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Emerging drugs for treatment of focal segmental glomerulosclerosis

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Abstract

Background: Glomerulosclerosis represents the final stage of glomerular injury during the course of kidney disease and can represent a primary disturbance in disorders like focal segmental glomerulosclerosis or a secondary response to tubulointerstitial disease. Overall, primary focal glomerulosclerosis (FSGS), the focus of this review, accounts for 10–20% of patients of all ages who progress to end stage kidney disease. There are no FDA approved therapeutic options that effectively prevent or delay the onset of kidney failure.

Areas covered: Current immunosuppressive therapy and conservative management including inhibitors of the renin-angiotensin-aldosterone axis and sodium-glucose cotransporter are reviewed. Focal segmental glomerulosclerosis is now recognized to represent a heterogeneous entity with multiple underlying disease mechanisms. Therefore, novel approaches targeting the podocyte cytoskeleton, immunological, inflammatory, hemodynamic and metabolic pathways are highlighted

Expert opinion: A number of factors that are driving the development of drugs to treat focal segmental glomerulosclerosis in particular and glomerulosclerosis in general including growing awareness of the burden of chronic kidney disease, improved scientific understanding of the mechanism of injury, the development of non-invasive profiles to identify subgroups of patients with discrete mechanisms of glomerular injury.

Keywords

glomerulosclerosis; FSGS; biomarker profiling; targeted therapy; precision medicine

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1. Background

Glomerulosclerosis, or scarring of the filtering units of the kidney, is a histopathological term and does not represent a specific diagnostic entity. It is a final common pathway of all renal diseases that progress to organ failure. The scarring can be focal and affect a part of the glomerular tuft or it can be global with hyalinization of the entire glomerulus. It is invariably linked to interstitial fibrosis, a parallel process in the tubular portion of the kidney. The adverse consequences of kidney diseases can influence both compartments in a bidirectional manner. Thus, glomerular barrier dysfunction and glomerulosclerosis induces tubulointerstitial injury as a consequence of proteinuria and activation of inflammatory pathways. In turn, tubular injury triggers disturbances in podocyte structure and glomerular damage. Scarring of the glomeruli was considered an inexorable irreversible process. Recent findings indicate that glomerulosclerosis can be halted and potentially reversed with restoration of kidney function [1].

This review will focus on focal segmental glomerulosclerosis (FSGS), a primary glomerular disorder that affects children and adults [2,3]. FSGS is a heterogeneous disorder. It is considered primary if it is caused by genetic abnormalities or production of a circulating factor that increases glomerular permeability to protein. Secondary causes include reduction in kidney mass, infections, medications (2,3). Despite improvements in diagnostic methods, the underlying cause of FSGS often unknown. Nearly 40–50% of patients with this disease fail to respond to current treatments including corticosteroids and calcineurin inhibitors, and will steadily lose renal function and progress to end stage kidney disease (ESKD). In FSGS, scarring of the filtering units is the initial site of injury and disease progression. This review will discuss molecular pathways that are targets of current therapy including inhibitors of the renin-angiotensin–aldosterone axis, sodium-glucose cotransporter 2, and endothelin. In addition, novel pathways such as TNF and JAK-STAT signalling will also be presented and assessed for potential application in clinical therapeutics.

FSGS qualifies as a rare disease based on the federal criterion, namely that it affects less than 200,000 people in the United States. The prevalence is based on results of biopsy registries and the national oversight of renal replacement therapy. However, the financial and health costs of FSGS and other forms of glomerulosclerosis are substantial because in the aggregate these disorders account for approximately 10% of the total number of patients with end stage kidney disease (ESKD).

2. Medical need

There is a steadily growing number of patients with chronic kidney disease (CKD), defined as abnormalities in kidney function or structure lasting at least three months. CKD stage 3, namely glomerular filtration rate (GFR) <60 ml/min, is currently estimated to effect nearly 10–15% of the US population and is associated with increased risk of cardiovascular disease and mortality [4]. It is attributable to primary glomerular disease in a significant subgroup, ranging from 10–20% of the CKD population. These patients are at high risk of progression to ESKD and premature mortality secondary to cardiovascular disease complications.

Patients with glomerulosclerosis are treated with a wide range of immunosuppressive medications. Most patients receive a course of corticosteroids as initial therapy. Calcineurin inhibitors are the most common second-line agent. Other options include alkylating agents, anti-proliferative drugs such as mycophenolate mofetil, and biological agents such as rituximab (see next section, Existing treatment). However, these therapies are effective in achieving complete or partial remission in a minority of patients. Moreover, they are associated with significant short- and long-term adverse effects some of which are serious such as acute kidney injury and bacterial and viral infections (see Section 3). Finally, there is no consensus on the sequence of these options or the optimal dose or duration of therapy [5,6].

Therefore, conservative medical management is foundational and consists of dietary sodium, protein, and phosphorus restriction and control of blood pressure, edema, and anemia. Agents that reduce proteinuria in a non-specific manner are prescribed as renoprotective agents. There is a paucity of specific therapies for most glomerular diseases that target the underlying mechanism of injury. Therefore, there is a huge unmet clinical need for novel therapies that can control the primary disease process and prevent or reverse glomerular scarring [7]. This would enable preservation of kidney function at a level compatible with health and wellbeing without compromise in quality of life. This would lead to an attendant reduction on clinical disease burden and the financial costs of treating patients with advanced CKD and ESKD.

3. Existing treatment

Existing treatment of glomerulosclerosis and FSGS focus on non-specific treatment of blood pressure and agents that reduce proteinuria. Normalization of blood pressure is associated with delayed disease progression. Blood pressure control involves dietary control of sodium, potassium, and calcium intake and prescription of safe and tolerated anti-hypertensive drugs. Implementation of drugs that inhibit the activity of the renin-angiotensin-aldosterone system (RAAS) are especially useful in this regard because they not only lower blood pressure but they reduce proteinuria and are renoprotective. Anti-proteinuric drugs generally act by reducing intra-glomerular hemodynamics and inhibiting molecular pathways such as TGF-β and endothelin that are involved in glomerular dysfunction and fibrosis [8]. Recent studies suggest that administration of oral sodium-glucose transport protein 2 (SGLT2) inhibitors can also lower blood pressure, reduce proteinuria, and stabilize kidney function in patients with type 2 diabetes and kidney disease [9].

The application of these promising findings to other forms of glomerular disease and causes of CKD such as FSGS is under current investigation. However, they are generic interventions that are applicable to virtually all types of kidney disease and do not address the underlying mechanism of glomerular injury. Specifically, they do not target the podocyte which is the major cell involved in primary glomerular disease.

4. Market review

Glomerular disease is estimated to contribute approximately 10% of the health burden and mortality attributable to CKD in the US. Assuming that 10% of the American population has CKD, then 30 million people have CKD of whom 3 million may have underlying glomerular disorders. The most common cause is diabetes followed by hypertension (possibly APOL1-mediated disease) and then a wide range of specific disorders. Although CKD is associated with an increased risk of premature mortality, there remains a large number of patients in need of effective renoprotective therapies that can be added to RAAS and SGLT2 inhibitors. In addition, there is a complete lack of targeted agents that can be prescribed for patients with specific forms of glomerular disease.

The health care costs of ESKD are exceedingly high and currently patients requiring renal replacement therapy consume approximately 10% of the Medicare budget, at least an order of magnitude greater than their percentage of the United States population. Prevention of ESKD will curtail the rising spiral of ESKD costs. Effective treatment of FSGS and other forms of glomerulosclerosis that preserve kidney function will be associated with improvements in quality of life and be widely accepted by patients.

5. Current research goals

Current research efforts aimed at treating glomerulosclerosis involve whole animal studies and investigations using isolated glomeruli and single cell technology. Specific signaling pathways and molecules are evaluated by genetic manipulation (standard knockout or CRISPR/Cas9 gene editing methods) or pharmacological inhibition. These most up-to-date approaches enable delineation of discrete processes in resident cells including podocytes, parietal epithelial cells, endothelial cells, and mesangial cells and infiltrating cells in that cause glomerular scarring. It can define subtypes within each cell category that may contribute differently over the course of the disease. The genomic, proteomic and metabolomic profiles of these discrete anatomic segments and cell populations can then be analysed using sophisticated bioinformatics approaches to pinpoint the molecular processes mediating glomerulosclerosis in specific disease subtypes in an effort to provide precise individualized treatments for patients with primary glomerular disease. Recently introduced experimental approaches include organoids and gene chip technology are facilitating high throughput screening of potential therapeutic agents for glomerular diseases [10].

6. Scientific rationale

6.1 Overview

The scientific rationale guiding the development of novel therapies to treat glomerulosclerosis and FSGS in particular is based on a classification of the underlying mechanism and identification of pharmacological agents that can prevent or reverse the fibrotic process. The following sections are organized by the putative injury pathway and details agents in each category that are in testing or in development for the treatment of glomerulosclerosis

6.2. Podocyte cytoskeleton

6.2.1. Calcineurin inhibitors—Calcineurin inhibitors (CNI) were originally thought to act via the IL-2 receptor and NFAT signalling and modulation of the immune system. Recent data indicate that these drugs also have direct effects on the podocyte cytoskeleton that account in part for their anti-proteinuric action [11,12]. This may occur via interaction with and regulation of dynamin-mediated changes in synaptopodin or Rac1 activation [13]. There is no means to assess these podocyte specific effects and to target these agents accordingly.

6.2.2. Integrins, α1 and β3—Integrins, α1 and β3 mediate cell adhesion to the extracellular matrix and contribute to signalling between the cell interior and exterior [14,15]. Potential therapeutic agents in FSGS have been proposed to act through this pathway. Abatacept modulates α1-talin interaction while suPAR may interact with β3 integrins and preserve a normal podocyte phenotype. However, the abatacept trial in steroid-resistant FSGS and minimal change disease (MCD) was terminated prematurely because of poor enrollment [16]. To date, no trials have been conducted to test the efficacy of a suPAR antagonist in FSGS.

6.2.3. TRPC5—The calcium channel TRPC5 has been linked to activation of Rac1 and an altered podocyte with an excessively motile phenotype that is associated with glomerular dysfunction and sclerosis [17]. Elevated levels of angiotensin II increase the membrane expression of TRPC5 and may drive this injurious pathway in positive feedback loop [18]. There continues to be some uncertainty about the role of TRPC5 in the pathogenesis of FSGS because overexpression of the channel in animals is not associated with nephrotic syndrome. Nonetheless, an oral antagonist to TRPC5 has been developed and has been demonstrated to reduce proteinuria in two models of FSGS – DOCA-salt uninephrectomy rats and transgenic mice with overexpression of the angiotensin type 1 receptor [18]. The drug has been tested in healthy volunteers and it is anticipated that clinical trials will commence in the near future for patients with FSGS, TR-MCD, and diabetic nephropathy.

6.3. Immunological

6.3.1. Rituximab—The monoclonal antibody, Rituximab, has been shown to effectively reduce the relapse rate in children with frequently relapsing or steroid-dependent nephrotic syndrome [19]. The antibody was presumed to work via elimination of B-cells and disruption of interactions between B-cell and T-cells that cause proteinuria and glomerulosclerosis [20]. However, there are conflicting data about the direct effect of rituximab exerts on the podocyte by binding to] sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) and preserving its expression [21,22]. This is associated with attenuation of proteinuria and renal damage in experimental models of FSGS [20]. Responsiveness to rituximab in patients with FSGS may be correlated with the circulating level of suPAR (unpublished observations). This served as the rationale for a pilot study that was closed after the enrollment of nine patients who failed to show any improvement in proteinuria (https://www.clinicaltrials.gov/ct2/show/NCT01573533?term=rituximab&cond=FSGS&draw=2&rank=2). There is a pressing need for controlled clinical trials to assess the efficacy of rituximab in this clinical condition.

6.3.2. CCR2—CCR2 is a chemokine receptor that is expressed on the cell surface of podocytes. It mediates the activity of the monocyte chemoattractant protein-1 (MCP-1) and promotes mononuclear cell infiltration into the glomerulus and local inflammation. An oral inhibitor of CCR2, CCX140-B, has been developed and it reduced proteinuria in patients with diabetic nephropathy [23]. In the adriamycin and remnant kidney models of FSGS, administration of the same agent lowered albuminuria and preserved glomerular structure. Pediatric and adult patients with FSGS have increased urinary excretion of MCP-1 and suggestive evidence that CCR2 is involved in the glomerular injury [24]. However, the findings in preclinical models using this drug have not been tested in the clinical setting

6.3.3. C5a: The complement pathway is part of the innate immune system. It promotes killing and clearance of infectious agents but can also cause cell injury. There are three pathways of complement activation – classical, alternative, and mannose binding lectin – which converge on C3 convertase and lead to release of inflammatory degradation products of C3 and C5 and formation of the cytolytic membrane attack complex (SMAC or SC5b-9). There is evidence of activation of the alternate pathway of complement in approximately 20% of patients with FSGS [25].

A variety of complement inhibitors are in clinical testing for treatment of glomerular disease and transplant rejection. Avacopan, an inhibitor of the C5a receptor has been proven to be effective in ANCA-associated vasculitis and is approved for this use. A clinical trial is underway in C3 glomerulopathy (https://www.clinicaltrials.gov/ct2/results?cond=C3+Glomerulopathy&term=Avacopan&cntry=&state=&city=&dist=) and a similar study is being planned for patients with FSGS.

6.4. Inflammatory

6.4.1. TNF—Circulating levels of TNF and synthesis of the cytokine by cultured peripheral blood mononuclear cells is increased in patients with FSGS. Moreover, TNF promote fibrosis in models of kidney disease. In patients with FSGS, there is evidence of activation of genes regulated by TNF in approximately 20% of patients. There was a comparable response rate to the anti-TNF antibody adalimumab in all of the combined total of 17 patients who received this agent in the PK (n=10) and randomized portion (n=7) of the FONT study [26]. These patients are characterized by increased levels of proteinuria, reduced eGFR and a more rapid of decline in kidney function compared to other patients with FSGS. A urinary biomarker signature – elevated levels of MCP-1 and TIMP-1 – has been defined that identifies patients characterized by TNF gene activation in the kidney tissue (bioRxiv). This has led to the design of a pilot study to determine whether administration of adalimumab, a monoclonal antibody to TNF, can normalize the biomarker signature (https://www.clinicaltrials.gov/ct2/show/NCT04009668?term=adalimumab&cond=FSGS&draw=2&rank=1). This will justify long-term follow-up clinical trials to determine the efficacy of anti-TNF therapy in patients with the biomarker profile consistent with TNF gene activation.

6.4.2. JAK/STAT—There is evidence of increased activation of the JAK-STAT pathway and enhanced mmunohistochemical staining of the kidney tissue in patients with FSGS.

Similar to the circumstance with TNF, a biomarker signature, namely increased urinary excretion of CXCL10 (IP10), identifies patients with intra-renal activation of the JAK-STAT pathway [27]. This mechanism of injury can be targeted with FDA approved drugs such as baricitinib and tofacitinib. However, clinical trials assessing the efficacy of these agents in FSGS have not been conducted.

6.4.3. TGF—In virtually all models of FSGS and glomerulosclerosis there is increased expression of TGFβ. This is not unexpected because this cytokine appears to be pivotal in the regulation of fibrosis and unrestrained upregulation can cause scarring and permanent organ injury [28]. However, trials of polyclonal antibodies to TGFβ in patients with diabetic nephropathy showed no efficacy based on changes in proteinuria or GFR [29]. A dose-ranging, single dose administration study of fresolimumab, a monoclonal antibody to TGFβ1 showed a potential response at lower doses (1–2 μg/kg per dose) [30]. However, a more extended Phase 2 study of this antibody was terminated prematurely because of poor enrollment (https://www.clinicaltrials.gov/ct2/show/NCT01665391?term=fresolimumab&cond=FSGS&draw=2&rank=2). Enthusiasm for systemic antagonism of TGFβ is dampened by the recognition that TGF exerts anti-inflammatory effects that may be abrogated by antibody neutralization. Newer strategies are being considered to harness the potential benefits of TGF blockade. These include efforts to target the delivery of TGFβ to sites of injury in the kidney to limit systemic effects, to block downstream fibrotic mediators of TGFβ activity such a connective tissue growth factor, or to design molecules that dissociate the profibrotic and anti-inflammatory actions of the cytokine [31]. To date, none of the approaches has been brought to clinic for testing. Pirfenidone, a drug that acts similarly to TGF-β blockade, has been studied in small open-label studies and shown to stabilize kidney function without lowering proteinuria. However, it has not advanced to larger scale Phase 2 trials [32].

6.4.4. Nrf2—Nrf2 is a transcription factor that binds to Kelch-like ECH-associated protein (KEAP) in the cytosol. When Nrf2 is released, it translocates to the nucleus and promotes the translation and synthesis of a variety of anti-inflammatory pathways [33,34]. Bardoxolone is an Nrf2 agonist that was additional tested in patients with diabetes. It was abandoned when clinical trials demonstrated that it increased the risk of heart failure and mortality. In addition, it caused an increase in GFR, raising concerns about long-term consequences of sustained hyperfiltration [35]. Reassessment of the cardiac risks and better delineation of eligible subjects prompted reassessment of the impact of this drug in kidney disease [36]. The Cardinal trial has documented the ability of bardoxolone to increase eGFR in patents with Alport syndrome [unpublished data, 37,38]. Persistence of this change after drug withdrawal of the drug suggested that the effect was not merely hemodynamic and reflected beneficial permanent changes in glomerular structure and function. A Phase 2 study assessing the efficacy of bardoxolone in patients with FSGS has completed enrollment but the results have not been reported (https://www.clinicaltrials.gov/ct2/show/NCT03366337?term=bardoxolone&cond=FSGS&draw=2&rank=1).

6.4.5. p38—p38 is an inflammatory mediator that is downstream of MAP kinase signalling and is activated in animal models of podocyte injury and diabetic nephropathy

[39]. Drugs that inhibit p38 have had a modest effect in patients with ANCA associated vasculitis [40,41]. However, studies in patients with FSGS have been disbanded because of poor enrolment.

6.5. Hemodynamic

6.5.1. Endothelin—The potent vasoconstrictor peptide, Endothelin, is produced by endothelial cells within the glomerulus. It interacts locally with podocytes to disrupt mitochondrial function and cellular bioenergetics. This in turn leads to reciprocal adverse effects on endothelin cell integrity. Endothelin antagonists, primarily acting on the endothelin type A receptor, reduce proteinuria and glomerulosclerosis in the adriamycin model of FSGS [42]. A recent report demonstrated the efficacy of atrasentan, an endothelin antagonist, in reducing the risk of renal events, namely, doubling of serum creatinine or onset on ESKD, inpatients wit type 2 diabetic nephropathy [43]. In the DUET trial, an 8-week double blind, active control study, sparsentan a dual receptor AT1 and ETB receptor blockade, reduced proteinuria more effectively than irbesartan [44]. The long-term effects of endothelin blockade in patients with FSGS are being evaluated in the DUPLEX trial. This is an ongoing 2-year study with the primary objective of documenting a reduction in the rate of decline in eGFR compared to irbesartan [45].

6.6. Metabolic

6.6.1. SGLT2 inhibitors—SGLT2 inhibitors are a novel class of drugs that have been shown to significantly reduce the risk of cardiovascular events and renal complications in patients with type 2 diabetes [9]. The drug has numerous favourable actions including glycosuria, reduction in blood pressure, lowering of intra-glomerular pressure, reduced inflammation, and anti-fibrosis [46]. All of these actions may contribute to the observed effects in diabetics. There is a single study evaluating SGLT2 inhibitors in FSGS. Short-term (8 weeks) administration of the SGLT2 inhibitor dapagliflozin did not modify renal hemodynamic function, GFR, or attenuate proteinuria in humans or in an experimental model of FSGS [47]. This negative finding may be related to downregulation of renal SGLT2 expression in FSGS. Follow-up investigations of the impact of SGLT2i on markers of kidney disease in patients FSGS and with other causes of nondiabetic CKD are needed.

6.6.2. PPARγ—In the 5/6 nephrectomy model blockade of peroxisome proliferator activating receptor-γ (PPAR-γ) signalling with thiazolidinediones reduces TGFβ signaling and renal fibrosis. This action has been confirmed in in vivo and vitro studies [48]. Preliminary efforts to apply these findings were stymied by reports of a higher risk of heart failure in elderly diabetic patients receiving rosiglitazone [49]. The design of safer molecules that block this pathway and preserve the antifibrotic properties have been developed and warrant testing in patients with FGS provided proper precautions are taken to reduce the risk of heart failure and other major cardiovascular complications [50]

6.6.3. FXR—Experimental models of glomerulosclerosis are characterized by numerous disturbances in fatty acid disposition and other aspects of intermediary metabolism, The FXR system modulates the metabolic response and antagonists are associated with reduced fibrosis in models of liver disease [51]. There is evidence that this benefit may apply to

preclinical models of renal fibrosis. This class of agents has not been tested in clinical trials of patents with FSGS or glomerulosclerosis

6.6.4. Cyclodextrin—Cyclodextrin may deplete cells of lipid deposits that are implicated in disease pathogenesis. There is evidence that TNF may disrupt the expression of transporters involve in the uptake and exit of cholesterol from cells [52]. Studies have been performed that document efficacy of cyclodextrin in reducing proteinuria and renal fibrosis in models of FSGS and Alport syndrome [53]. Cyclodextrin is used to treat patient with Niemann Pick disease and is safe and well tolerated. Trials are planned to test whether thrice weekly intravenous administration of this drug is effective in reducing proteinuria in patients with FSGS.

6.6.4 LDL apheresis—Adsorbent columns have been developed that facilitate the removal of circulating lipids and are used to treat hereditary forms of hypercholesterolemia. LDL apheresis has been applied to the treatment of refractory FSGS in small case series with moderate success [54]. The device is provisionally approved for use by the FDA. However, the need for venous access to enable repeated extracorporeal treatments has limited the use of this therapeutic modality.

The following Table summarizes the drugs that are currently available for the potential treatment of FSGS.

7. Competitive environment

Over the last 30 years, nephrology has occupied the unenviable position of last place, trailing all other subspecialties in the performance and completion of randomized clinical trials. Moreover, even the completed studies are usually smaller in sample size and often lack rigorous control arms and sufficient procedural integrity to ensure validity of the findings (55). This has been especially noteworthy in trials for glomerular disease. With the exception of the vasculitic syndromes for which a collaborative and productive consortium has been established and which has completed a number of well-designed clinical trials (56), there has been little progress in glomerulosclerosis and in FSGS in particular.

However, over the last decade there has been a renaissance in clinical research in nephrology. There have been striking advances in the molecular and genetic understanding of glomerulosclerosis and what was once viewed as a single homogeneous entity is now considered a heterogeneous group of disorders each with a specific pathogenetic mechanism of injury that can be targeted for intervention [57]. This has resulted in a resurgence in interest in CKD in general and rare glomerular diseases such as FSGS in particular. There has been a veritable explosion of clinical trials in glomerular and where there were less five ongoing trials as recently as 5 years ago, there are now over 20 ongoing on planned RCTs in this clinical space [7]. In view of the rare disease status of glomerular diseases in general, this will create a very competitive environment that will create a premium for thoughtful allocation of patients into studies and development of novel trials design to facilitate timely completion of trials.

Reviewing the studies registered at the Clinicaltrials.gov website, indicates many ongoing studies evaluating standard immunosuppressive agents and novel therapies. Sparsentan, a dual receptor angiotensin receptor type 1 and endothelin type A receptor blocker, is the first drug that has been developed and evaluated exclusively for the indication as a treatment for FSGS. A phase 2 trial (DUET) has been completed (44) and a Phase 3 trial (DUPLEX) is underway (45). Over 200 patients have been enrolled with a target sample size of 300 participants. There are ongoing Phase 2 studies of CXA-10, voclosporine, and PF-06730512 and a more expanded trial of CXA-10 is about to launch. A Phase 1 study of GFB-887, an oral TRPC5 channel blocker, has demonstrated safety in healthy volunteers and a Phase 2 study in patients with FSGS, treatment-resistant MCD and diabetic nephropathy is expected to be open to recruitment in the second half of 2020. A small molecule inhibitor of Robo2, a receptor that binds to Slit2 and modulates the podocyte cytoskeleton and motility, is also being evaluated in a multicentre Phase 2 study [58]. There are many other agents that are in the planning stage, underscoring the intense interest that has emerged in the biotechnology sector to develop new and effective therapies for glomerulosclerosis and FSGS.

8. Potential development issues

There are a number of potential issues that may arise in the development of therapies to treat FSGS and glomerulosclerosis. These are rare disorders that generally qualify for provisions that pertain to orphan disease drug development. FSGS and other forms of glomerular disorders are often asymptomatic and thus a challenge to diagnose in the early stages. The effort to target specific mechanism of injury only compounds the difficulty in identifying suitable patients for enrolment in precision-based clinical trials. Methods to address this problem include expedited laboratory testing to identify patients with defined biomarker profiles that will determine trial eligibility.

Second, novel trial designs will potentially be needed to reduce the required sample size. Potential formats include platform trials – basket or umbrella – that increase the options available for testing [59]. Shared well phenotyped control groups will reduce the logistical burden of creating this cohort in each trial and lower one obstacle to patient enrollment. Adaptive and SMART designs can maximize the utility of each patent and provide valuable information on prioritization and sequencing of novel therapies [60,61,62].

Third interaction with regulatory agencies may lead to new valid endpoint to assess efficacy and facilitate the timely completion of trials. For example, the novel FSGS partial remission endpoint, a 40% reduction in the urine protein:creatinine ratio to a level below 1.5, may be a valuable surrogate marker to enable accelerated approval of novel therapies [63]. The FDA is considering change in GFR slope as a valid clinically relevant endpoint which has the potential to reduce the sample size and study duration necessary to document a beneficial outcome [64].

Finally, consideration needs to be given to support drug development and monitor drug pricing so that the costs of new therapies are not prohibitive and that new drugs are made available to patients in need [65,66]. Thoughtful evaluation of existing drugs that have been developed for other indications and that base on molecular analysis can be repurposed for

the treatment of FSGS and glomerulosclerosis may be another way to control the price of new drug development. The voice of patients and caregivers needs to be incorporated into drug development so that candidate therapies have an acceptable safety burden and feasible means of administration.

9. Conclusion

These are exciting times in nephrology. There is a confluence of a number of factors that are driving the development of drugs to treat FSGS in particular and glomerulosclerosis in general. These include: (1) growing awareness of the burden of CKD; (2) improved scientific understanding of the mechanism of injury in affected patients; and (3) the development of non-invasive genomic and proteomic profiles to identify subgroups of patients with discrete mechanisms of glomerular injury. These medical aspects are fortuitously joined by intense interest from biopharmaceutical companies in the timely development of novel therapies for FSGS and glomerulosclerosis and an openness by regulatory to consider creative approaches to assess efficacy of novel therapies in an effort to bring drug to the clinic and to address the huge unmet need of patients with FSGS and glomerulosclerosis. Taken together, it is likely that over the next 5–10 years, we will witness significant advances in the scope of effective therapeutics that will be available to treat patients with glomerulosclerosis and FSGS in particular.

Clear communication skills must be deployed to describe complex scientific concepts in such a manner that the basic principles of the specific disease target can be appreciated and the patient/caregiver can satisfy himself/herself that the proposed treatment is scientifically tenable and worth considering. Interaction with patient advocacy groups for glomerular disease will help in the design and implementation of the clinical trials and translational of new findings into clinical practice.

Taken together, it is likely that a range of novel therapies will be developed over the next decade and that their widespread clinical application will result in significant improvement in health outcomes of children and adults with FSGS and glomerulosclerosis.

10. Expert opinion

FSGS and glomerulosclerosis are heterogeneous disorders. Effective treatment mandates identification of the underlying mechanism of injury in order to develop safe and effective therapies for each individual patient. There is a great need to define the range of pathways involved in causing FSGS and glomerulosclerosis and to develop the technology to identify these pathways in real time so that patients can be classified by disease mechanism and directed to the appropriate therapy in a timely and efficient manner. In addition, a new biostatistical and administrative infrastructure will be needed to conduct clinical trials in FSGS and glomerulosclerosis using novel approaches that will promote scientific and financial efficiency.

Current research in nephrology using state of the art genomic, proteomic and metabolomic analytics and single cell and organoid systems has the potential to define each patient by the underlying injury pathway. The ultimate goal is to provide precision medicine defined

therapy to each patient with FSGS. This is the approach being applied in oncology with great success and should be as effective in nephrology. Precision medicine approaches in nephrology are in their infancy and there are too few candidates being developed to pick clear-cut winners at this stage. Those drugs in active field trials such a sparsentan have the opportunity to be the first FDA-approved therapies for FSGS. The application of drugs will represent a balance between modest effect in a broad range of glomerular diseases versus normalization of proteinuria and "cure" in a select subgroup of patients. A closer integration and partnership between academic centres and industry to develop accurate diagnostic methods and effective treatments is highly anticipated because without successful cooperation it may prove difficult to achieve these goals in rare glomerular disease

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* of interest

** of considerable interest

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Table 1

Currently available options for the treatment of FSGS

Drug	Mechanism of action
Corticosteroids	Stabilization of podocyte
Calcineurin inhibitors	Stabilization of podocyte cytoskeleton Inhibition of NFAT signaling
Mycophenolate mofetil	Altered NFAT signalling
Rituximab	B-cell depletion Modulation of podocyte SMPDL-3b
Abatacept	T cell co-stimulatory blockade
Adalimumab	Blockade of TNF-α signaling
Baricitinib	Blockade of JAK/STAT signaling

Table 2

Competitive Environment

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Sparsentan	Retrophin	Oral compound	FSGS	Phase 3	Blockade of AT1 and ETA receptors
GFB-887	Goldfinch	Oral compound	FSGS/DN	Phase 1	TRPC5 inhibitor
CXA-10	Complexa	Oral compound	FSGS	Phase 2	Nrf2 activator
Voclosporin	Aurinia	Oral compound	FSGS	Phase 2	Calcineurin inhibitor
PF-06730512	Pfizer	IV agent	FSGS	Phase 2	Robo2 inhibitor