MINI REVIEW

Therapeutics for chronic kidney disease in the next generation

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ABSTRACT

Chronic kidney disease (CKD) is a primary cause of death. There is currently no cure for the disease, with current treatment focusing on blood pressure control and glycemic control by blockage of the renin-angiotensin system. Such methods can only postpone the onset of end-stage kidney disease and come with a slew of negative side effects. Several unique mechanisms leading to the development of CKD, such as vascular alterations, loss of podocytes and renal epithelial cells, matrix deposition, inflammation, and metabolic deregulation, have recently been identified, revealing new possible therapeutic methods for CKD. This review will look at new CKD treatment techniques and medicines, as well as the hurdles they face in clinical trials.

Key Words: *Dialysis; Kidney disease; Hypertension*

INTRODUCTION

CKD affects around 20 million people in the United States, with half a million of those suffering from the most severe form, end-stage renal disease (ESRD). Dialysis or transplantation is the only treatments for ESRD. However, individuals on dialysis might die at a rate of up to 20% each year and transplantation is limited due to organ shortages. Diabetes, which accounts for about half of all instances of chronic and ESRD in the United States, is followed by hypertension (25%), with other causes including glomerulonephritis's and polycystic kidney disease. In people with CKD, cardiovascular disease (CVD) is still the major cause of death. Despite significant success in lowering CVD death rates in the general population, this has not been replicated in patients with CKD [1]. The reduction in CVD in the general population is significantly correlated with serum cholesterol, smoking status, and blood pressure, however when comparing standard CVD risk assessments, the mortality of CKD people is much higher than non-CKD subjects. The accumulation of many toxins and metabolites, known as "non-traditional risk factors," may contribute to the higher mortality of patients with CKD. The most frequent definition of CKD is based only on the estimation of the glomerular filtration rate (eGFR), with a GFR of less than 60ml/min/1.73m2 for more than 3 months being used to diagnose CKD [2]. Based on GFR criteria, different stages of CKD have been proposed. Stage G1 is when GFR is greater than 90 cc/min, stage G2 is when GFR is between 90 and 60 cc/min, stage G3 is when GFR is between 60 cc/min and 30 cc/min, stage G4 is when GFR is between 30 cc/min and 15 cc/min, and stage G5 is when GFR is less than 15 cc/min. The stages were created primarily for research purposes, and there is now no apparent differentiation between them; rather, GFR decline reflects an ever-increasing danger of death [3].

There is also a broader definition of CKD that considers structural, functional, pathological, laboratory, or imaging problems. One such functional defect that has gained increased emphasis in the current classification rules is albumin or protein leakage in the urine. Because albumin and its breakdown products account for the vast majority of urine proteins, most clinical investigations use the terms albuminuria and proteinuria interchangeably [4]. Albuminuria is highly linked to the development of ESRD, increased CVD, and mortality, whereas albuminuria reduction is frequently linked to protection from functional decline. The histological and structural aspects of CKD include glomerular sclerosis and interstitial fibrosis. Glomerular alterations are usually specific for illness etiology and, as previously stated, are utilized to diagnose and classify diseases. Tubulointerstitial fibrosis is linked to kidney function and is a common architectural alteration in the kidney that involves the formation of matrix and collagen by epithelial cells and activated myofibroblasts. Epithelial cells have a critical role in the development of fibrosis, according to mouse genetic research [5].

DISCUSSION

In tubule epithelial cells, genetic overexpression of Notch, KIM, and HIF was enough to cause epithelial degradation, dedifferentiation, and the whole spectrum of fibrosis, whereas genetic deletion of these pathways protected against fibrosis formation. Fibrosis is a reactive process that occurs primarily as a result of epithelial injury and is nearly always accompanied by inflammation, as evidenced by increased cytokine expression and the buildup of macrophages and inflammatory cells. By limiting food supply to epithelial cells, vascular injury and capillary loss increase epithelial injury at later stages. Over the last few years, our understanding of fibrosis has vastly advanced, revealing new possible treatment targets. Most forms of chronic renal disease do not have a cure at this time. Reduced renal perfusion, nephrotoxic medications, and urinary blockage are only a few of the circumstances linked to reversible renal failure. Although steroids and other immunosuppressive medications can help individuals with IgA neuropathy, lupus nephritis, membranous nephropathy, focal segmental glomerular sclerosis, vacuities, and MCD, they have not been found to help patients with diabetes and hypertension with kidney disease [6].

Hemodynamic alterations are important in the progression of CKD, and methods to reduce excessive blood pressure have had a substantial impact on the condition. A rise in systemic blood pressure can cause glomerular filtration to increase, resulting in hyper filtration, an increase in glomerular size, and a greater strain on glomerular cells. Furthermore, because the veins that give nutrients to the kidney come from the efferent region of the glomerulus, these modifications diminish post-glomerular blood flow, resulting in ischemia changes in the kidney. Using either angiotensin converted enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) to inhibit the renin angiotensin system, which is involved in the regulation of blood pressure and fluid balance, reduces glomerular hyper filtration and albuminuria, and slows the decline in kidney function. As a result, these drugs have become the cornerstone of CKD treatment. This method, however, simply slows the loss of renal function and does not treat CKD [7]. Furthermore, these drugs might have serious side effects, such as an increase in serum potassium levels, which can restrict their therapeutic utility. Several more medications targeting CKD hemodynamic alterations are currently being developed. Smoking cessation also reduces the progression of the disease. Many practitioners advocate protein restriction, statin medication, and metabolic acidosis correction; however the benefits of these interventions have yet to be proven in major randomized trials. New treatment methods, such as targeting inflammation, fibrosis, or podocytes, are emerging as our understanding of CKD pathogenic pathways improves. We will review existing and new tactics for treating the two major kinds of CKD - diabetic and hypertensive CKD - as well as critical problems and concerns in the development of innovative medicines and future clinical trial design in this Review.

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The need for innovative therapies for the progression of CKD has never been stronger. While mortality rates have been declining for most diseases, it has risen for people with chronic renal disease. Since 2001, no new drugs for the treatment of chronic renal disease have been approved. Inflammation, fibrosis, cellular metabolism, vascular, and monocyte changes have all been identified as potential novel therapeutic targets in recent research, with several relevant drugs now in Phase II and III clinical trials. Most renal clinical trials are still enrolling participants with stage 3 CKD and a high level of albuminuria, as these are the subjects who are most likely to attain the trial's end-point (death, dialysis, or a doubling of serum creatinine) first [8]. The SONAR study is the only one that takes a more personalized approach and selects patients who are more likely to react to therapy and have fewer adverse effects. The targeted strategy is only now gaining traction. Drugs that target metabolism, for example, would almost certainly need to be introduced early, which is a tough issue because these trials require big cohorts to be investigated for lengthy periods of time. Other approaches, such as reducing inflammation, are expected to be effective even as the disease progresses. Clinically validated indicators linked to decreased fibrosis are not available to measure efficacy in brief phase II studies, making therapeutics that specifically target fibrosis but not albuminuria particularly difficult.

Once a single treatment has shown to postpone the progression of functional decline, it will be crucial to see if drug combination tactics can accomplish not only prevention but also remission. Combining hemodynamic targeting with metabolic targets, podocyte specific targets, and an anti-inflammatory could provide benefits beyond single medication treatments in this area. In the treatment of renal illness, opportunities in the field of "genetic medicine" are also emerging. Polycystic kidney disease (PKD) and kidney disease associated with an Apo lipoprotein L1 mutation are two hereditary illnesses for which this represents a potential strategy (APOL1). Customizing specific therapeutic combinations for these genetically specified disorders should improve efficacy and reduce the number of individuals that need to be treated. The "genetic revolution" has revolutionized various areas of medicine, the most notable of which being cancer. The Cancer Genome Atlas (TCGA), a large collaborative initiative, is enabling systematic investigation of the genetics, genomes, epigenetics, and proteomics of all cancer types by collecting hundreds of patient samples and clinical data. Implementing a collaborative team strategy for CKD, which is unlikely to be a homogeneous disease and is virtually entirely diagnosed based on clinical description, could be quite beneficial. Although kidney biopsy is not recommended for everyone with CKD, it appears to be becoming increasingly safe, and tissue samples are rather easy to obtain [9].

The cost of developing new CKD medicines continues to be a major roadblock. The challenges to quickly identifying and enrolling the relevant patients in these studies are at the top of the list of development expenditures. Patient registries and innovative trial designs, as well as the validation of novel trial end-points, could help solve some of the challenges mentioned above. Adaptive clinical trial design, which begins early in a clinical trial by evaluating patients' reactions to a treatment and then adapts the trial based on those findings, may also be effective in CKD. Indeed, this design, according to industry estimates, can cut the cost of bringing a medication to market by a third.

CONCLUSION

In conclusion, CKD care is becoming one of the most expensive and fast growing illness burdens facing society. Despite the fact that drug research for CKD has lagged behind other therapeutic areas, recent effort in this area has accelerated, owing to a growing awareness of this unmet medical need. Despite this, the pharmaceutical industry's systematic engagement has been insufficient, mainly due to a lack of success, operational issues (e.g. sluggish patient enrolment), and long-term outcomes trials. Early patient-centric discovery approaches, as well as broad academic, industrial, and patient advocacy alliances, can help increase patient therapeutic response, illness awareness, and clinical trial efficiencies. It is possible to engage scientists and stakeholders across the breadth of medical delivery and payer systems, but it are necessary in the twenty-first century, stem the tide of renal disease.

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