Kidney Medicine

The Pursuit of New Treatments for Focal Segmental Glomerulosclerosis: Harmonizing Innovation With the DUET Study of Sparsentan

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Focal segmental glomerulosclerosis (FSGS) is the histopathological term applied to the most common idiopathic etiology for a complex progressive kidney disorder for which improvements in treatment over the past 50 years have yet to be entirely curative.[1] Approximately 20% of new onset nephrotic syndrome cases in children and 40% in adults will be classified as steroid resistant, and, subsequently, among those undergoing a kidney biopsy, FSGS will be discovered as either a focal, segmental, or global lesion of glomerular scarring. First identified as the major clinical-pathological finding in steroid-resistant children in the International Study of Kidney Disease in Children, more recent kidney classifications have provided evidence that this varied disorder is a result of podocyte dysfunction and regulation, which, in some cases, is associated with specific genetic mutations or risk factors, including *APOL1* G1 or G2 variants.

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Despite a lack of a concrete immunologic etiology for primary podocytopathies, glucocorticoids have served as the first line of defense since the early treatment with adrenocorticotropic hormone (ACTH) over a half a century ago (Fig 1). Additional immunosuppression, first with cyclophosphamide and then with chlorambucil, calcineurin inhibitors, mycophenolate mofetil, mTOR inhibitors, and anti-CD20 agents (eg, rituximab, ofatumumab and other monoclonal antibodies including bleselumab or abatacept) have been used with varied responsiveness in terms of lowering proteinuria and arresting progression. Additionally, even in the absence of hypertension, inhibitors of the renal angiotensin system (RAAS) have been used to treat FSGS. There have been occasional reports of FSGS patients achieving either a partial or complete remission of proteinuria on RAAS inhibitors alone. In those not responding to therapies, FSGS results in kidney failure in 12% of pediatric and 5% of adult patients, with a high incidence of recurrence in the transplanted kidney. The current treatment approach for primary FSGS typically involves corticosteroids in addition to other immunomodulating agents and RAAS inhibitors aimed at reducing proteinuria. However, use of these drugs can be limited by therapy-related adverse effects.

The search for effective and safe treatments to mitigate kidney parenchymal injury and reduce proteinuria in primary FSGS led to the emergence of endothelin type A receptor antagonists as a promising therapy. Preclinical experimental models first supported a role for angiotensin II and endothelin-1, either alone or in combination, as possible mediators of glomerular injury.[2] Endothelin-1 and angiotensin II exhibit similar effects in glomeruli, paralleling their vascular action.[2] They are implicated in various processes within the glomeruli, including mesangial cell contraction and proliferation and extracellular matrix production, which contributes to the development of glomerulosclerosis and tubulointerstitial fibrosis. Endothelin-1 receptor antagonists have the potential to augment the action of RAAS inhibitors.[2] Emerging evidence suggests that endothelin-1 also plays specific roles in podocyte alteration by inducing podocyte apoptosis and loss and cytoskeletal derangement, ultimately leading to foot process effacement and podocytopathy, thereby contributing to worsening proteinuria and glomerular filtration rate decline, the characteristic features of FSGS.[3]

Sparsentan is a first-in-class, oral medication that acts as a selective antagonist of both the angiotensin II receptor and the endothelin A receptor.[2] This dual mechanism of action makes sparsentan an intriguing candidate for the treatment of FSGS, potentially offering enhanced efficacy in reducing proteinuria compared to single-agent therapy with RAAS inhibitors or with endothelin A receptor antagonists alone. The initial report entitle "DUET: A Phase 2 Study Evaluating the Efficacy and Safety of Sparsentan in Patients with FSGS" compared the effects of this dual endothelin type A and angiotensin II type I receptor antagonist with those of the angiotensin II type 1 receptor antagonist irbesartan in primary FSGS.[4] This randomized, double-blind, active-control, dose-escalation study reported that, after 8 weeks of treatment, there was a reduction in proteinuria in the group randomized to sparsentan. In addition, the investigators applied a novel surrogate endpoint in FSGS, termed the FSGS partial remission endpoint, as a meaningful treatment outcome. This was defined as a reduction of 40% in the urinary protein-creatinine ratio (UPCR) to a value of <1.5 g/g. The study provided the rationale for the long-term assessment of treatment with sparsentan on kidney outcomes.

In this issue of *Kidney Medicine*, Campbell et al[5] report on the open-label extension of the DUET Trial. Participants who initially were randomized to sparsentan continued with the same dose as the last day of the double-blind period, whereas those assigned to irbesartan were transitioned to sparsentan.[5] A total of 109 patients were enrolled

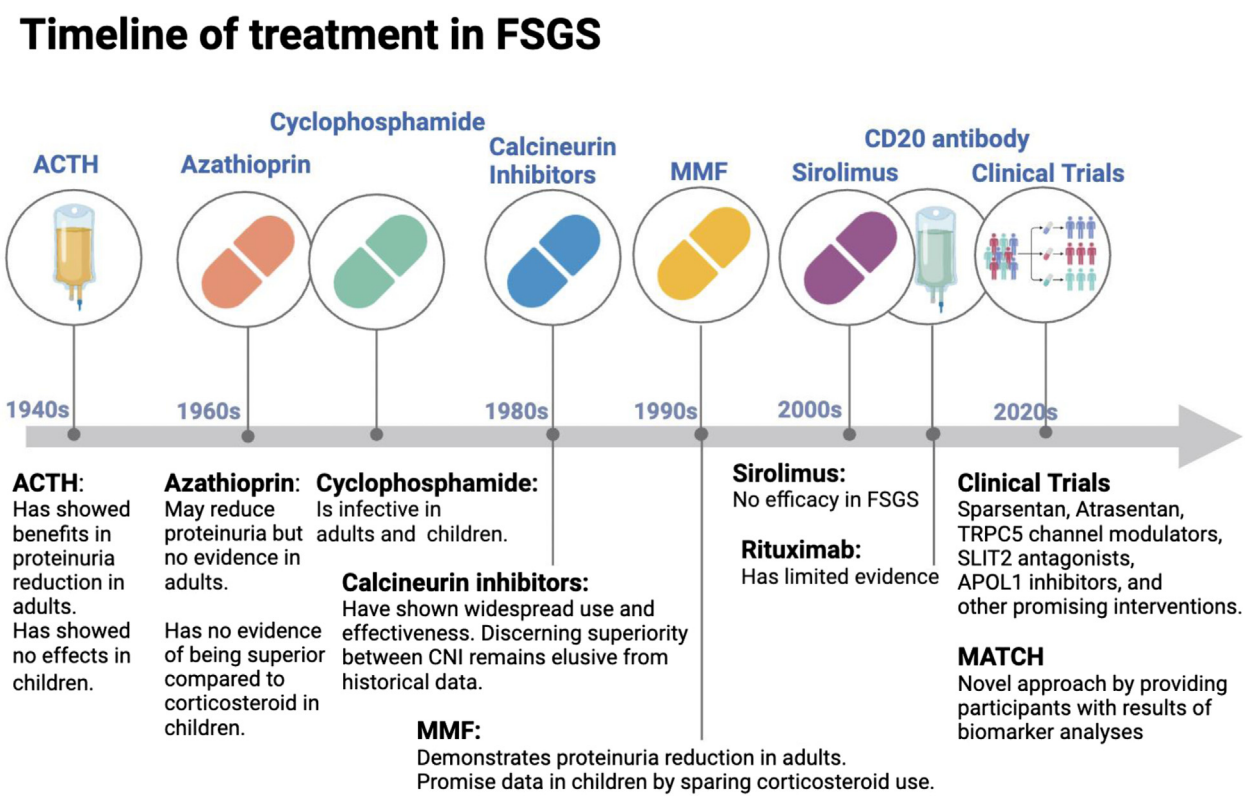

Figure 1. Timeline of treatment in FSGS. ACTH, Adrenocorticotropic hormone; MMF, mycophenolate mofetil.

for a median time to sparsentan treatment discontinuation of 3.9 years. A rapid decline in the UPCR was observed by 8 weeks with a sustained antiproteinuric effect in >50% of patients over the first year. Of note was the observation that a slower rate of decline in estimated glomerular filtration rate occurred in those achieving the FSGS partial remission endpoint within the first 9 months; this pattern continued throughout the first 2 years, corroborating results from the DUET trial for those with complete remission at least once in 43% of participants. The phase 3 trial, Sparsentan versus Irbesartan in Focal Segmental Glomerulosclerosis, also found a partial remission of proteinuria in 42% of individuals treated with sparsentan at 108 weeks without a difference between the estimated glomerular filtration rate slope compared with the irbesartan group.[6] This open-label extension of the DUET study had several limitations, including the lack of a comparison group, the small number of African American participants, the overall heterogeneity of FSGS, and the absence of analysis of how participants with genetic forms of FSGS responded. However, the overall excellent safety profile combined with a favorable reduction in proteinuria support the need for additional long-term studies and offer further hope in treating this problematic disease.

Addressing FSGS remains a formidable challenge. Patients often commence treatment with RAAS inhibitors for associated proteinuria, followed by trials of corticosteroids among those with nephrotic-range proteinuria. Persistent high-grade proteinuria prompts consideration of second-line immunosuppressive options like calcineurin inhibitors, antimetabolites, mycophenolate mofetil and B-cell-targeted interventions. Calcineurin inhibitors have shown widespread use and effectiveness in FSGS cases; however, discerning superiority between them remains elusive from historical data.[7] Antimetabolites' efficacy in adults is contentious, with a lack of definitive data on their role in FSGS treatment. Studies from the Study of Kidney Disease in Children (ISKDC) concluded that antimetabolites were ineffective in pediatric FSGS cases.[8] Mycophenolate mofetil (MMF) emerges as an option for patients with limited alternatives, demonstrating proteinuria reduction in 44%-50% of FSGS cases and showing promise in children by sparing corticosteroid use and potentially benefiting kidney function. The enigma of rituximab's mode of action adds intrigue; although effective when administered during proteinuria-free periods alongside other immunosuppressive agents, conclusive evidence remains scarce. Nevertheless, research underscores the limited efficacy and contentious nature of these approaches.[9] The landscape is evolving with ongoing clinical trials investigating innovative avenues, such as sparsentan, atrasentan, TRPC5 channel modulators, SLIT2 antagonists, APOL1 inhibitors, and other promising interventions.[10]

Clinical trials in FSGS have faced many challenges. One of the earliest trials, the National Institutes of Health-supported FSGS clinical trial comparing cyclosporin to

MMF, illustrated common challenges in FSGS clinical trial design. The FSGS clinical trial intended to include those with primary FSGS; however, the exclusion of those with obesity or other forms of secondary FSGS limited the eligible population for enrollment, resulting in insufficient power. This trial was unable to detect a difference between cyclosporine and MMF, with fewer than one-third of participants responding to therapy.[11] Genetic testing was also not widely available during the time of the trial; thus, there was likely heterogenous inclusion of both nongenetic and genetic forms of FSGS. Both limited sample sizes and heterogeneity of the underlying disease remain ongoing challenges for FSGS clinical trials, including the sparsentan studies reported above. Despite current recommendations that enrolling in a clinical trial be the next step after failing standard of care, another barrier to clinical trial enrollment includes willingness of the primary nephrologist and participant to enroll in studies, particularly when one of the arms includes a placebo.[12] Finally, the eligible population for clinical trial enrollment may be affected by the heterogeneity of the FSGS clinical course. Those patients with FSGS who progress rapidly may lose kidney function so quickly that they may not be eligible for clinical trials. Conversely, those with partial response to standard of care (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or SGLT2 inhibitors) may not have sufficient proteinuria to be eligible for clinical trials. There is a critical need for other biomarkers to monitor for treatment response in those with lower degrees of proteinuria.

Before the 2018 inclusion of FSGS by the Food and Drug Administration as a rare disease to which the Orphan Drug Act applied, pharmaceutical company-supported FSGS clinical trials were rare. After this designation, there was marked growth with over 20 pharmaceutical company-supported clinical trials targeting FSGS. A sudden need to recruit participants into these studies is challenged by the relatively small numbers of eligible FSGS patients at individual centers. Further, the heterogeneity of FSGS underscores the need to develop precision medicine approaches for clinical trial design. Nephrology continues to lag behind other fields, such as oncology, in providing these options. If the correct target population can be identified, there will be a greater chance of successful trials. Prospective observational studies, such as the Nephrotic Syndrome Study Network (NEPTUNE), that include multiple "omics," including proteomics, metabolomics, and genetics, can pave the way to new approaches for FSGS clinical trial design. As a part of the NEPTUNE study, the NEPTUNE MATCH provides a novel approach by providing participants with results of biomarker analyses that may predict better response to therapy.[13] The primary outcome of the MATCH trial is whether investigators can effectively communicate results of these biomarkers to participants. A secondary outcome is whether getting the biomarker results increases enrollment into those clinical trials.

As highlighted at a recent National Institutes of Health workshop on precision medicine (Preparing for Kidney Precision Medicine Trials Workshop, Bethesda, Maryland, March 18-19, 2024), patients and families with nephrotic syndrome and FSGS and patient-led organizations such as Nephcure are calling on nephrology researchers to prioritize precision medicine approaches. As new immunologic therapies as well as nonimmunologic therapies, such as sparsentan, emerge as therapeutic options for people with FSGS, identifying biomarkers to predict who is most likely to respond to which therapies is critical for optimizing outcomes and minimizing side effects.

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