Novel Therapies for FSGS: Preclinical and Clinical Studies

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Focal segmental glomerulosclerosis (FSGS) is a rare but important cause of end-stage kidney disease in children and adults. Current therapy, consisting of corticosteroids and calcineurin inhibitors, fails to achieve a sustained remission in most patients. Therefore, there is a pressing need to develop new treatments for this glomerulopathy. Traditional approaches have focused on agents that modulate the immune system. In this review, we summarize preclinical and clinical data with newer agents that may ameliorate FSGS. We focus on drugs that inhibit immune injury or inflammation, such as abatacept, rituximab, adalimumab, and stem cells. The potential of agents that block the glomerular action of circulating permeability factors such as soluble urokinase receptor is reviewed. Finally, because fibrosis represents the final common pathway of glomerular damage in FSGS, the experience with a wide range of antifibrotic agents is presented. Despite extensive research on the podocyte dysfunction in the pathogenesis of FSGS, there are few agents that directly target podocyte structure or viability. We conclude that FSGS is a heterogeneous disorder and that intensified translational research is vital to improve our understanding of distinct subtypes that have a defined prognosis and predictable response to targeted therapeutic interventions.

Key Words: FSGS, Inflammation, Immune modulators, Fibrosis, Circulating factors

Introduction

Focal segmental glomerulosclerosis (FSGS) is one of the most common forms of glomerular disease. The entity is defined based on the finding of segmental glomerular sclerosis and hyalinosis.[1] Various histopathologic variants including tip lesion and a collapsing form have been identified, and they may shed light on response to therapy and prognosis.[2] Disturbances in podocyte structure, number, and function are considered pivotal to the development of all forms of FSGS, and this glomerular disease is now classified as a podocytopathy.[3]

FSGS accounts for nearly 5% to 10% of pediatric and adult patients who progress to end-stage kidney disease (ESKD). Among those patients who require kidney replacement therapy, 15% to 30% will develop recurrent disease in a transplanted kidney.[1] The etiology of FSGS is divided into 3 categories—primary or idiopathic, genetic, and secondary disease associated with various medications (eg, pamidronate), infections (eg, HIV, parvovirus 19), medical conditions (obesity, reflux nephropathy), or critical reduction in kidney mass (eg, subtotal nephrectomy for Wilms' tumor).[1,4]

The goal of treatment in patients with FSGS is normalization of urinary protein excretion and preservation of kidney function. However, even partial reduction in proteinuria is beneficial. Studies in children and adults have demonstrated a direct relationship between the degree of lowering of proteinuria and prolongation of kidney survival. The standard of care for patients with primary FSGS includes initial treatment with a course of corticosteroids. Up to 25% of patients will respond to this therapy, and their prognosis is more favorable.[1] For those who are steroid resistant, the next option is a calcineurin inhibitor with an expected complete or partial remission rate in 40% to 50% of patients.[5] If these drugs are ineffective, then there is no proven therapy that can consistently achieve a significant and sustained reduction in proteinuria. The current treatment of FSGS has recently been reviewed in this journal.[6]

There are a number of possible disease mechanisms that can be targeted by novel therapies for FSGS. These include modulation of immunologic pathways, inflammation, podocyte cell growth and survival, actin cytoskeleton, circulating factors, and fibrosis. In the following sections, we will review preclinical and clinical data that support the potential use of novel therapies that are directed at each of these pathophysiological abnormalities.

Animal Models of FSGS

Much of our knowledge on the pathophysiology and potential therapeutic targets for FSGS has come from different kinds of animal models that have been developed to mimic the clinical and pathological features of human FSGS. These models induce damage to podocytes. These animal models include the reduction of kidney mass by resecting five-sixth of the kidney tissue (unilateral nephrectomy and removal of two-thirds of the contralateral kidney), injury to the kidney parenchyma because of drug-induced FSGS using adriamycin (ADR), puromycin aminonucleoside (PAN), or streptozocin, virus-induced FSGS, genetically-induced FSGS, such as via Mpv-17 inactivation and α-actinin 4, and podocin knockouts using Cre/lox P recombination.[7,8] Unfortunately, almost all of these animal models are based on the induction of secondary forms of FSGS and are consequently limited in the ability to mimic primary idiopathic human FSGS.

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Modulation of Immunological Pathways and Inflammation

Rituximab

Rituximab, a monoclonal antibody against CD20 on B cells, was first demonstrated to induce remission of proteinuria in a single patient with a transplant-related lymphoma and recurrent FSGS after kidney transplantation.[9] Subsequent reports have evaluated the effect of rituximab in case series of patients with primary FSGS. Overall, the response has been low, in the range of 20% to 30%, suggesting that this therapy may have a role in selected patients with primary FSGS.[10] There is evidence that rituximab may have off-target effects on lipid metabolism in podocytes by binding to sphingomyelin phosphodiesterase acid-like 3b protein and regulating acid sphingomyelinase activity. This action may contribute to the efficacy of rituximab in post-transplant FSGS.[11] Further research is required to place rituximab into a rational framework for the treatment of FSGS.

ACTH

Injections with adrenocorticotropic hormone (ACTH), a pituitary neuroimmunoendocrine polypeptide, were one of the first therapies used for childhood nephrotic syndrome.[12,13] Broad clinical and experimental evidences had long suggested that ACTH has antiproteinuric, lipid-lowering, and renoprotective properties,[14] and the drug was reintroduced as a treatment alternative for nephrotic syndrome, initially in Europe with a synthetic ACTH depot and then in the United States with natural ACTH gel. Hogan and colleagues[15] treated 24 adult patients with steroid-resistant or steroid-dependent FSGS with ACTH and achieved remission in 7 (29%), indicating that this drug may represent an alternative in patients who do not respond to steroids and other common second-line agents. It is suggested that ACTH may have actions beyond those attributable to corticosteroids, possibly acting via anti-inflammatory mechanisms or directly on podocytes via the melanocortin 1 receptor.[16]

CLINICAL SUMMARY

- Current therapy of focal segmental glomerulosclerosis is generally ineffective and cannot prevent progression to end-stage kidney disease in most patients.
- Novel therapies are under development that target immune-mediated inflammation and glomerular damage, inhibit the action of circulating permeability factors, or prevent glomerular fibrosis.
- None of the novel therapies have been successfully applied to the treatment of patients with focal segmental glomerulosclerosis. Intensified translational research is vital to develop targeted therapeutic interventions for patients with this serious glomerulopathy.

Abatacept

Abatacept (CTLA-4-Ig) is a costimulatory inhibitor that targets B7-1 and is currently approved for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. Reiser and others[17] have shown that induction of the T-cell costimulatory molecule B7-1 in podocytes is associated with nephrotic syndrome. Yu and colleagues randomly selected biopsy specimens of native human kidneys and identified a subpopulation of patients with minimal change disease or primary FSGS who had B7-1 immunostaining of podocytes. The authors selected 5 patients with FSGS and B7-1 staining of podocytes in kidney biopsy for management with abatacept. Four of these patients had rituximab-resistant recurrent FSGS after transplantation and 1 patient had glucocorticoid-resistant primary FSGS. Clinical remission, more specifically, nephrotic-range proteinuria, resolved in all the patients over a period of weeks to months.[18] If validated, abatacept may be a new therapeutic tool for the subgroup of patients with FSGS who exhibit B7-1 immunostaining in the kidney biopsy specimens. This drug may stabilize β1-integrin activation in podocytes and reduce proteinuria in patients with B7-1-positive glomerular disease.

Adalimumab

Monoclonal antibodies are increasingly being used in the treatment of steroid-resistant and steroid-dependent FSGS. Adalimumab is a human monoclonal antibody directed against tumor necrosis factor-α (TNF-α). Because TNF-α is upregulated in both human and experimental models of FSGS, attempts to lower proteinuria by inhibiting TNF-α have been made. In the phase 1 trial conducted by the "Novel Therapies for Resistant FSGS" (FONT) study group in children and adults, adalimumab was well tolerated, and after 16 months of follow-up, 4 patients of the adalimumab-treated group ($n = 10$) showed stabilization of kidney function and reduced proteinuria.[19,20] This observation suggests that adalimumab may have a role in slowing the progression of FSGS in a selected subgroup of patients, but further studies are needed to confirm this.

Circulating Factors

The rapid recurrence of FSGS after kidney transplantation, the ability of plasma from patients with FSGS to induce proteinuria after infusion into animals, and the remission of post-transplant FSGS achieved by plasmapheresis have fostered the notion that proteinuria in FSGS is caused by excessive levels of circulating factors that cause dysfunction of the glomerular filtration barrier in some patients.[21] Over the years, a number of molecules have been proposed as circulating permeability factors including hemopexin and vascular endothelial growth factor. Savin and colleagues have searched for these molecules by using a volumetric assay of changes in glomerular size after imposition of an oncotic gradient. They have linked high levels of a circulating FSGS permeability factor with recurrence of disease after transplant and investigated the effect of various therapeutic interventions on the glomerular permeability to albumin.[21]