Gene Therapies: Any Merit in Nephrology?

In depth review

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ABSTRACT
Gene therapy is an innovative medical approach that involves altering or replacing defective genetic material to treat or potentially cure genetic disorders. This technique primarily uses viral or non-viral vectors to deliver genetic material into cells, aiming to restore normal gene function. The therapy has the potential to address a wide range of diseases, including genetic, cardiovascular, and neurodegenerative disorders. In this review, the focus will be on gene therapies related to kidney diseases. Topics to be covered include the use of messenger ribonucleic acid (mRNA) therapies for conditions such as hypertension and kidney cancer, as well as targeted gene therapies using small interfering RNA (siRNA) and adeno-associated viruses to treat glomerular diseases and prevent kidney damage. The application of gene therapies in treating well-known genetic conditions, such as Alport syndrome and cystinosis, will also be discussed. Additionally, the review will explore the progress of RNA interference (RNAi) therapies in acute kidney injury (AKI) and chronic kidney disease (CKD). Finally, the challenges and risks associated with gene therapy, including immune responses, insertional mutagenesis, and the high costs of treatment, will be examined.

KEYWORDS: Gene Therapy, Kidney Diseases, Molecular Nephrology, Nephrogenetics

Introduction to Gene Therapy

Gene therapies represent a cutting-edge approach in modern medicine, offering the potential to treat or even cure a range of genetic disorders by altering or replacing the genetic material within the cells. Gene replacement therapies generally use viral (adenovirus, or lentivirus) or non-viral vectors to transfer the new genetic material. These therapies aim to reconstitute the expression of the mutant genes responsible for recessively or dominantly inherited genetic disorders, such as cancer, cardiovascular, and neurodegenerative diseases. Some therapies are based on delivering genetic material without integrating into the patient's genome. On the other hand, some therapies including Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 (CRISPR-Cas9) can provide long-lasting or permanent potential therapeutic effects by inserting, removing, or altering genetic sequences [1].

Gene Therapy in Kidney Diseases

Chronic kidney disease (CKD) is a major global health problem, affecting approximately 10-15% of the adult population worldwide. Beyond its impact on morbidity and mortality, CKD significantly impairs patients' quality of life and imposes a substantial economic burden on healthcare systems due to the high costs of long-term medical care and renal replacement therapies [2, 3]. While acquired causes remain prevalent, a growing body of evidence highlights the important role of genetic factors in the etiology of kidney diseases [4]. Advances in genetic sequencing technologies have dramatically increased the recognition of inherited kidney diseases, revealing that up to 20-30% of early-onset or familial cases have an identifiable genetic basis [5, 6]. Becherucci et al. developed a multi-stage diagnostic approach consisting of patient selection based on specific referral criteria, whole exome sequencing (WES), reverse phenotyping and multidisciplinary board evaluation to make the diagnosis of genetic kidney diseases more efficient and cost-effective. This method achieved a 67% diagnosis rate, confirming the clinical prediagnosis in 48% of cases and changing the diagnosis in 19%. Genetic diagnosis was achieved in 64% of children and 70% of adults. Cost analysis showed that early genetic testing resulted in cost savings of 20-41% per patient. Thus, a model of genetic diagnosis with high diagnostic success and economic advantage is possible [7]. However, current management strategies for many genetic kidney diseases remain largely symptomatic, aiming to slow disease progression and address complications rather than correct the underlying genetic defects. In this context, gene-based therapies have emerged as a promising frontier in nephrology, offering the potential to directly target the molecular causes of disease.

Messenger ribonucleic acid (mRNA) therapies for kidney diseases are still largely experimental, with preclinical studies showing promising results [8]. For instance, a study on hypertension showed that zilebesiran, a ribonucleic acid (RNA) interference (RNAi) drug, effectively lowers blood pressure by targeting hepatic angiotensinogen [9]. mRNA vaccines have also been explored for treating kidney cancer, showing promising results in early studies [10].

A targeted gene therapy using small interfering RNA (siRNA) may be delivered via specialized nanoparticles to treat kidney diseases. The nanoparticles, made of siRNA and cationic liposomes coated with PAI-1R, specifically target glomerular cells. When tested in a nephritic rat model, the therapy effectively reduced transforming growth factor-β1 (TGF-β1) levels in the glomeruli, improving glomerulosclerosis without affecting other organs. This approach shows promise for treating kidney diseases by specifically silencing mutant genes in the glomeruli [11]. Additionally, thymosin β4 (TB4), an actin-sequestering peptide, plays a crucial role in maintaining podocyte cytoskeleton integrity. A lack of endogenous TB4 exacerbates podocyte injury. Administration of an adeno-associated viral vector (AAV) encoding TB4, increased circulating TB4 levels, preventing

adriamycin-induced podocyte loss and albuminuria. TB4 gene therapy also restored the disorganized actin cytoskeleton in vitro. These findings suggest that systemic gene therapy with TB4 expression could prevent podocyte injury and maintain glomerular filtration, offering a novel treatment strategy for nephrotic syndrome [12].

Gene therapies may be useful in Alport syndrome, a disease with a well-known genetic mechanism. It is caused by mutations in the genes for alpha 3, alpha 4, and alpha 5 chains of type IV collagen. This condition leads to symptoms such as hematuria, proteinuria, progressive kidney dysfunction, hearing loss, and eye problems. The mutation results in an abnormal collagen network in the glomerular basement membrane, impairing kidney function. Current conservative treatments, like angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) or mineralocorticoid receptor antagonists have limited effectiveness. Gene therapy offers a potential solution by aiming to correct the mutations and restore normal collagen production. Advances in recombinant AAVs are making progress in kidney gene therapy, with ongoing research focused on developing effective treatments for Alport syndrome [13].

Investigational gene therapies can also be used to treat some clinical conditions that do not have a clear genetic basis. Acute kidney injury (AKI) is a serious condition with significant morbidity, even mortality and no definitive treatment. The RNAi is a potential solution by using engineered red blood cell-derived extracellular vesicles (REVs) to deliver therapeutic siRNAs to injured kidneys. The REVs, tagged with a peptide that binds to kidney injury molecule-1 (KIM-1), specifically targeted damaged kidney tubules in mouse models. They successfully delivered siRNAs targeting the transcription factors P65 and snail family transcriptional repressor 1 (Snai1), which are involved in inflammation and fibrosis. Therefore, anti-inflammatory and anti-fibrotic effects of this treatment lead to an improvement in kidney function and prevention of progression to chronic kidney disease (CKD) [14]. However, some patients may develop CKD despite all interventions. CKD is primarily driven by progressive fibrosis, making it essential to target and reverse the profibrotic processes in affected tissues. Nanoparticles offer a new method for delivering antifibrotic treatments directly to the kidneys. Chitosan nanoparticles coated with hyaluronan can deliver plasmid DNA encoding bone morphogenetic protein 7 (BMP7) or hepatocyte growth factor/NK1 (HGF/NK1) to the kidneys. These nanoparticles promote cellular growth and reduce fibrosis by inhibiting fibrotic gene expression. When administered to mice with unilateral ureteral obstruction, the nanoparticles successfully delivered about 40-45% of the genetic material to the kidneys. This treatment reduced fibrosis, improved kidney function, and either reversed fibrosis and regenerated tubules or halted CKD progression and reduced collagen deposition [15].

Kidney transplantation is the best option among kidney replacement therapies in patients who develop kidney failure. However, ischemia-reperfusion injury can sometimes lead to adverse outcomes [16]. Normothermic machine perfusion (NMP) is a state-of-the-art method of organ preservation that overcomes the limitations of traditional hypothermic techniques in solid organ transplantation. It allows for the assessment and recondition of organs prior to transplantation and enables the delivery of therapeutic agents to organs. In a recent study, an oligonucleotide-based therapy, antagomir targeting microRNA-24-3p was successfully delivered to human kidneys during NMP. This treatment localized to the endothelium and proximal tubular cells of the kidney, showed specific interaction with the microRNA target and increased the expression of associated genes. It demonstrated a potential to target and block harmful microRNAs prior to transplantation [17]. Thus, it may be beneficial in increasing graft survival in kidney transplantation.

Investigational gene therapies have also been used in certain systemic diseases affecting the kidney such as cystinosis. Cystinosis, a lysosomal storage disorder caused by mutations in the *CTNS* gene, leads to cystine buildup due to the loss of cystinosin function. The kidneys are the most affected

organs, with damage progressing to kidney failure. While cysteamine is the current treatment, it only lowers cystine levels without restoring kidney function and has significant side effects [18]. In a study, synthetic mRNA can successfully restore cystinosin expression in *CTNS*$^{-/-}$ kidney cells and zebrafish following delivery via lipofection. A single dose of *CTNS* mRNA reduced cellular cystine for up to 14 days in vitro and improved kidney function in zebrafish, enhancing tubular reabsorption, reducing proteinuria, and restoring key receptor functions. That study provides early evidence that mRNA-based therapies could offer a new approach to treating cystinosis by restoring cystinosin expression and improving kidney function [19]. In another study, hematopoietic stem cell (HSC) transplantation shows potential for treating cystinosis by delivering a functional *CTNS* gene to various organs. A clinical trial of allogeneic HSC transplantation in a cystinosis patient led to improved symptoms but severe complications, underscoring the risks. As a safer alternative, a Phase I/II trial is exploring autologous HSC transplantation, where a patient's HSCs are genetically modified to express *CTNS*, potentially reducing risks and offering new treatment options [20].

As can be seen, gene therapies are being tested in the treatment of various diseases in the field of nephrology. However, so far, gene therapy has only been approved for the treatment of primary hyperoxaluria [21]. Primary hyperoxaluria (PH) type 1 (PH1) is a rare autosomal recessive genetic disorder caused by mutations in the *AGXT* gene. This condition impairs the enzyme alanine glyoxylate aminotransferase (AGT), leading to oxalate overproduction and subsequent kidney damage, including nephrocalcinosis, nephrolithiasis, chronic kidney disease, kidney failure. Systemic oxalosis may also be seen. Conventional medical treatments for PH1 are generally inefficacious except for pyridoxine in cases with pyridoxine-sensitive mutations. Current strategies mainly involve targeting the liver to block oxalate production. Lumasiran is the first RNAi therapy approved for PH1, receiving approval from the US Food and Drug Administration and the European Union in November 2020. The phase III trials demonstrated that lumasiran effectively lowers oxalate levels in urine and plasma across various patient groups, including children, adults, and those with advanced kidney disease with a good safety profile [22, 23]. Nedosiran, another RNAi therapy, reduces hepatic lactate dehydrogenase activity, a key factor in all genetic forms of PH. In a double-blind study with 35 participants with PH1 or PH 2 (PH2) received either nedosiran or placebo monthly for 6 months, nedosiran significantly reduced plasma oxalate in PH1 and was generally well tolerated [24]. It was first approved in the USA in 2023 for PH1 patients aged 9 years and older with relatively preserved kidney function [25].

Challenges and Risks of Gene Therapy

Gene therapy has made remarkable progress over the past 50-60 years, with new treatments now available for previously untreatable diseases. While advancements in gene editing technologies have significantly improved the precision and feasibility of these treatments, their clinical application is still carefully regulated due to potential risks. The immune system may react to the viral vector used in therapy, causing inflammation, fever, or more serious reactions [26]. Another potential side effect is called insertional mutagenesis, where the therapeutic gene integrates into the wrong part of the genome. This can disrupt the function of other genes and lead to cancer or other disorders [27]. Additionally, the therapy may affect non-target cells or tissues, resulting in unintended tissue damage [28]. Even if the therapeutic gene is placed in the right position, overproduction can lead to inflammation or tissue damage may occur [29]. Despite its effectiveness, there might be serious adverse events, such as thrombotic microangiopathy or immune hepatitis, associated with viral vector-based gene therapies [30]. The long-term effects of gene therapies are not yet fully understood. Factors such as the impact on future generations or the long-term presence of the therapeutic gene are still under investigation [31]. From an economic perspective, high costs for

these therapies pose significant barriers to access. This issue may be exacerbated by complex health insurance systems. Recent discussions highlight the need for solutions to make these therapies more affordable and accessible, ensuring that advancements in gene therapy benefit all patients equally and fairly [32].

Conclusion

Gene therapy has made remarkable progress in recent years, offering promising therapeutic potential for a variety of genetic and acquired kidney diseases. However, despite the scientific progress, the high costs and limited accessibility of these therapies present significant challenges to widespread adoption. Moving forward, ongoing research is essential to refine the safety and efficacy of gene therapies, while addressing economic and logistical barriers to ensure equitable access for all patients. The future of gene therapy holds great promise, with the potential to transform the treatment landscape for kidney diseases, offering hope where conventional therapies have been limited.

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