Current and Future Therapeutics for Focal Segmental Glomerular Sclerosis in the Era of Precision Medicine: A Review

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Focal segmental glomerulosclerosis (FSGS) is not a single disease. Instead, it is a histopathological entity that is the manifestation of a wide range of clinical insults that injure the podocyte, a key structural element in the glomerular filtration barrier. The current classification of FSGS includes 4 subtypes: primary immune-mediated, genetic, secondary, and undetermined cause. Based on this scheme, patients are treated empirically with a combination of nonspecific renoprotective drugs and immunosuppressive agents in an effort to reduce proteinuria and preserve kidney function. However, there are no medications approved by the US Food and Drug Administration for FSGS. Moreover, current therapy is successful in achieving disease remission in less than a quarter of patients, and all of the available options are associated with significant side effects that limit their use in practice. Ongoing research using a full array of muti-omics analytical tools—including genomic, transcriptomic, proteomic, and metabolomic assessment—suggest that patients with FSGS can be characterized mechanistically by the primary process(es) initiating and promoting disease progression. This work is summarized in this review and raises the potential to individualize therapy for each patient with FSGS. This would usher in the potential for precision medicine to be applied in the treatment of those affected by this rare but serious glomerular disease.

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Focal segmental glomerulosclerosis (FSGS) is a histopathological term that was first coined in the 1950s to describe a distinct pattern of hyalinosis and scarring with collapse of capillary loops involving a segment of the glomerular tuft and a minority of the glomeruli in the kidney parenchyma.[1,2] The lesion was detected most often in kidney biopsy specimens obtained from patients with asymptomatic proteinuria or overt nephrotic syndrome. Clinical–pathology correlation studies indicated that, in a counterintuitive manner, this finding was associated with a substantial risk of declining kidney function and progression to kidney failure (KF).

FSGS is now known to account for approximately 10% of patients who progress to KF and who require kidney replacement therapy (KRT). It occurs in patients across the life span of all racial and ethnic backgrounds and has a similar prognosis regardless of age, gender, or ethnicity.[3] Moreover, it is now recognized that FSGS is not a single disease entity but rather a nonspecific diagnostic category that can be the result of a wide variety of triggering events where the target is the visceral glomerular epithelial cell or podocyte[2]; thus, FSGS is a "podocytopathy." In FSGS, the podocytes, considered to be terminally differentiated, nonproliferating cells, are injured, detach from the glomerular basement membrane (GBM), shed into the urine, and gradually lost, leading to podocytopenia, glomerular scarring, and tubulointerstitial fibrosis.[4]

The current classification schemes for FSGS have moved beyond traditional histological categories. The current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines leverage accessible clinical and laboratory data to identify 4 subcategories of FSGS: (I) primary, presumably immune-mediated; (II) genetic; (III) secondary; and (IV) undetermined cause.[5] Efforts are underway to move beyond this taxonomy and to categorize FSGS into subtypes by their underlying disease mechanism.[6] Using rapidly evolving cellular and molecular profiling technologies will ideally allow stratification of patients with FSGS based on the primary pathways that are operating to damage the podocyte. This approach has the potential to enable selection of treatments that are most likely to succeed in each individual patient.

It is against this evolving background that the therapy for FSGS will be discussed and evaluated in this review. The KDIGO framework provides a useful context to describe current approaches to care, and molecular profiling points the way to precision medicine–based therapeutics that are currently emerging.

Mechanism of Disease

Based on the KDIGO classification scheme, there are 3 basic mechanisms of podocyte injury in patients with FSGS. Primary FSGS is presumed to result from a dysregulation of the immune cells leading to the elaboration of molecule(s) that increase glomerular permeability to protein.[7] The immune defect may originate in the T- or B-cell; current evidence supports a contribution from both populations.[8] Disturbances in the ratio of T-cell subsets and in the size of the regulatory T-cell population have been described in patients with FSGS.[9] A number of vasoactive substances—including hemopexin, interleukin (IL) 6, IL-8, IL-17, cardiotrophin-like cytokine-1 (CLC-1), tumor necrosis factor (TNF), and

soluble urokinase plasminogen activator receptor (suPAR)—produced by circulating lymphocytes and monocytes have been documented to be elevated in disease cohorts.[10-12] However, despite active investigation into the role of "circulating factors" in the pathogenesis of FSGS, no molecule has been consistently detected in affected patients and has sufficient sensitivity and specificity to enable diagnosis or guide treatment.[13] In addition, many of the candidate circulating factors have only been evaluated in research studies and have not been validated for clinical use. The recent discovery of antinephrin antibodies in approximately 10% of patients with FSGS and the experimental studies confirming antibody-mediated injury to podocytes underscore the role of the immune system in the pathogenesis of FSGS.[14]

Genetic variants in the podocyte can impact cell viability, leading to podocytopenia and glomerular sclerosis.[15] The number of causative variants for FSGS is increasing annually, and they encode proteins that run the gamut of cell functions, including the actin cytoskeleton, cell motility and adherence, metabolic function, nuclear pore proteins, and cell-cell communication.[3,16] Genetic variants can be inherited in an autosomal dominant or recessive pattern.[17] The likelihood of identifying a causative genetic variant in a patient with FSGS declines with age. Whereas the likelihood of the presence of a genetic cause exceeds 70% in the first year of life,[18] this likelihood declines to approximately 30% in older pediatric patients.[19] Although the diagnostic yield was thought to be much lower in adults, recent reports have suggested that up to 15% of older patients with FSGS may have a causative variant, supporting a greater role for genetic testing in the evaluation of patients with FSGS, regardless of age.[20]

Finally, a number of metabolic or inflammatory mediators associated with systemic conditions such as obesity, autoimmune disorders, and infection can lead to podocyte dysfunction and secondary FSGS.[21]

It is important to note that, in all 3 scenarios of podocyte injury and loss, proteinuria is the main manifestation of cell damage, and increased urinary protein excretion is a key factor contributing to progressive glomerulosclerosis and tubulointerstitial fibrosis.[22,23] This underscores the biological plausibility of the clinical benefit of treatments for FSGS that achieve a meaningful, sustained reduction in proteinuria. Based on these observations, the PARASOL Initiative (Proteinuria and Other Biomarkers as Endpoints for Clinical Trials in Kidney Disease) is an ongoing effort to assess whether proteinuria is a valid surrogate end point in FSGS clinical trials.[24]

The precise basis for the glomerular dysfunction and development of FSGS in patients with an undetermined cause is, of course, unknown. It is likely that this ill-defined subcategory contributes to the significant clinical heterogeneity of FSGS and the historically low rate of success of randomized clinical trials for this disease entity.

Current Therapy

There have been few large-scale, high-quality, randomized, controlled trials performed in patients with FSGS (Table 1). Therefore, current therapy is largely empirical and is based on uncontrolled observations or small trials. In addition, there are limited active trials evaluating the efficacy of new treatments (Table 1). The current treatment options are described herein.

Corticosteroids

In general practice, as per KDIGO guidelines, most patients with FSGS are treated initially with corticosteroids (CS) because they are effective in a subset of patients and failure to respond to CS has prognostic implications. In pediatric patients, CS are usually implemented empirically before a kidney biopsy is performed because the vast majority of children have minimal change disease (MCD). The diagnosis of FSGS is often established when a biopsy is required in children because of steroid resistance. In adults, a kidney biopsy is usually performed before initiating therapy because of the wider range of diagnostic possibilities.

The duration of CS therapy ranges from 2 to 6 months, with varying combinations of daily and every-other-day dosing schedules up to 2 mg/kg per day to determine responsiveness to CS therapy.[25] In both children and adults, 20% to 25% of patients will have a favorable response with complete remission of proteinuria.[26] However, because of the adverse side-effect profile of CS, alternative treatment strategies are needed.[27]

The exact mechanism of action of CS in the treatment of FSGS has been the subject of intense scrutiny. The podocyte expresses the glucocorticoid receptor, and exposure of podocytes to CS in vitro is associated with stabilization of the actin cytoskeleton and improved cell viability.[28] Thus, CS may have a salutary effect on podocytes that is independent of their systemic immune modulation. The zinc finger transcription factor, Kruppel-like factor 15 (KLF15), is up-regulated on exposure to CS and may mediate the downstream cytoprotective effect of these agents in kidney cells.[29] Recent research has detailed the development of a small molecule activator of KLF15 that replicates the beneficial effects of CS in vitro and in animal models of nephrotic syndrome and FSGS.[30] This exciting finding raises the possibility that KLF15 may be a potential therapeutic target in podocytes, harnessing the beneficial effects of CS to reduce proteinuria without requiring chronic CS administration in patients with FSGS.

Calcineurin Inhibitors

Calcineurin inhibitors (CNIs) are the only drugs recommended for use in patients with FSGS who are resistant to CS therapy.[31] Administration of cyclosporine or tacrolimus in combination with CS is more effective in inducing partial or complete remission of proteinuria compared

Table 1. Completed and Ongoing Clinical Trials in FSGS

Trial	Therapeutic Intervention	Study Population	Outcome
Cattran et al[32]	Cyclosporine + prednisone vs prednisone	49 Adults	69% PR/CR in cyclosporine/prednisone vs 4% in prednisone arm
Lieberman and Tejani[69]	Cyclosporine vs placebo	25 Pediatric patients	Cyclosporine yielded 76% greater reduction in proteinuria
Rheault et al[53]	Sparsentan (dual angiotensin II/ endothelin-1 receptor antagonist) vs irbesartan	371 Adult and pediatric patients	Sparsentan achieved 26% relative increase in antiproteinuric effect and 0.9 mL/min/1.73 m^2 reduction in chronic eGFR slope (NS)
Trachtman et al[70]	BI 764198 (TRPC6 channel inhibitor)	60 Adults	Results pending[71]
NCT06090227	Metformin (AMP kinase inhibitor)	Adults	Ongoing
NCT05183646	Dimerix-200 (MCP-1 inhibitor)	Adults and adolescents	Ongoing
NCT06664814	ManNac (increased sialylation)	Adults	Ongoing
NCT02235857	Liposorber LA-15 (to reduce lipids and remove circulating factors)	Adults	Ongoing
NCT06466135	Anti-suPAR antibody (to reduce suPAR levels)	Adults	Ongoing, part of basket trial

Abbreviations: AMP, adenosine monophosphate; CR, complete remission; FSGS, focal segmental glomerular sclerosis; ManNAc, *N*-acetyl-D-mannosamine; MCP-1, monocyte chemoattractant protein-1; NS, nephrotic syndrome; PR, partial remission; suPAR, soluble urokinase plasminogen activator receptor; TRPC6, transient receptor potential channel 6.

with CS alone.[32,33] There are no head-to-head studies that have compared different CNIs to one another or as a single agent versus CS in patients with FSGS.[34]

CNIs likely act by modulating the immune system, an important consideration in patients with primary, presumed immune-mediated disease.[35] CNIs are reported to also act directly on the regulatory mechanisms that stabilize the actin cytoskeleton and improve podocyte viability and prevent cell loss.[31,35] This effect may be nonspecific and account for the broad efficacy of CNIs, even in the subset of patients with an underlying genetic etiology.[36]

CNIs are associated with a wide range of side effects including tremor, cosmetic changes, nephrotoxicity, hypertension, hyperlipidemia, and hypomagnesemia. These collectively mandate close monitoring of the serum concentration of the drug to avoid supratherapeutic levels, a practical concern that has constrained their use.[37] Voclosporin is a newer, chemically modified CNI that has been shown to be superior to cyclosporine or tacrolimus in patients with lupus nephritis. In that setting, it is less nephrotoxic, and there is no need to monitor the serum level as with other CNIs[38]; however, it has not been evaluated in patients with FSGS.

A recent preliminary study using advanced multi-omic profiling aimed to identify a noninvasive biomarker profile that would indicate a low likelihood of response to CNIs in patients with FSGS.[39] Validation of such biomarker-profiling approaches to individualize therapy is ongoing. Implementation of these approaches in practice may enable more rational use of CNIs by maximizing the therapeutic benefit and reducing the potential harms related to long-term administration of these agents in patients who are less likely to respond.

In patients with persistent proteinuria despite administration of CS and/or CNIs, there are no formal recommendations on the next step in management, and they may be treated with one of the following classes of agents based on individual nephrologist's preference or offered participation in clinical trials.

Anti–B-Cell Therapies

Based on the favorable impact of rituximab on steroid-sensitive nephrotic syndrome, this biologic agent has been prescribed for patients with FSGS. There are reports of favorable responses, but the response rate varies widely; in larger scale studies, the response has not generally exceeded 20% to 25%.[13] In a recent summary of the outcomes after rituximab treatment in 183 adults with difficult-to-treat nephrotic syndrome, 63 of whom had FSGS and 22% who were steroid resistant, complete or partial remission of proteinuria was achieved in 82% at 6 months.[40] It is important to note the heterogeneity of the population in this study and the inclusion of patients with MCD and those who were steroid-responsive, both factors associated with an increased likelihood of a response to rituximab.

There have been no randomized clinical trials of rituximab that address its efficacy specifically in patients with steroid-resistant FSGS, nor any comparative studies of rituximab versus other more active monoclonal antibodies that target B-cells such as obinutuzumab. Newer biologics directed at other cells involved in antibody production such as felzartamab, which is directed against CD38 on mature plasma cells, have not been evaluated for the treatment of FSGS.

The relevance of an immune-based approach to therapy has been enhanced with the recent discovery of anti-nephrin antibodies in a subset of patients with FSGS.[14] This finding is fostering renewed investigations into ways to identify patients with FSGS in whom immune cell activation and antibody production are pivotal for initiating podocyte injury.

Miscellaneous

Other agents currently used to treat FSGS include antiproliferative agents such as mycophenolate mofetil and adrenocorticotropic hormone (ACTH). A review of 3 randomized controlled trials and 18 uncontrolled pre–post studies suggested that mycophenolate mofetil is no more effective than CNI for promoting kidney function preservation when used in addition to CS.[41] In a study of 24 patients with FSGS who were treated with ACTH gel, 7 (29%) had a reduction in proteinuria.[42] Although the presumed mechanism of action of these drugs is immunomodulatory, it is important to note that the ACTH receptor is expressed in the podocyte, supporting the potential for a direct protective effect of the peptide on the glomerular epithelial cell.[43] Overall, the response to these drugs is below 30%, and there is no established method to identify patients who are likely to respond to them.[41,42]

Agents that block the renin-angiotensin-aldosterone axis are considered a key part of the standard of care for patients with FSGS. Although there is evidence to support the use of sodium/glucose cotransporter 1 inhibitors in patients with IgA nephropathy,[44] there is uncertainty about the efficacy of this class of agents for FSGS.[45]

Precision Medicine Therapy

In light of the heterogeneity of FSGS as a diagnostic entity and the inability of current histopathological or clinically based classification schemes to predict prognosis or identify the optimal treatment for each individual patient, new state-of-the-art approaches are underway to better understand the pathogenesis of FSGS. The overall hypothesis is that delineating the molecular mechanism(s) of disease initiation and progression will define subtypes of FSGS amenable to precision treatment. Molecular profiling of these subtypes can allow for the identification of candidate treatments—repurposed drugs or novel agents—that target the predominant pathway leading to podocyte injury.

Experimental and Bioinformatic Methods

Over the last 15 years, the Nephrotic Syndrome Study Network (NEPTUNE) observational cohort study has assembled a multidimensional database of patients with FSGS. It includes demographic, clinical, standard laboratory, digital pathology, genomic, transcriptomic, single-cell and single-nucleus RNA-seq, epigenomic, proteomic, and metabolomic data.[46] Based on the bioinformatic analyses of this comprehensive data repository, preliminary steps have been taken to translate this knowledge into potential precision medicine approaches for the treatment of FSGS.[6]

Given this knowledge framework, a structured approach for FSGS drug development is emerging to develop treatments that are targeted to individual patients.[6] Standard preclinical models that recapitulate key elements of FSGS pathobiology, including 5/6 nephrectomy and Adriamycin (doxorubicin)-treated animals, are investigated. In the first step, gene expression profiles are defined in untreated animals and compared with diseased animals exposed to a putative novel therapy. This enables delineation of genes that are differentially regulated by the disease and reversed back to the healthy state by the test intervention.

In the second step, the information about gene expression is analyzed to define the key signaling pathways that are modulated by the test agent, be it a repurposed or new drug. Pathways can include stabilization of the actin cytoskeleton, cellular metabolism, B-cell and immune antibody-mediated injury, intrarenal inflammatory processes, and fibrosis. To refine the understanding of the mechanism and site of action, the impact of the drug or biological agent can be further evaluated in human kidney organoids with a high degree of podocyte differentiations.

Once the intrarenal signaling pathways that are targeted by the test therapy have been identified, the third step identifies noninvasive indicators of intrarenal activation of the pathway. The candidate biomarkers can include a wide variety of molecules such as growth factors, inflammatory mediators, chemokines, and structural proteins.

In step four, a feasible panel is selected based on the availability of validated assays that can be used to measure the molecule(s) in urine and/or blood samples. The noninvasive biomarker profile is designed based on measurements in healthy controls and a broad spectrum of patients with primary glomerular disease. The distribution of the biomarkers across these populations can define thresholds to be used for evidence of pathway activation and potential enrollment into a trial to test treatments that target that specific mechanism of disease.[47] It is important to emphasize that this discovery process is not unique to FSGS, and it can be applied to any form of glomerular disease.

Table 2 provides a summary of novel biomarkers that may be linked to the pathogenesis of FSGS and represent therapeutic targets. However, it is important to acknowledge that ongoing efforts to identify biomarkers indicative of specific intrarenal pathway activations are experimental in nature. Unlike in clinical oncology, none have been validated or approved for clinical application. We provide

Table 2. Novel Biomarkers Associated With Pathogenesis of FSGS

Biomarker	Biological Action
suPAR	Activation of podocyte and alteration of cytoskeleton
MCP-1	Activation of inflammation
CXCL10	Activation of JAK-STAT pathway
B-cell activation markers (BAFF, APRIL)	Autoantibody production
Anti-nephrin antibodies	Autoantibody production
miRNA193a	Activation of podocytes
Cardiotrophin-like cytokine-1	Permeability factor

Abbreviations: APRIL, a proliferation-inducing ligand; BAFF, B-cell–activating factor; CXCL10, C-X-C motif chemokine ligand 10; FSGS, focal segmental glomerular sclerosis; JAK-STAT, Janus kinase/signal transducers and activators of transcription; MCP-1, monocyte chemoattractant protein-1; miRNA193a, microRNA 193a; suPAR, soluble urokinase plasminogen activator receptor.

examples of this approach to identifying pathway activation and corresponding biomarker signatures.

Tumor Necrosis Factor

Clinical evidence from the FSGS Novel Therapies Trial (FONT) suggested that approximately 20% of patients with resistant FSGS may achieve a 50% reduction in proteinuria in response to a 6-month course of adalimumab, a monoclonal human antibody to TNF.[48,49] Molecular and transcriptomic profiling indicate that a comparable percentage of patients with FSGS had evidence of intrarenal activation of a TNF signaling cascade. These patients were clinically distinguishable from patients who did not have evidence of TNF pathway activation. In particular, they were less likely to achieve a remission in proteinuria and were more likely to manifest disease progression—namely, a 40% decline in estimated glomerular filtration rate (eGFR) or the initiation of KRT. A noninvasive biomarker signature that included increased urinary excretion of MCP-1 (monocyte chemoattractant-1) and TIMP-1 (tissue inhibitor of metalloproteinase-1) was developed and accurately identified the patients with the intrarenal TNF activation transcriptomic signature.[50]

Based on these findings, a proof-of-concept study was undertaken to test for target engagement.[51] Specifically, the objective of the pilot project was to determine whether short-term administration of adalimumab in 5 biweekly doses over 8 weeks could reverse the abnormal biomarker profile indicative of TNF activation. Seven patients were enrolled, mean age 24 years, eGFR of 57 mL/min/1.73 m^2, and proteinuria of 12.1 mg/mg creatinine. The trial recruited mainly multidrug-resistant patients who had fairly advanced kidney disease.[51,52] Unfortunately, the patients did not show a significant effect of adalimumab on systemic or kidney inflammatory biomarkers, and no consistent reduction in the urinary levels of MCP-1 or TIMP-1 was documented.

The negative findings may reflect (1) implementation of the test intervention relatively late in the disease course when advanced tissue damage might not allow reversal of pathogenetic TNF signaling; (2) an inability to deliver the drug to the relevant kidney compartment in later stages of the disease; or (3) an inability to confirm target engagement.

This experience represents the first application of precision medicine in the treatment of FSGS. It motivated efforts to define the stages of inflammation-mediated or -associated tissue damage in FSGS and to identify where and when a patient might respond to immunomodulation (see the previous discussion of CNIs). It is imperative to build on the experience of this pilot study to improve patient selection, refine the biomarker signatures, and implement innovative study designs to enable timely assessment of efficacy of novel therapies.

Endothelin Blockade

Sparsentan is a novel dual endothelin type A angiotensin II type 1 receptor antagonist that has been evaluated in a randomized clinical trial (DUPLEX) that enrolled 371 patients with FSGS. The results demonstrated that, over a 104-week treatment period and compared with irbesartan, the active control sparsentan achieved a consistently greater and sustained reduction in proteinuria.[53]

In order to develop a noninvasive biomarker signature to understand the intrarenal mode of action of this novel therapy, a differentially regulated gene set was assessed in the rat kidney cortex using the Adriamycin (doxorubicin) model of FSGS treated with sparsentan. Using human transcriptome data collected in the NEPTUNE cohort study, 189 mapped genes showed concordant regulation between rats and humans with increased endothelin signaling in FSGS.[54] A noninvasive biomarker profile indicating activation of this pathway which was reversed by sparsentan treatment was established—namely, increased urinary α_2-macroglobulin/creatinine ratio and plasma concentration of platelet-derived growth factor-β—and is currently being evaluated in sparsentan-treated patients.

Baricitinib, JAK-STAT Inhibition

Patients with 2 high-risk apolipoprotein L1 (*APOL1*) genotypes have a greater lifetime risk of developing FSGS and more rapid disease progression if they, in fact, have FSGS.[55,56] In the first study to assess the efficacy of an *APOL1* antagonist in this population, administration of inaxaplin, an *APOL1* channel blocker, to 11 patients for 13 weeks resulted in a 48% reduction in proteinuria.[57] Interferon-γ, via JAK-STAT (Janus kinase/signal transducers and activators of transcription) signaling, is linked to the progression of *APOL1*-associated glomerular disease in African American patients and FSGS.[58] STAT1 transcriptional activity is correlated with intrarenal C-X-C motif chemokine ligand 10 (CXCL10, also called IP-10) messenger RNA (mRNA) levels.[59] CXCL10 mRNA expression is elevated in the kidney of patients with *APOL1* high-risk alleles and correlates with urinary IP-10/creatinine.

Importantly, the increased urinary IP-10 levels were used as a target engagement biomarker in response to treatment with the JAK1/2 inhibitor baricitinib in a phase 2 clinical trial of diabetic kidney disease.[60] This supports the JAK-STAT dependence of CXCL10 in human proteinuric diseases such as FSGS and provides the rationale for using elevated urinary levels of IP-10 as a predictor of response to baricitinib in an ongoing trial for *APOL1*-mediated FSGS (JUSTICE trial; NCT05237388).

CNI Response Signature

As outlined previously, CNIs are important second-line immunosuppressive agents that are widely used in pediatric and adult patients with steroid-resistant FSGS. However, the response is unpredictable, and the side effects are consequential. To provide a more solid biological basis from which to guide the implementation of this class of drugs, a combination of plasma biomarkers (kidney injury molecule-1, matrix metalloproteinase-7, and human

Table 3. Pathway Activation Signatures for Targeted Treatment of FSGS

Test Therapy	Pathway/ Disease Status	Biomarker Signature
Adalimumab	TNF signaling	Urinary TIMP-1 and MCP-1
Sparsentan	Endothelin signaling	Urinary α_2-macroglobulin and plasma PDGF
Baricitinib	JAK-STAT	Urinary CXCL10 (IP-10)
DMX-200	CCR2 signaling	Urinary MCP-1
Calcineurin inhibitors	Advanced disease	Urinary MMP-7, KIM-1, and HE4

Abbreviations: CCR2, C-C chemokine receptor type 2; CXCL10, C-X-C motif chemokine ligand 10; FSGS, focal segmental glomerular sclerosis; HE4, human epididymal protein 4; JAK-STAT, Janus kinase/signal transducers and activators of transcription; KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1; MMP-7, matrix metalloproteinase-7; PDGF, platelet-derived growth factor; TIMP-1, tissue inhibitor of metalloproteinase 1; TNF, tumor necrosis factor.

epididymal protein-4) are being evaluated for their ability to predict a poor response to CNIs.[39]

Genetic Investigations

It is important to note that patients with genetic causes of FSGS represent the ideal candidates for precision medicine—namely, correction of the specific disease-causing variant in each case. Using an adenovirus delivery system for gene therapy in cases of monogenic disease, Ding et al[61] have demonstrated the ability to prevent disease progression in an animal model of podocin variant–related FSGS. Efforts are underway to commercialize this effort and to bring this cutting-edge precision medicine treatment to the clinic.[62]

Taken together, all these approaches offer the possibility of improving the efficacy of both current and future treatments of FSGS. The ongoing efforts to develop pathway activation signatures to guide precision medicine-based treatment of FSGS are summarized in Table 3.

Future Prospects for the Treatment of FSGS

Learning From IgA Nephropathy

Globally, IgA nephropathy is a more common glomerular disease than FSGS. Although it was originally considered relatively benign, recent data have suggested that there is a significant lifetime risk of progression to kidney failure in patients with IgA nephropathy.[63] The underlying autoimmune pathogenesis of the disease is well defined, and a 4-hit model captures the onset and progression of disease.[64] A feasible, reasonably likely surrogate end point has been developed based on reduction in proteinuria, and it can be deployed in interim analysis of trial results and enable accelerated approval of novel therapeutics that target the disease-causing immunological disturbances.[65] This has led

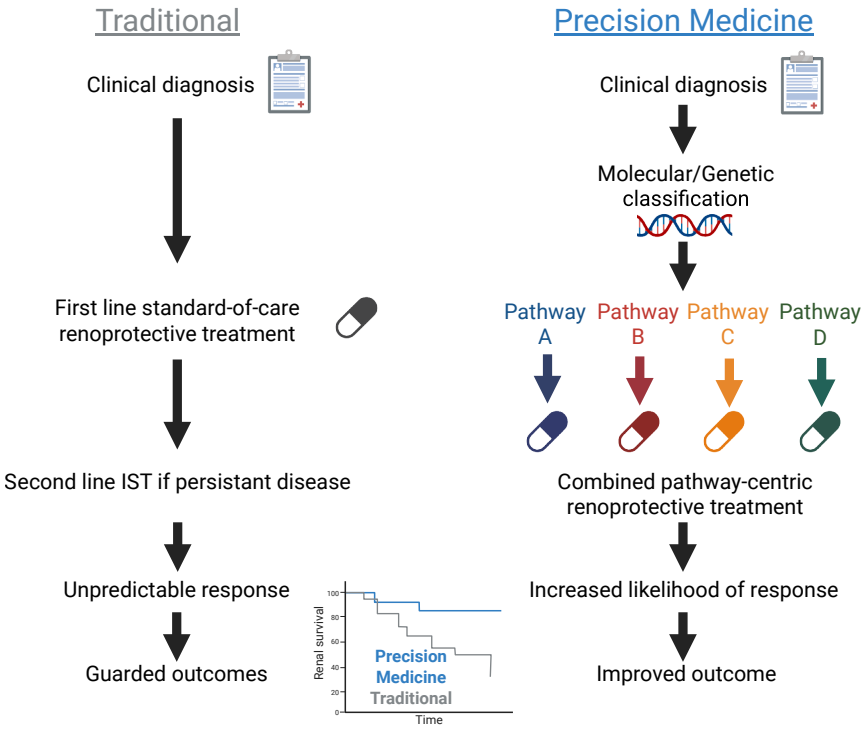

Figure 1. The schematic diagram compares traditional versus precision medicine approaches to the treatment of FSGS. By categorizing FSGS into subtypes based on noninvasive molecular and genetic profiling, precision medicine enables initiation of disease-modifying therapy that targets the injury pathway activated in an individual patient together with nonspecific renoprotective drugs. This combined treatment regimen will increase the likelihood of a treatment response and achieve improved kidney health outcomes compared with sequential prescription of renoprotective agents followed by empirical immunosuppressive therapy. Created with BioRender.com. Abbreviations: FSGS, focal segmental glomerular sclerosis; IST, immunosuppressive therapy.

to a paradigm shift in the approach to the treatment of IgA nephropathy. Thus, there is an evolving view that these disease-modifying drugs should be used earlier in the patient journey, synchronous with the prescription of nonspecific renoprotective therapies including sodium/glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and endothelin blockers in order to arrest the primary disease process and improve outcomes.[66,67]

FSGS is a more heterogeneous entity compared to IgA nephropathy. It has a wider range of underlying causes, making it unlikely that a single approach will be equally effective in all patients.[68] Discovery work being done that leverages all the rich knowledge network now available in FSGS hopefully will successfully define subtypes amenable to targeted therapy, similar to what has been achieved in IgA nephropathy.

The contribution of the primary disease pathway will vary and likely wane over the course of disease in patients with FSGS. As a consequence, it will be vital to characterize the stage of disease to guide formulation of a treatment strategy that balances targeting and arresting/modifying the primary disease process and inhibiting nonspecific progression factors. Stabilization of kidney function in patients with FSGS at a level that is compatible with a healthy productive life would represent a meaningful achievement for patients. The impact of improved understanding of the pathogenesis of FSGS on the approach to treatment is illustrated in Figure 1. It is anticipated that this approach will maximize the likelihood of therapeutic efficacy and minimize the adverse effects associated with ineffective treatments.

Conclusion

FSGS is a challenging and heterogeneous disease entity, which has discouraged basic science and biotechnology investments in the identification of novel therapeutics. However, advances across the board—from accessible preclinical disease models, bioinformatic approaches to analyzing multidimensional data sets, and improvements in trial design and implementation—have made it highly likely that the next 10 years will bring substantial improvements to the treatment of patients with FSGS.

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