflammatory or fibrotic pathways (Fig. 1). Anti-inflammatory steroids and immunosuppressive medications are successful in treating acute glomerulonephritides, but it is less known how well they work in treating chronic kidney disease. 74–76.

TABLE 1 : Selected Ongoing Phase 2 and Phase 3 Drug Development Programs for the Treatment of Diabetic Nephropathy

Drug	MOA Target	Hypothesized Benefit	Phase NCT	Trial Design	Notes
Atrasentan (AbbVie)	Endothelin Receptor A antagonist	Hemodynamic	Phase 3 NCT01858532 SONAR	Phase 3 enrolment (est) n = 4148; completion (est): July 2018	Primary end point: time to the first occurrence of a component of the composite creatinine doubling or ESRD

Canagliflozin (Janssen)	SGLT2 inhibitor	Hemodynamic	Phase 3 NCT02065791 CREDENCE	Phase 3 enrolment (est) n = 4200; completion (est): February 2019	Time to composite end point including end-stage kidney disease (ESRD), doubling of serum creatinine level, renal or cardiovascular death
Pyridorin (Nephrogenex)	Vitamin B6 analog reducing advanced glycosylation end product; protein modification	Antioxidant	Phase 3 NCT02156843 Pioneer	Phase 3 enrollment (est) n = 600; study terminated	Time to the composite end point: >=100% serum creatinine increase or ESRD
Finerenone BAY 94-8862 (Bayer)	Mineralocorticoid-receptor antagonist	Hemodynamic, anti-inflammatory	Phase 3 NCT02540933 FIDELIO-DKD	Phase 3 enrollment n = 4800; est completion May 2019	Time to the onset of kidney failure, a sustained decrease in eGFR ≥ 40%, and renal death
ASP8232 (Astellas)	Vascular adhesion protein 1 inhibitor	Anti-inflammatory	Phase 2 NCT02358096 (ALBUM)	Phase 2 enrollment (est) 110; completion (est) November 2016	Evaluate ASP8232 as add-on therapy to ACEi (or ARB) in reducing albuminuria in patients with T2DM and CKD
Baricitinib (Eli Lilly)	JAK1/2 inhibition	Anti-inflammatory	Phase 2 NCT01683409	Phase 2 enrollment 131; completed	Outcome showed ~30%–40% decrease in UACR
CCX-140 (Chemocentry)	CCR2 antagonist	Anti-inflammatory	Phase 2 NCT01447147	Phase 2 enrollment = 332; completed	Significant 24% reduction in in first morning urinary ACR at 12 wk

CTP-499 (CoNCErt)	Deuterium-containing pentoxyfyl linemetabolite, a multisubtype PDE inhibitor	Antifibrotic	Phase 2 NCT01487109	Phase 2 enrollment 170; completed January 2015	No reported significant change in UACR in CTP-499 compared with placebo at 24 wk
GKT13783 1 (Genkyotex)	NOX1/4 inhibitor	Anti-oxidant	NCT02010242	Phase 2 enrollment (est) n = 200; study completed March2015	Failure to achieve primary outcome of ACR reduction in DN
VPI-2690B	Monoclonal Ab to αVβ3	Inhibition of IGF1	NCT02256790	Phase 2 enrollment	Albuminuria reduction and

	integrin	signaling		(Est) 300;est completion August2017	eGFR preservation 50 wk
GS-4997 (Gilead)	ASK1 inhibitor	Protein kinase inhibitor anti-inflammatory	NCT02 177786	Phase 2 enrollment (est) 300; estimated completion September 2016	Change inestimatedglomerular filtration rate from baseline at week48;UACR reduction

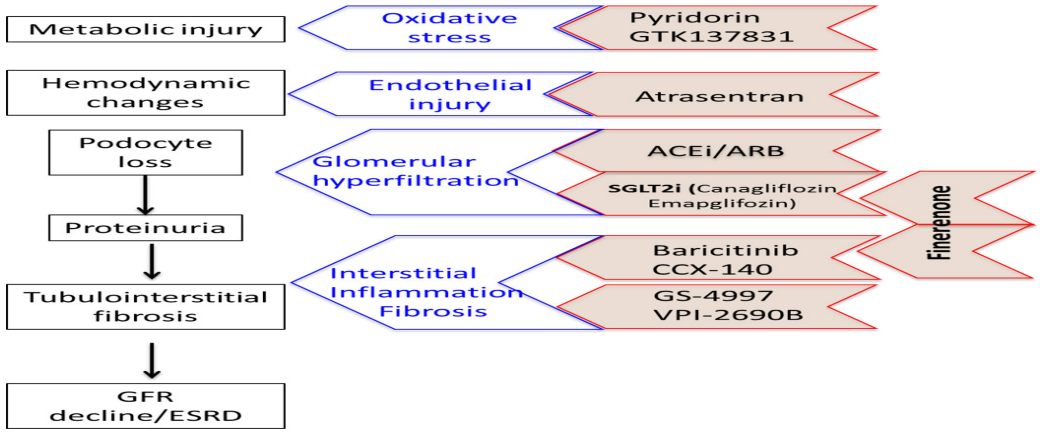
Abbreviations :est, estimated; IGF, insulin-like growth factor; SONAR, Study Of Diabetic Nephropathy With Atrasentan; UACR, urinary albumin creatinine ratio.

There are long-established links between inflammation and progressive CKD, including diabetic renal failure. Increased tubulointerstitial inflammatory cell infiltrates have been linked by Bohle et al35,77 to higher blood creatinine levels and longer disease duration in human kidney biopsy specimens from patients with CKD and diabetic nephropathy. More recent messenger RNA profiling of renal biopsy samples from diabetic nephropathy patients has confirmed that inflammatory pathways are significantly increased in glomeruli and tubules 32,33,78 and has provided evidence for stimulation of macrophage and dendritic cell maturation pathways and cytotoxic T-lymphocyte-mediated apoptosis, in both glomeruli and tubulointerstitial compartments. Leukocyte migration and complement system activation signals were seen in glomeruli in later stages of diabetic nephropathy. 33.

Complement Inhibition

The pathophysiology of numerous renal disorders, such as membranoproliferative glomerulonephritis, post-infectious glomerulonephritis, hemolytic uremic syndrome, and IgA nephropathy, is known to be influenced by complement activation. 80,81 In order to inhibit the production of the pro-inflammatory peptide C5a and the membrane-attack complex C5b-9, eculizumab (Alexion Pharmaceuticals) suppresses the cleavage of the C5 complement protein to C5a and C5b. Patients with atypical hemolytic uremic syndrome and the related thrombotic microangiopathy experienced an increase in eGFR after receiving eculizumab medication. 82,83 Despite the fact that these phase 2 trials were tiny, the effects were strong enough to warrant eculizumab's registration, for which it has since received approval. Complement activation has been suggested to play a role in the pathogenesis of immunological glomerulonephritides as well as diabetic nephropathy, possibly through the glucose-related generation of neoepitopes that activate the lectin complement pathway. 84,85 Additional evidence in favour of this theory comes from molecular profiling tests on kidney biopsy samples and plasma from people with diabetic nephropathy, which reveal complement to be one of the most active pathways. Human diabetic nephropathy kidney biopsy samples exhibit strong expression of 33,86 C3. 33 Complement suppression in animal models of the disease supports possible therapeutic benefit, even though it has not been tried clinically in diabetic nephropathy. 87 Eculizumab is expensive, which makes it difficult to evaluate it for conditions other than atypical hemolytic uremic syndrome. Potential risks of increased infections using this approach must be balanced with efficacy.

FIGURE 1



JAK/STAT Inhibition

Tofacitinib and baricitinib are examples of JAK inhibitors that are currently licenced or under regulatory assessment for the treatment of autoimmune inflammatory disorders such rheumatoid arthritis and ulcerative colitis. 88–90 These medications block JAK and STAT, which are crucial intracellular mediators of inflammatory signalling by IL-6, IL-12, and IL-23 as well as other growth factors like erythropoietin, growth hormone, and epidermal growth factor. 91,92 When a ligand binds to a receptor, a multimer or homodimer is formed, which activates JAK's autophosphorylation activity and STAT's subsequent phosphorylation and nuclear translocation93, additional proinflammatory target genes, such as MCP1, GATA3, IL24, LTB, and SOC3, are transcribed. 94–96. Increased expression of these genes is a key genetic marker for both lupus nephritis and diabetic nephropathy. 32,79,97,98 There has also been evidence of JAK/STAT activation in animal models of kidney illness, such as diabetic mice and rats,32,79 and the administration of a nonselective JAK inhibitor (AG-490) dramatically decreased the excretion of urine protein in diabetic rats. 99 A phase 2 investigation has been launched to examine the clinical efficacy of these JAK inhibitors in kidney disease in light of the anti-inflammatory efficacy of JAK inhibitors that has been clinically demonstrated, as well as the gene pathway signature in diabetic nephropathy. 100,101. In 129 patients with proteinuric diabetic nephropathy who were already on ACE inhibitors or ARBs for the decrease of albuminuria, the effects of 24 weeks of treatment with the JAK1 and JAK2 inhibitor Baricitinib (Eli Lilly/Incyte) on albuminuria were examined. 100 Treatment with baricitinib was linked to a dose-dependent reduction in albuminuria of 30% to 40%. However, one of the negative effects of this family of medications is that they lower haemoglobin levels. Baricitinib was shown to lower haemoglobin by 1.0 to 0.35 g/dL, but did not lower blood pressure. 100 Whether or if these effects on albuminuria decrease translate into long-term advantages for renal function and mortality is still up for debate.

Monocyte Chemoattractant Protein-1/Chemokine Receptor 2 Inhibition

Monocyte chemoattractant protein-1 (MCP-1), also known as chemokine (C-C motif) ligand 2, is not only enhanced by JAK/STAT signalling but may also trigger it. The precise cytokines that activate JAK-STAT signalling in particular kidney disorders are still unknown. By interacting with the chemokine receptor 2 (CCR2) receptor on T cells and macrophages, MCP-1, a secreted protein containing 99 amino acid residues, attracts these cells to the areas of tissue injury101,102 and activates JAK2. 103 Patients who have proteinuric nephropathy have higher levels of MCP-1 in their kidneys, which are primarily found in the tubulointerstitium rather than the glomerulus. 104–106 Patients with diabetic nephropathy also have higher urinary MCP-1 excretion, and higher urine MCP-1 levels seem to be an indicator of worse renal outcomes. 107. Finally, in animal models, blocking CCR2, which is the MCP-1 receptor, slowed the progression of diabetic nephropathy in both diabetic Ins2C96Y Akita mice and db/db mice. 108,109 . A number of businesses have set up clinical trials to evaluate the effectiveness of CCR2 inhibitors in treating human diabetic nephropathy. Oral receptor antagonists for MCP-1/CCR2 (CCX140) and CCR2/CCR5 (PF489791) from Chemocentryx and Pfizer, respectively, are currently undergoing clinical testing to see if they will lower proteinuria in individuals with diabetic nephropathy. 110.

The primary end point of a 52-week, phase II clinical trial of CCX140 in 332 patients with diabetic nephropathy80, 111 was met, demonstrating that treatment with CCX140 added to an ACEi or ARB statistically significantly reduced the urinary albumin creatinine ratio above that attained with standard of care. The 5-mg dosage group experienced the greatest therapeutic benefit, an 18% decrease in urine albumin creatinine ratio, at 12 weeks, and persistent albuminuria reduction caused by CCX140 compared to SOC alone was seen over the course of the entire year. 111 It will need to be determined whether the reported decrease in albuminuria will result in long-term benefits in patient outcomes and slow the rate of decline in renal function. Antifibrotic/anti-inflammatory drugs are still being tested. An endothelial sialoglycoprotein called vascular adhesion protein 1 has its cellular expression stimulated by inflammatory circumstances. 112,113 Vascular adhesion protein 1, also known as amine oxidase, copper-containing 3, interacts with Siglec-9 and 10, two leukocyte adhesion molecules, and has monoamine oxidase activity. Leukocyte egress into inflamed tissue is facilitated by both of these actions, which are crucial. 114,115 Based on these results, Astellas has started a phase 2 research in 110 patients with diabetic nephropathy using ASP8232, a small-molecule inhibitor of amine oxidase, copper containing 3 activity. 116.

Although not yet clinically established, further antifibrotic and anti-inflammatory strategies are under development. The monoclonal antibody VPI-2690B from Vascular Pharmaceuticals interacts to the integrin V3 C-loop domain sequence. 117 This antibody has been demonstrated to lessen atherosclerosis and albuminuria in diabetic pigs and rats. 107,108 It has been suggested that these effects are mediated by inhibiting integrin V3's capacity to activate insulin-

like growth factor 1 signalling in mesangial cells and vascular smooth muscle cells. 117,118 Phase 2 clinical trials for the treatment of diabetic nephropathy are now being conducted on VPI-2690B. 119.
Reactive oxygen species and tumour necrosis factor-activated tumour necrosis factor receptor 1 are two examples of stimuli that can activate the mitogen-activated protein kinase Apoptosis Signal Regulating Kinase 1 (ASK1), a stress responsive kinase.120–122 According to a recent study, ASK1 inhibition significantly reduced albuminuria while significantly enhancing glomerulosclerosis in a mouse model of diabetic nephropathy. 123 The selective ASK1 inhibitor GS-4997 will be put to the test in a 300-patient phase 2 study by Gilead Sciences on people with diabetic nephropathy. The change in eGFR after 48 weeks of treatment will be the main result. The percentage of participants attaining an albuminuria reduction of at least 30% from baseline at week 48 will be the secondary outcome. 124,125. difficulties in developing drugs for chronic renal disease Despite the fact that phase 2 trials for chronic kidney disease are typically conducted with proteinuric patients in whom signs of efficacy are explored based on a reduction in proteinuria,54 drug registration for the treatment of CKD requires demonstration of a reduction in the number of patients developing renal failure, having their creatinine double, or dying. 9 While the development of drugs for indications like rheumatoid arthritis or depression can be finished within weeks, accumulating a sufficient number of events in phase 3 trials may take years, placing CKD at a competitive disadvantage within pharmaceutical companies compared with these other disease indications.

The value of drugs offering these intermediate benefits will probably be less compelling to payers than showing a decrease in the number of patients needing dialysis, even though regulatory agencies have shown a willingness to consider alternative end points that could shorten trials, such as a 40% decrease in eGFR for CKD drug registration126. Renal outcomes trials must be enriched for patients who are expected to advance quickly to the prespecified renal events in order to produce reliable trial results. High levels of proteinuria at enrollment continue to be the best indicator of renal disease progression. 127–130. It has becoming harder to identify patients with high baseline proteinuria since all renal outcomes trials must be conducted against the backdrop of the current standard of care (i.e., in patients who are best treated with ACEis or ARBs, which reduce proteinuria). However, it is yet unknown whether the disease aetiology in these patients is due to ischemia or some other mechanism,131 complicating the interpretation of studies in which they are included. It is true that an increasing percentage of diabetic patients exhibit CKD without proteinuria.

Another significant obstacle to the development of medications for chronic kidney illness has been the slow patient enrolment into renal trials. Despite the fact that most patients have some degree of CKD, it has been difficult to identify a sufficient number of patients who have ACEi/ARB-resistant proteinuria and are therefore most likely to advance. The enrollment rates (e.g., 0.2 patients/site/mo) are less than one-fourth of those for other disease reasons, which may not be surprising given the low patient and physician awareness of the diagnosis of CKD4,132 (eg, diabetes mellitus or hyperlipidemia). Another competitive disadvantage for renal drug development in the resource-constrained pharmaceutical environment is that it may take four times longer to enrol a study for CKD than for many other diseases. Although some of these differences can be attributed to actual variations in disease incidence, the disproportionate societal cost of treating people with kidney illness should more than make up for the lower prevalence. 2,133–135 For instance, in 2011, although though ESRD patients made up just 1.4% of the Medicare population, they used up more than 7% of the program's resources. 136 To speed up enrollment in CKD therapy studies, patient and physician awareness raising campaigns are essential. The development of medicines for chronic renal disease may be sped up by using patient registries and therapeutic trial networks.

As the population ages, type 2 diabetes mellitus and autoimmune illness are becoming more common in younger people, which will cause a silent tsunami of renal failure to break out in the coming decades. 11 In addition to being exceedingly expensive financially, CKD is also fatal. Both society at large and the medical establishment as a whole are unprepared to handle these catastrophes. The development of new therapeutics will need more sophisticated scientific understanding of disease heterogeneity, better biomarkers predictive of disease progression, improved patient awareness, and streamlined patient enrollment in order to succeed. New therapeutics offer the hope of delaying this unwelcome reality. Through concerted efforts on these fronts, the renal community will play a central role to help limit renal death.

Conflict of Interests

The author states there are no any Conflicts of Interests

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