Drugs of the Future 2009, 34(10): 821-829

CCC: 0377-8282/2009
DOI: 10.1358/dof.2009.34.10.1426670

OVERVIEW OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS

J.K.J. Deegens

Department of Nephrology 464, Radboud University Nijmegen Medical Center, PO Box 9101, 6500 HB Nijmegen, The Netherlands

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ABSTRACT

Focal segmental glomerulosclerosis (FSGS) is one of the main causes of the nephrotic syndrome in adults. FSGS is not a single disease but a histological finding on renal biopsy, which can be a primary (idiopathic) disorder or secondary to other diseases. It is important to differentiate between idiopathic and secondary FSGS, as the treatment of these disorders can differ significantly. Idiopathic FSGS may respond to immunosuppressive drugs, such as corticosteroids, whereas secondary FSGS fails to respond to immunosuppressants. Moreover, patients with FSGS should receive symptomatic therapy to reduce proteinuria and lower blood pressure. Alkylating agents such as cyclophosphamide can be used to induce a more stable remission in patients with steroid-dependent FSGS. In steroid-resistant forms, however, ciclosporin is more effective than cyclophosphamide. Additionally, mycophenolate mofetil or rituximab can be considered as rescue therapy in patients not responding to corticosteroids, cyclophosphamide and ciclosporin.

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is defined by findings on renal biopsy. The classic lesion of FSGS, as first described by Rich in 1957 (1), consists of a scarring lesion in a portion (segment) of some (focal) but not all glomeruli (1, 2). The scar comprises increased mesangial matrix with collapsed glomerular capillaries, an adhesion between the tuft and Bowman's capsule, and hyalin deposits (3). The glomerular scar can also be accompanied by features such as mesangial hypercellularity and foam cells. Over the years, the pathological description of FSGS has evolved and, in addition to the classical form, other variants have been described and are discussed below (4).

Currently, FSGS is one of the most common patterns of glomerular injury encountered in human renal biopsies (5-7). FSGS accounts for up to 35% of all adult nephrotic syndrome cases in the U.S. (8). Moreover, end-stage renal disease (ESRD) as a result of FSGS has increased more than 10-fold over the past two decades (9).

It is important to realize that FSGS is a descriptive diagnosis and not a single disease entity. It can be idiopathic (primary; of unknown cause) or secondary to a variety of clinical conditions (4, 10). Treatment of idiopathic and secondary FSGS is aimed at reducing proteinuria to prevent progression to ESRD. This review provides an overview of idiopathic and secondary FSGS with special emphasis on treatment options.

ETIOLOGY AND PATHOPHYSIOLOGY

It is now well recognized that FSGS is a common final pathway of glomerular injury, particularly involving the podocyte (11, 12). Podocytes are highly specialized epithelial cells that cover the entire outer aspect of the glomerular basement membrane (13). Their foot processes form a complex interdigitating pattern with slits (slit pores) that are bridged by extracellular protein–protein contacts to form the slit diaphragm. Podocytes play a critical role in maintaining the glomerular permselectivity and structural integrity of the glomerular filtration barrier, preventing loss of proteins into the urinary space (14).

By definition, the pathogenesis of idiopathic FSGS is unknown. However, there is strong evidence that idiopathic FSGS may be the result of injury to podocytes due to a circulating plasma factor or factors (15, 16). Shalhoub proposed that the circulating factor may be produced by a clone of T lymphocytes (17). The best evidence supporting the presence of a circulating factor comes from recurrent FSGS after renal transplant. Proteinuria may develop within minutes or hours after renal transplant, and plasma exchange instituted early in the course of recurrent disease removes the putative factor and results in a remission of proteinuria (16, 18). In addition, rats infused with serum from patients with recurrent FSGS or with plasma fractions enriched for the permeability factor develop proteinuria (19, 20). Further evidence for a permeability factor is offered by a case report that described the transient occurrence of the nephrotic syndrome in a neonate whose mother had known FSGS (21). After

birth, proteinuria in the child decreased and then disappeared, suggesting a strong correlation with a factor transmitted from the mother. Recently, cardiotrophin-like cytokine factor 1 (BSF-3), a member of the interleukin-6 (IL-6) family, was identified as a candidate for the FSGS permeability factor (22).

With our increase in knowledge, the number of secondary causes of FSGS has steadily grown (Table I). Secondary forms of FSGS were generally considered to result from maladaptive responses due to the loss of functioning nephrons, hyperfiltration or increased glomerular pressure. Studies in experimental rat models have demonstrated that loss of podocytes may be pivotal in this form of FSGS (23). FSGS can also result from direct injury to the podocytes due to viral infections or the use of drugs (24-28). More recently, FSGS resulting from genetic mutations in genes encoding for podocytic proteins has been described (29). The clinical severity and age of onset of FSGS vary depending on the underlying mutation.

HISTOLOGICAL CLASSIFICATION

Several different histological variants of FSGS have been described (1, 30). A group of renal pathologists redefined these histological variants and proposed a standardized pathological classification system for FSGS based on light microscopic examination that can be applied to both idiopathic and secondary FSGS (4, 10). This working classification defines five morphological variants: FSGS not otherwise specified (NOS) and tip variant, perihilar, cellular and collapsing FSGS. Some pathological variants are more likely to occur in relation to certain causes. The perihilar variant of FSGS is associated with hyperfiltration, whereas HIV- and drug-induced FSGS typically result in collapsing FSGS. However, there is a clear overlap, and patients with idiopathic FSGS may present with either variant (31).

Clinical presentation and sociodemographic findings differ among the FSGS variants (31-33). Collapsing FSGS is more common in younger patients and Afro-Americans and typically presents with substantial renal insufficiency. Collapsing and tip variant FSGS usually manifest with more severe proteinuria than perihilar and NOS FSGS. Patients with the last two morphological variants tend to have higher blood pressure and pathologically more arteriosclerosis. Renal function is usually preserved in patients with tip variant and these patients achieve complete remission more often than those with collapsing FSGS, which has worse renal survival rates. The cellular variant, which is relatively rare (accounting for only 3-4% of FSGS cases), has a similar clinical presentation to the collapsing and glomerular tip variant, with a rate of remission between that for collapsing and tip variant FSGS (32, 33).

Some studies suggest that the different variants may reflect diseases with different causes and pathogenesis (34, 35). Alternatively, the different variants may just be a reflection of a different stage of FSGS, dependent on the activity and time of disease onset (36). In a nephrectomy specimen from a patient with recurrent FSGS after renal transplant, different FSGS variants were observed depending on the kidney section, suggesting that a single cause can result in different FSGS variants (37).

Table I. *Etiology of secondary FSGS.*

1. Familial or sporadic genetic mutations
   - A. Mutations in α-actinin-4
   - B. Mutations in nephrin
   - C. Mutations in podocin
   - D. Mutations in *WT1*
   - E. Mutations in CD2-associated protein
   - F. Mutations in *TRPC6*
   - G. Mutations in *PLCE1*
   - H. Mitochondrial cytopathies
2. Virus-associated
   - A. HIV-associated nephropathy
   - B. Parvovirus B19
3. Medication
   - A. Heroin nephropathy
   - B. Interferon alfa
   - C. Lithium
   - D. Pamidronate/alendronate
   - E. Ciclosporin
   - F. Anti-VEGF monoclonal antibody*
4. Mediated by adaptive structural–functional responses

   4.1 *Reduced renal mass*
   - A. Oligomeganephronia
   - B. Unilateral renal agenesis
   - C. Renal dysplasia
   - D. Cortical necrosis
   - E. Reflux nephropathy
   - F. Surgical renal ablation
   - G. Chronic allograft nephropathy
   - H. Any advanced renal disease with reduction in functioning nephrons

   4.2 *Initially normal renal mass*
   - A. Diabetes
   - B. Hypertension
   - C. Obesity
   - D. Cyanotic congenital heart disease
   - E. Sickle cell anemia

   4.3 *Nonspecific pattern of FSGS caused by renal scarring in glomerular disease*
   - A. Focal proliferative glomerulonephritis (IgA nephropathy, lupus nephritis, pauci-immune focal necrotizing and crescentic glomerulonephritis)
   - B. Hereditary nephritis (Alport's syndrome)
   - C. Membranous glomerulopathy
   - D. Thrombotic microangiopathy

Adapted from D'Agati et al. (4, 10). *These patients were also using pamidronate.

CLINICAL PRESENTATION AND DIAGNOSIS

Proteinuria is the most common symptom of FSGS. Patients with idiopathic FSGS or FSGS secondary to infection typically present with nephrotic syndrome, a constellation of symptoms characterized by heavy proteinuria (> 3 g/day), peripheral edema, hypoalbuminemia (< 30 g/L) and hyperlipidemia (38). FSGS secondary to hyperfiltration or functional adaptation is usually gradual in onset and not associated with hypoalbuminemia or other manifestations of the nephrotic syndrome, even in the presence of nephrotic-range proteinuria (38, 39). Clinical parameters such as serum albumin are often sufficient to distinguish between idiopathic FSGS and FSGS secondary to maladaptive responses (38). However, in patients with a serum albumin of between 30 and 35 g/L without an apparent

secondary cause, differentiating between idiopathic and secondary FSGS often poses a challenge (40). It has been suggested that these forms could be differentiated by evaluation of podocytic foot process effacement using electron microscopy, with mild effacement occurring in secondary FSGS and complete effacement in idiopathic FSGS (39, 41). A quantitative assessment of foot process effacement was performed by determining the mean foot process width in patients with FSGS. The mean foot process width was significantly greater in idiopathic FSGS than secondary FSGS mediated by adaptive structural–functional responses. The degree of overlap in foot process width between idiopathic and secondary FSGS was low, suggesting that quantitative assessment of foot processes may provide a means for distinguishing between idiopathic and secondary FSGS (36). Unfortunately, measurement of foot process width is quite laborious and cannot be performed routinely.

THE NATURAL HISTORY OF FSGS

Both the level of plasma creatinine and the amount of proteinuria are of prognostic significance. Patients with a serum creatinine concentration of < 115 µmol/L at presentation have a better renal survival rate than those with higher serum creatinine (42, 43). Prognosis is excellent in patients with non-nephrotic proteinuria, whereas patients with a proteinuria of > 3 g/day have a 50% chance of reaching ESRD within 5-10 years (44). Renal survival is even worse if proteinuria exceeds 10 g/day, with the majority of patients reaching ESRD within 5 years after presentation. In contrast, attainment of a remission of proteinuria (either spontaneous or after treatment with corticosteroids) is the single best predictor of a favorable outcome (45). Troyanov demonstrated that even a partial remission (> 50% reduction in peak proteinuria to subnephrotic levels of < 3.5 g/day) of proteinuria can both slow FSGS progression and improve renal survival (46). Most reported remissions were induced by steroid therapy and it is generally suggested that spontaneous remissions occur infrequently in patients with FSGS. However, a high spontaneous remission rate of 60% was demonstrated in patients with idiopathic FSGS who presented with normal renal function and selective proteinuria (selectivity index of < 0.2). These patients were also characterized by serum albumin of > 20 g/L and proteinuria of < 8 g/day at 3 months after renal biopsy (47).

In addition to the quantity, the composition of proteinuria may determine outcome. Bazzi et al. demonstrated that a fractional excretion (FE) of IgG of < 0.14 was associated with a high remission rate after treatment, whereas an FE IgG of 0.14 or greater predicted progression to ESRD (48). However, our own data do not support the conclusion that FE IgG predicts resistance to immunosuppressive medication. In patients with idiopathic FSGS and an FE IgG of > 0.14, the remission rate after immunosuppressive therapy was high (59%) and not different from patients with an FE IgG of < 0.14. Therefore, until more data become available, FE IgG should not be used to guide treatment in patients with FSGS.

TREATMENT OF FSGS

Symptomatic treatment

Blood pressure control and reduction of proteinuria significantly slow the progression of renal insufficiency in patients with proteinuric nondiabetic renal disease (49-53). Therefore, all patients with FSGS should receive symptomatic therapy. Proteinuria should be reduced to < 0.5 g/day, and target blood pressure is 130/80 mmHg or less in patients with proteinuria of 1 g/day or less and 125/75 mmHg or less in patients with proteinuria of > 1 g/day (51, 54). Angiotensin-converting enzyme inhibitors (ACEi) or, if side effects are an issue, angiotensin receptor blockers (ARB), are preferred because they are more effective than other antihypertensive agents in slowing the progression of most nondiabetic kidney diseases (49, 54, 55). Despite the recognized beneficial effect of ACEi in patients with a nephrotic syndrome, little is known about the efficacy of ACEi in patients with idiopathic FSGS. Although ACEi reduce proteinuria in idiopathic FSGS, the few available studies suggest that ACEi rarely induce a complete remission and development of ESRD is not prevented (56, 57). However, there is some evidence that ACEi slow progression to ESRD (58). Furthermore, treatment with ACEi also improves the hypoalbuminemia and hyperlipidemia that is associated with idiopathic FSGS (59). Therefore, treatment with ACEi is recommended for all patients with FSGS.

Abnormal lipid metabolism is usually present in a nephrotic syndrome. Most prominent are hypertriglyceridemia and increased LDL cholesterol and lipoprotein A (LP[a]) (60, 61), which is a highly atherogenic combination (62, 63). 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are very effective in lowering total and LDL cholesterol, and to a lesser degree triglycerides and LP(a) (64, 65). Although a cardioprotective effect of statins has never been proven in patients with nephrotic syndrome, prevention studies in the general population with similar lipid disorders have shown a marked reduction in cardiovascular diseases (66, 67).

Treatment of secondary FSGS

In patients with secondary FSGS, therapy should also be directed at the underlying disorder or removal of the inciting drug. In patients with severe obesity, weight loss (> 10% of body mass index [BMI]) induces a significant decrease in proteinuria, which is almost similar to the effect of ACEi (68). However, maintaining the weight loss is often difficult and many patients relapse (69). Small cohort studies suggest that antiretroviral therapy improves renal survival in patients with HIV-associated FSGS (70, 71). Case reports also provide support for the use of antiretroviral therapy, with recovery of dialysis-dependent renal failure being demonstrated after initiation of antiretroviral therapy (72). FSGS associated with hematological conditions such as multiple myeloma and (non-)Hodgkin's lymphoma often responds with a resolution of the proteinuria after successful treatment of the underlying hematological condition (73, 74). Familial forms of FSGS are steroid-resistant (75-78), with a possible exception being patients with a nonfamilial (sporadic) heterozygous podocin mutation (79).

Immunosuppressive therapy

In most patients with secondary FSGS or non-nephrotic proteinuria (< 3 g/day), immunosuppressive therapy is not effective and may even exacerbate the underlying disease (80). Therefore, immunosuppressive therapy should only be considered in patients with idiopathic FSGS and proteinuria of > 3 g/day. Patients presenting with

normal renal function and selective proteinuria are more likely to attain a spontaneous remission and a wait-and-see approach should be considered in these patients.

Corticosteroids

Corticosteroids induce their pharmacological effects via both classic genomic and nongenomic mechanisms (81). The important anti-inflammatory and immunomodulating effects of corticosteroids are mediated predominantly by genomic mechanisms; the lipophilic corticosteroid passes across the cell membrane and attaches to the cytosolic glucocorticoid receptor, binds to corticosteroid-responsive elements on genomic DNA and interacts with nuclear transcription factors (82). Corticosteroids also exert effects characterized as nongenomic, which occur within minutes of drug administration. The nongenomic glucocorticoid effects differ from the classic, transcription-dependent glucocorticoid action and involve the production of second messenger molecules and activation of signal transduction pathways, either by the nuclear glucocorticoid receptor or by a membrane glucocorticoid receptor (83). The mode of action of corticosteroids in FSGS is still unclear, although it is likely that corticosteroids exert their effect both by an immunosuppressive effect on lymphocytes and a direct antiproteinuric effect on podocytes (84). Both podocytes and glomerular endothelial cells express glucocorticoid receptors through which corticosteroids could exert their effect (55).

Treatment with daily high-dose prednisone is currently the recommended first-line treatment in patients with idiopathic FSGS. This recommendation is almost entirely based on retrospective studies (43, 85-87). These studies show a significantly improved likelihood of remission in patients treated with high-dose prednisone (1 mg/kg/day) (45). The median time until remission is 3-4 months, with the majority of patients entering remission within 6 months (45, 85, 88). Remission rates vary from 40% to 80%, depending on initial renal function, the pathological variant and the extent of interstitial fibrosis on renal biopsy (86, 88-91). Unfortunately, it is not possible to predict at presentation which patients with idiopathic FSGS will respond to treatment with corticosteroids. FSGS is usually considered to be steroid-resistant if no reduction in proteinuria is observed after 12-16 weeks of high-dose prednisone treatment.

Cyclophosphamide

Cyclophosphamide is an alkylating agent that possesses potent antitumor and immunosuppressive activity. It is transformed via hepatic and intracellular enzymes to the active metabolites 4-hydroxycyclophophosphamide, aldophosphamide, acrolein and phosphoramide mustard. Cyclophosphamide-induced immunosuppression is thought to be mediated by a direct cytotoxic effect on immunocompetent lymphocytes, particularly those that have undergone genetic differentiation and division. The rationale for using cyclophosphamide, as with the use of other immunosuppressive agents, is based on the hypothesis that FSGS is a T-cell-driven immunological disease.

Data on the efficacy of cyclophosphamide in patients with FSGS are limited. Retrospective studies suggest that initial therapy with cyclophosphamide and prednisone is no more effective than prednisone monotherapy (3). However, initial treatment with cyclophosphamide may induce a more stable remission (92), and therefore, cyclophosphamide is often used in frequently relapsing or corticosteroid-dependent FSGS. A course of cyclophosphamide can induce a new remission in > 70% of patients (45, 92). In contrast, cyclophosphamide is not very effective in steroid-resistant FSGS (93). The most optimistic retrospective study reported a remission rate of only 24% in patients with steroid-resistant FSGS (94, 95).

Calcineurin inhibitors

The calcineurin inhibitors ciclosporin and tacrolimus are immunosuppressive drugs widely used in organ transplantation and autoimmune diseases. Their immunosuppressive effect depends on the formation of a complex with T-cell cytoplasmic receptor proteins: cyclophilin for ciclosporin and tacrolimus-binding protein (FKBP) for tacrolimus. This complex prevents the activation of calcineurin and the subsequent expression of several cytokine genes that promote T-cell activation and proliferation (96). A further effect of cytokine inhibition by ciclosporin is a reduction in B-cell activation and antibody production (94). The rationale for treating idiopathic FSGS patients with calcineurin inhibitors is based on the assumption that these drugs inhibit the production of the responsible plasma factor by T cells, in the same way that they inhibit IL-2 production. However, there is consistent evidence from both experimental and human studies that ciclosporin also diminishes or abolishes proteinuria in FSGS by nonimmunological mechanisms (97-101). Sharma et al. provided evidence that ciclosporin has a direct protective effect on the glomerular filtration barrier (102). Ciclosporin prevented the increase in glomerular albumin permeability in vitro in isolated rat glomeruli incubated with serum from patients with FSGS (102). This effect was accompanied by a 5-fold increase in glomerular cAMP, without ultrastructural changes of epithelial or endothelial cells (103). In patients with membranous nephropathy, ciclosporin lowered proteinuria by enhancing barrier size selectivity (99), while Faul et al. demonstrated that ciclosporin acts directly on podocytes to stabilize their actin cytoskeleton and reduce proteinuria (104).

Ciclosporin can induce a new remission in 73% of patients with corticosteroid-dependent FSGS (45). However, compared with cyclophosphamide, a new relapse is more common after treatment with ciclosporin (92). Whereas cyclophosphamide is of little benefit in steroid-resistant FSGS, the remission rate improves significantly after treatment with ciclosporin. Two prospective trials comparing 6-12 months of treatment with ciclosporin with placebo have been conducted in adults (105, 106). The remission rate was significantly higher in patients treated with ciclosporin (60-69%) compared to placebo (4-33%). However, within 1 year of discontinuing ciclosporin, between 60% and 80% of the patients had relapsed. Nevertheless, renal function was better preserved at 4 years in patients treated with ciclosporin. The high relapse rate may decrease with prolonged use of ciclosporin, as continuing treatment with ciclosporin for 1 year followed by a slow tapering of the dose resulted in a more durable remission (107).

Continuous use of ciclosporin for more than 12 months is associated with a significant increase in tubulointerstitial fibrosis. In most cases, serum creatinine does not significantly change despite the aggrava-

tion of fibrosis. In addition, ciclosporin may accelerate the progression of FSGS. The number of glomeruli with sclerotic lesions increases significantly during treatment with ciclosporin, even in patients with a partial or complete remission. Ciclosporin nephrotoxicity is associated with higher doses (> 5 mg/kg/day), a higher percentage of glomeruli with FSGS lesions and renal insufficiency prior to treatment (creatinine clearance of < 40-60 mL/min/1.73 m^2) (107).

The experience with tacrolimus in the treatment of patients with FSGS has been limited to uncontrolled trials in adult patients (108-110). Although tacrolimus may be useful in some ciclosporin-resistant patients with FSGS and in those who are intolerant of ciclosporin, more studies are needed before treatment with tacrolimus can be recommended in patients with FSGS.

Sirolimus

The immunosuppressive activity of sirolimus is mediated by a different mechanism than the calcineurin inhibitors (96). Sirolimus binds to the same cytoplasm-binding protein as tacrolimus; however, rather than blocking calcineurin, this complex inhibits the protein designated target of rapamycin (TOR). Inhibition of TOR prevents cytokine-driven T-cell proliferation. In a nonrandomized study in 21 patients with steroid-resistant FSGS, treatment with sirolimus reduced proteinuria in 57% of patients. However, the safety and efficacy of sirolimus in the treatment of FSGS have been questioned by other studies. A study in 11 patients with proteinuric glomerulopathies, including 6 patients with FSGS, documented acute renal failure after treatment with sirolimus (111). In patients who had undergone renal transplant, the use of sirolimus in conjunction with calcineurin inhibitors was also associated with acute renal failure (112). Moreover, sirolimus may induce de novo FSGS in transplant patients (113). The current consensus is that sirolimus is not recommended for the treatment of FSGS due to the associated renal toxicity.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) was introduced as an immunosuppressive agent for organ transplant. MMF blocks de novo synthesis of T- and B-cell lymphocytes through noncompetitive, reversible inhibition of inosine monophosphate dehydrogenase (96). Limited information is available on the use of MMF for the treatment of FSGS. In an open-label 6-month trial, 18 patients with steroid-resistant FSGS were treated with MMF. Of these patients, 75% were also resistant to alkylating agents and/or a calcineurin inhibitor. None of the patients attained a complete remission, although a sustained reduction (up to 1 year post-treatment) in proteinuria of > 50% was observed in 22% (n = 4) of the patients (114). In a retrospective study, 18 steroid-resistant or steroid-dependent patients with FSGS and/or progressive renal dysfunction were treated with MMF with or without ciclosporin. Treatment resulted in a statistically significant decrease in proteinuria, with eight patients (44%) attaining proteinuria remission. Corticosteroids could be withdrawn completely in 8 of 12 patients. In a series of 22 patients with corticosteroid- and ciclosporin-resistant FSGS, 55% of patients treated with MMF attained a remission of proteinuria (2 complete and 10 partial remissions) (115).

More data are needed before these agents can be routinely used in patients with FSGS. Recruitment has been completed for a prospective clinical trial to examine whether treatment with MMF in conjunction with pulse steroids is superior to treatment with ciclosporin in inducing remission in steroid-resistant FSGS (ClinicalTrials.gov Identifier NCT00135811). However, treatment with MMF can be considered in patients with FSGS who are resistant to prednisone and have not responded or should not be exposed to ciclosporin, or who have a partial response to prednisone and/or ciclosporin but have signs of steroid or ciclosporin toxicity.

Rituximab

Rituximab is a chimeric murine/human antibody directed against the CD20 antigen expressed on the cell surface of immature and mature B cells (but not plasma cells) (116). Treatment with rituximab results in B-cell depletion through antibody-dependent cell-mediated cytotoxicity, complement-mediated lysis and apoptosis. The first report of benefit from rituximab involved a 16-year-old boy diagnosed with FSGS when he was 2 years of age, with a clinical course characterized by multiple relapses despite treatment with steroids, ciclosporin, cyclophosphamide and tacrolimus. He became severely dependent on steroids and the diagnosis of idiopathic thrombocytopenic purpura (ITP) was subsequently made. Neither steroids nor immunoglobulins induced permanent remission; however, after treatment with rituximab, no relapse of proteinuria or thrombocytopenia occurred (117). Since then, several case reports have described the effect of rituximab in children with FSGS (118). However, rituximab failed to improve the nephrotic syndrome in 6 of 10 adult patients with FSGS who continued to show massive proteinuria and exhibited rapidly deteriorating renal function in 3 cases. Among the remaining four patients, one attained a complete remission, two showed an improvement of renal function and a remarkable proteinuria reduction, and one experienced a beneficial but transitory effect (118, 119).

Although anti-CD20 antibodies appear to show promise for the treatment of patients with nephrotic syndrome due to idiopathic FSGS, positive results should be viewed with the necessary caution, since they may be overestimated due to publication bias. Controlled studies must be performed to prove the efficacy of rituximab and to determine whether patients will benefit.

EXPERIMENTAL DRUGS IN FSGS

New drugs to treat FSGS are being evaluated in prospective trials (Table II). Pirfenidone is an orally administered antifibrotic agent that has shown benefit in animal models of renal fibrosis and clinical trials of pulmonary fibrosis, multiple sclerosis and hepatic cirrhosis. The effect of pirfenidone is likely to be due to its effect on TGF-β, which represents the final common pathway for a number of fibrotic renal diseases such as FSGS. An open-label trial in patients, primarily with idiopathic FSGS, demonstrated a 25% improvement in the rate of decline in glomerular filtration rate compared with pretreatment (120). This study had some limitations, including a small number of patients, lack of a placebo control group and all of the patients had moderate to severe chronic kidney disease, which does not apply to all patients with FSGS (121). Before pirfenidone can be used, the results of this trial should be confirmed by a larger

Table II. *Ongoing clinical trials for the treatment of FSGS.*

Study description	Purpose of the study	ClinicalTrials.gov identifier
Phase I, multicenter, open-label, dose-escalating study of single doses of GC-1008 in patients with treatment-resistant idiopathic FSGS	This study will investigate whether GC-1008, an antibody that neutralizes TGF-β, is safe	NCT00464321
Phase II, nonrandomized, open-label, uncontrolled trial of rituximab for the treatment of recurrent or primary resistant FSGS	To determine whether rituximab is effective in the treatment of steroid-resistant idiopathic FSGS	NCT00550342
Phase II, randomized, open-label, active-controlled trial of novel therapies for resistant FSGS	This study will investigate whether rosiglitazone and/or adalimumab can safely reduce proteinuria and protect kidney function better than standard treatment in patients with treatment-resistant FSGS	NCT00814255
Randomized, open-label, active-controlled trial of prednisone plus *Tripterygium wilfordii* to treat adult patients with idiopathic FSGS	To assess safety and efficacy	NCT00801463
Phase II, open-label trial of plasma exchange plus cyclophosphamide treatment in FSGS	One of the purposes of this trial is to identify immunosuppressive agents that are successful in inducing sustained reduction in permeability factor. Treatment will consist of standard therapies (daily prednisone, cyclophosphamide) and experimental therapies (pulse dexamethasone, pirfenidone)	NCT00007475
Randomized, open-label, active-controlled trial of tacrolimus to treat patients with idiopathic FSGS	To assess efficacy, safety and tolerability of tacrolimus versus steroid treatment	NCT00302536
Phase III, open-label, uncontrolled trial of rituximab in steroid-dependent or multirelapsing MCD or FSGS (NEMO Study)	To evaluate the efficacy of rituximab in preventing nephrotic syndrome recurrence after complete withdrawal of steroids and other immunosuppressive treatments in patients on sustained remission for at least 1 month	NCT00981838
Phase III, randomized, open-label, active-controlled trial of mycophenolate mofetil in membranous nephropathy and idiopathic FSGS	Comparison of mycophenolate mofetil and corticosteroid with prednisone monotherapy on proteinuria	NCT00404833
Phase III, open-label, randomized trial of pulse dexamethasone for podocyte disease	To determine if intermittent oral dexamethasone administered over 48 weeks can induce complete remission in idiopathic FSGS	NCT00065611

placebo-controlled trial. Another study, to investigate whether GC-1008, an antibody that neutralizes TGF-β, is safe to treat patients with FSGS resistant to immunosuppressive drugs is ongoing (ClinicalTrials.gov Identifier NCT00464321).

CONCLUSIONS

Secondary causes have to be ruled out in patients presenting with FSGS, as treatment for secondary FSGS should be aimed at the underlying disease. All patients with FSGS should receive symptomatic therapy, while immunosuppressive therapy is limited to patients with idiopathic FSGS. Since spontaneous remissions occur frequently in patients with idiopathic FSGS presenting with normal renal function and selective proteinuria, a wait-and-see approach should be considered in such patients. Otherwise, patients with idiopathic FSGS and nephrotic syndrome should initially be treated with high-dose prednisone for 4-6 months. In the elderly (> 65 years) an alternate-day regimen (2 mg/kg/day) is also effective, with fewer complications. In patients with steroid-dependent or frequently relapsing FSGS, cyclophosphamide for 2-3 months in combination with prednisone results in more stable remissions. In steroid-resistant FSGS, the most effective treatment consists of ciclosporin for 6 months. Treatment with ciclosporin should be limited to patients with relatively well-preserved renal function, to prevent nephrotoxicity. Upon remission, ciclosporin treatment should be continued for 1 year and then slowly tapered off to prevent relapse. In the absence of a remission, ciclosporin should be stopped after 6 months. MMF and rituximab may be considered in patients not responding to one of the above treatments, but sirolimus is not indicated in FSGS.

DISCLOSURE

The author states no conflicts of interest.

REFERENCES

1. Rich, A. *A hitherto undescribed vulnerability of the juxtamedullary glomeruli in lipoid nephrosis.* Bull Johns Hopkins Hosp 1957, 100(4): 173-86.
2. Habib, R. *Editorial: Focal glomerular sclerosis.* Kidney Int 1973, 4(6): 355-61.
3. Korbet, S. *Primary focal segmental glomerulosclerosis.* J Am Soc Nephrol 1998, 9(7): 1333-40.
4. D'Agati, V.D., Fogo, A.B., Bruijn, J.A. et al. *Pathologic classification of focal segmental glomerulosclerosis: A working proposal.* Am J Kidney Dis 2004, 43(2): 368-82.

5. Swaminathan, S., Leung, N., Lager, D.J. et al. *Changing incidence of glomerular disease in Olmsted County, Minnesota: A 30-year renal biopsy study.* Clin J Am Soc Nephrol 2006, 1(3): 483-7.
6. Braden, G.L., Mulhern, J.G., O'Shea, M.H. et al. *Changing incidence of glomerular diseases in adults.* Am J Kidney Dis 2000, 35(5): 878-83.
7. Briganti, E.M., Dowling, J., Finlay, M. et al. *The incidence of biopsy-proven glomerulonephritis in Australia.* Nephrol Dial Transplant 2001, 16(7): 1364-7.
8. Haas, M., Meehan, S., Karrison, T. et al. *Changing etiologies of unexplained adult nephrotic syndrome: A comparison of renal biopsy findings from 1976-1979 and 1995-1997.* Am J Kidney Dis 1997, 30(5): 621-31.
9. Kitiyakara, C., Eggers, P., Kopp, J.B. *Twenty-one-year trend in ESRD due to focal segmental glomerulosclerosis in the United States.* Am J Kidney Dis 2004, 44(5): 815-25.
10. D'Agati, V.D. *The spectrum of focal segmental glomerulosclerosis: New insights.* Curr Opin Nephrol Hypertens 2008, 17(3): 271-81.
11. Kriz, W., Gretz, N., Lemley, K.V. *Progression of glomerular diseases: Is the podocyte the culprit?* Kidney Int 1998, 54(3): 687-97.
12. D'Agati, V.D. *Podocyte injury in focal segmental glomerulosclerosis: Lessons from animal models (a play in five acts).* Kidney Int 2008, 73(4): 399-406.
13. Pavenstadt, H., Kriz, W., Kretzler, M. *Cell biology of the glomerular podocyte.* Physiol Rev 2003, 83(1): 253-307.
14. Asanuma, K., Mundel, P. *The role of podocytes in glomerular pathobiology.* Clin Exp Nephrol 2003, 7(4): 255-9.
15. Savin, V.J., Sharma, R., Sharma, M. et al. *Circulating factor associated with increased glomerular permeability to albumin in recurrent focal segmental glomerulosclerosis.* N Engl J Med 1996, 334(14): 878-83.
16. Dantal, J., Bigot, E., Bogers, W. et al. *Effect of plasma protein adsorption on protein excretion in kidney-transplant recipients with recurrent nephrotic syndrome.* N Engl J Med 1994, 330(1): 7-14.
17. Shalhoub, R.J. *Pathogenesis of lipoid nephrosis: A disorder of T-cell function.* Lancet 1974, 2(7880): 556-60.
18. Deegens, J.K., Andresdottir, M.B., Croockewit, S. et al. *Plasma exchange improves graft survival in patients with recurrent focal glomerulosclerosis after renal transplant.* Transpl Int 2004, 17(3): 151-7.
19. Zimmerman, S.W. *Plasmapheresis and dipyridamole for recurrent focal glomerular sclerosis.* Nephron 1985, 40(2): 241-5.
20. Sharma, M., Sharma, R., McCarthy, E.T. et al. *"The FSGS factor": Enrichment and in vivo effect of activity from focal segmental glomerulosclerosis plasma.* J Am Soc Nephrol 1999, 10(3): 552-61.
21. Kemper, M.J., Wolf, G., Muller-Wiefel, D.E. *Transmission of glomerular permeability factor from a mother to her child.* N Engl J Med 2001, 344(5): 386-7.
22. Savin, V.J., Sharma, M., McCarthy, E.T. et al. *Cardiotrophin like cytokine-1: Candidate for the focal segmental sclerosis permeability factor.* J Am Soc Nephrol 2008, 19: 59A.
23. Kriz, W., Hosser, H., Hahnel, B. et al. *Development of vascular pole-associated glomerulosclerosis in the Fawn-hooded rat.* J Am Soc Nephrol 1998, 9(3): 381-96.
24. Markowitz, G.S., Appel, G.B., Fine, P.L. et al. *Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate.* J Am Soc Nephrol 2001, 12(6): 1164-72.
25. Pascual, J., Torrealba, J., Myers, J. et al. *Collapsing focal segmental glomerulosclerosis in a liver transplant recipient on alendronate.* Osteoporos Int 2007, 18(10): 1435-8.
26. Miller, K.D., Chap, L.I., Holmes, F.A. et al. *Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.* J Clin Oncol 2005, 23(4): 792-9.
27. Stokes, M.B., Erazo, M.C., D'Agati, V.D. *Glomerular disease related to anti-VEGF therapy.* Kidney Int 2008, 74(11): 1487-91.
28. D'Agati, V., Suh, J.I., Carbone, L. et al. *Pathology of HIV-associated nephropathy: A detailed morphologic and comparative study.* Kidney Int 1989, 35(6): 1358-70.
29. Daskalajis, N., Winn, M.P. *Focal and segmental glomerulosclerosis.* Cell Mol Life Sci 2006, 63(21): 2506-11.
30. Fahr, T. *Pathologische anatomie des morbus brightii*. In: Handbuch der Speziellen Pathologischen Anatomie und Histologie, Vol. 6. Henke, F., Lubarsch, O. (Eds.). Berlin, 1925.
31. Deegens, J.K., Steenbergen, E.J., Borm, G.F. et al. *Pathological variants of focal segmental glomerulosclerosis in an adult Dutch population—Epidemiology and outcome.* Nephrol Dial Transplant 2008, 23(1): 186-92.
32. Thomas, D.B., Franceschini, N., Hogan, S.L. et al. *Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants.* Kidney Int 2006, 69(5): 920-6.
33. Stokes, M.B., Valeri, A.M., Markowitz, G.S. et al. *Cellular focal segmental glomerulosclerosis: Clinical and pathologic features.* Kidney Int 2006, 70(10): 1783-92.
34. Swaminathan, S., Lager, D.J., Qian, X. et al. *Collapsing and non-collapsing focal segmental glomerulosclerosis in kidney transplants.* Nephrol Dial Transplant 2006, 21(9): 2607-14.
35. Ijpelaar, D.H., Farris, A.B., Goemaere, N. et al. *Fidelity and evolution of recurrent FSGS in renal allografts.* J Am Soc Nephrol 2008, 19(11): 2219-24.
36. Deegens, J.K., Dijkman, H.B., Borm, G.F. et al. *Podocyte foot process effacement as a diagnostic tool in focal segmental glomerulosclerosis.* Kidney Int 2008, 74(12): 1568-76.
37. Dijkman, H., Smeets, B., van der Laak, J. et al. *The parietal epithelial cell is crucially involved in human idiopathic focal segmental glomerulosclerosis.* Kidney Int 2005, 68(4): 1562-72.
38. Praga, M., Morales, E., Herrero, J. et al. *Absence of hypoalbuminemia despite massive proteinuria in focal segmental glomerulosclerosis secondary to hyperfiltration.* Am J Kidney Dis 1999, 33(1): 52-8.
39. Kambham, N., Markowitz, G., Valeri, A. et al. *Obesity-related glomerulopathy: An emerging epidemic.* Kidney Int 2001, 59(4): 1498-509.
40. Schmidt, A., Mayer, G. *The diagnostic trash bin of focal and segmental glomerulosclerosis—An effort to provide rational clinical guidelines.* Nephrol Dial Transplant 1999, 14(3): 550-2.
41. Barisoni L., Szabolcs, M., Ward, L., D'Agati, V. *Visceral epithelial cell alterations in focal segmental glomerulosclerosis.* Mod Pathol 1994, 7: 157A.
42. Korbet, S., Schwartz, M., Lewis, E.J. *The prognosis of focal segmental glomerular sclerosis of adulthood.* Medicine 1986, 65(5): 304-11.
43. Rydell, J.J., Korbet, S.M., Borok, R.Z., Schwartz, M.M. *Focal segmental glomerular sclerosis in adults: Presentation, course, and response to treatment.* Am J Kidney Dis 1995, 25(4): 534-42.
44. Korbet, S.M. *Clinical picture and outcome of primary focal segmental glomerulosclerosis.* Nephrol Dial Transplant 1999, 14(Suppl. 3): 68-73.
45. Korbet, S.M. *Primary focal segmental glomerulosclerosis*. In: Therapy in Nephrology and Hypertension: A Companion to Brenner and Rector's The Kidney, 2nd Ed. Brady, H.R., Wilcox, C.S. (Eds.). W.B. Saunders: Philadelphia, 2003, 223-36.
46. Troyanov, S., Wall, C.A., Miller, J.A. et al. *Idiopathic membranous nephropathy: Definition and relevance of a partial remission.* Kidney Int 2004, 66(3): 1199-205.

47. Deegens, J.K., Assmann, K.J., Steenbergen, E.J. et al. *Idiopathic focal segmental glomerulosclerosis: A favourable prognosis in untreated patients?* Neth J Med 2005, 63(10): 393-8.
48. Bazzi, C., Petrini, C., Rizza, V. et al. *Fractional excretion of IgG predicts renal outcome and response to therapy in primary focal segmental glomerulosclerosis: A pilot study.* Am J Kidney Dis 2003, 41(2): 328-35.
49. *Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia).* Lancet 1997, 349(9069): 1857-63.
50. Ruggenenti, P., Perna, A., Gherardi, G. et al. *Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy in Nephropathy.* Lancet 1998, 352(9136): 1252-6.
51. Peterson, J.C., Adler, S., Burkart, J.M. et al. *Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study.* Ann Intern Med 1995, 123(10): 754-62.
52. *K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease.* Am J Kidney Dis 2004, 43(5, Suppl. 1): 1-290.
53. Jafar, T., Stark, P., Schmid, C. et al. *Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient-level meta-analysis.* Ann Intern Med 2003, 139(4): 244-52.
54. *K/DOQI clinical practice guidelines in hypertension and antihypertensive agents in chronic kidney disease.* Am J Kidney Dis 2004, 43(Suppl. 1): 183-205.
55. Maschio, G., Alberti, D., Janin, G. et al. *Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group.* N Engl J Med 1996, 334(15): 939-45.
56. Praga, M., Hernandez, E., Montoyo, C. et al. *Long-term beneficial effects of angiotensin-converting enzyme inhibition in patients with nephrotic proteinuria.* Am J Kidney Dis 1992, 20(3): 240-8.
57. Stiles, K.P., Abbott, K.C., Welch, P.G. et al. *Effects of angiotensin-converting enzyme inhibitor and steroid therapy on proteinuria in FSGS: A retrospective study in a single clinic.* Clin Nephrol 2001, 56(2): 89-95.
58. Crenshaw, G., Bigler, S., Salem, M. et al. *Focal segmental glomerulosclerosis in African Americans: Effects of steroids and angiotensin converting enzyme inhibitors.* Am J Med Sci 2000, 319(5): 320-5.
59. Keilani, T., Schlueter, W.A., Levin, M.L. et al. *Improvement of lipid abnormalities associated with proteinuria using fosinopril, an angiotensin-converting enzyme inhibitor.* Ann Intern Med 1993, 118(4): 246-54.
60. Wanner, C., Rader, D., Bartens, W. et al. *Elevated plasma lipoprotein(a) in patients with the nephrotic syndrome.* Ann Intern Med 1993, 119(4): 263-9.
61. de Sain-van der Velden, M.G., Kaysen, G.A., Barrett, H.A. et al. *Increased VLDL in nephrotic patients results from a decreased catabolism while increased LDL results from increased synthesis.* Kidney Int 1998, 53(4): 994-1001.
62. Ordonez, J.D., Hiatt, R.A., Killebrew, E.J. et al. *The increased risk of coronary heart disease associated with nephrotic syndrome.* Kidney Int 1993, 44(3): 638-42.
63. Curry, R.C. Jr., Roberts, W.C. *Status of the coronary arteries in the nephrotic syndrome. Analysis of 20 necropsy patients aged 15 to 35 years to determine if coronary atherosclerosis is accelerated.* Am J Med 1977, 63(2): 183-92.
64. Kasiske, B.L., O'Donnell, M.P., Schmitz, P.G. et al. *Renal injury of diet-induced hypercholesterolemia in rats.* Kidney Int 1990, 37(3): 880-91.
65. Rabelink, A.J., Hene, R.J., Erkelens, D.W. et al. *Effects of simvastatin and cholestyramine on lipoprotein profile in hyperlipidaemia of nephrotic syndrome.* Lancet 1988, 2(8624): 1335-8.
66. Shepherd, J., Cobbe, S.M., Ford, I. et al. *Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group.* N Engl J Med 1995, 333(20): 1301-7.
67. Downs, J.R., Clearfield, M., Weis, S. et al. *Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study.* JAMA 1998, 279(20): 1615-22.
68. Praga, M., Hernández, E., Andrés, G. et al. *Effects of body-weight loss and captopril treatment on proteinuria associated with obesity.* Nephron 1995, 70(1): 35-41.
69. Praga, M., Hernández, E., Morales, E. et al. *Clinical features and long-term outcome of obesity-associated focal segmental glomerulosclerosis.* Nephrol Dial Transplant 2001, 16(9): 1790-8.
70. Szczech, L., Edwards, L., Sanders, L. et al. *Protease inhibitors are associated with a slowed progression of HIV-related renal diseases.* Clin Nephrol 2002, 57(5): 336-41.
71. Atta, M.G., Gallant, J.E., Rahman, M.H. et al. *Antiretroviral therapy in the treatment of HIV-associated nephropathy.* Nephrol Dial Transplant 2006, 21(10): 2809-13.
72. Wali, R.K., Drachenberg, C.I., Papadimitriou, J.C. et al. *HIV-1-associated nephropathy and response to highly-active antiretroviral therapy.* Lancet 1998, 352(9130): 783-4.
73. Dingli, D., Larson, D.R., Plevak, M.F. et al. *Focal and segmental glomerulosclerosis and plasma cell proliferative disorders.* Am J Kidney Dis 2005, 46(2): 278-82.
74. Mallouk, A., Pham, P.T., Pham, P.C. *Concurrent FSGS and Hodgkin's lymphoma: Case report and literature review on the link between nephrotic glomerulopathies and hematological malignancies.* Clin Exp Nephrol 2006, 10(4): 284-9.
75. Ruf, R.G., Lichtenberger, A., Karle, S.M. et al. *Patients with mutations in NPHS2 (podocin) do not respond to standard steroid treatment of nephrotic syndrome.* J Am Soc Nephrol 2004, 15(3): 722-32.
76. Frishberg, Y., Rinat, C., Megged, O. et al. *Mutations in NPHS2 encoding podocin are a prevalent cause of steroid-resistant nephrotic syndrome among Israeli-Arab children.* J Am Soc Nephrol 2002, 13(2): 400-5.
77. Fuchshuber, A., Gribouval, O., Ronner, V. et al. *Clinical and genetic evaluation of familial steroid-responsive nephrotic syndrome in childhood.* J Am Soc Nephrol 2001, 12(2): 374-8.
78. Boute, N., Gribouval, O., Benessy, F. et al. *NPHS2, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome.* Nat Genet 2000, 24(4): 349-54.
79. Caridi, G., Bertelli, R., Di Duca, M. et al. *Broadening the spectrum of diseases related to podocin mutations.* J Am Soc Nephrol 2003, 14(5): 1278-86.
80. Korbet, S.M. *Angiotensin antagonists and steroids in the treatment of focal segmental glomerulosclerosis.* Semin Nephrol 2003, 23(2): 219-28.
81. Buttgereit, F., Straub, R.H., Wehling, M. et al. *Glucocorticoids in the treatment of rheumatic diseases: An update on the mechanisms of action.* Arthritis Rheum 2004, 50(11): 3408-17.
82. Lipworth, B.J. *Therapeutic implications of non-genomic glucocorticoid activity.* Lancet 2000, 356(9224): 87-9.
83. Stellato, C. *Post-transcriptional and nongenomic effects of glucocorticoids.* Proc Am Thorac Soc 2004, 1(3): 255-63.
84. Meyrier, A. *An update on the treatment options for focal segmental glomerulosclerosis.* Expert Opin Pharmacother 2009, 10(4): 615-28.

85. Ponticelli, C., Villa, M., Banfi, G. et al. *Can prolonged treatment improve the prognosis in adults with focal segmental glomerulosclerosis?* Am J Kidney Dis 1999, 34(4): 618-25.
86. Cattran, D., Rao, P. *Long term outcome in children and adults with classic focal segmental glomerulosclerosis.* Am J Kidney Dis 1998, 32(1): 72-9.
87. Banfi, G., Moriggi, M., Sabadini, E. et al. *The impact of prolonged immunosuppression on the outcome of idiopathic focal-segmental glomerulosclerosis with nephrotic syndrome in adults. A collaborative retrospective study.* Clin Nephrol 1991, 36(2): 53-9.
88. Pokhariyal, S., Gulati, S., Prasad, N. et al. *Duration of optimal therapy for idiopathic focal segmental glomerulosclerosis.* J Nephrol 2003, 16(5): 691-6.
89. Chun, M.J., Korbet, S.M., Schwartz, M.M. et al. *Focal segmental glomerulosclerosis in nephrotic adults: Presentation, prognosis, and response to therapy of the histologic variants.* J Am Soc Nephrol 2004, 15(8): 2169-77.
90. Troyanov, S., Wall, C.A., Miller, J.A. et al. *Focal and segmental glomerulosclerosis: Definition and relevance of a partial remission.* J Am Soc Nephrol 2005, 16(4): 1061-8.
91. Stirling, C.M., Mathieson, P., Boulton-Jones, J.M. et al. *Treatment and outcome of adult patients with primary focal segmental glomerulosclerosis in five UK renal units.* QJM 2005, 98(6): 443-9.
92. Ponticelli, C., Edefonti, A., Ghio, L. et al. *Cyclosporin versus cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: A multicentre randomized controlled trial.* Nephrol Dial Transplant 1993, 8(12): 1326-32.
93. Korbet, S.M. *Treatment of primary focal segmental glomerulosclerosis.* Kidney Int 2002, 62(6): 2301-10.
94. Cattran, D.C., Alexopoulos, E., Heering, P. et al. *Cyclosporin in idiopathic glomerular disease associated with the nephrotic syndrome: workshop recommendations.* Kidney Int 2007, 72(12): 1429-47.
95. Matalon, A., Valeri, A., Appel, G.B. *Treatment of focal segmental glomerulosclerosis.* Semin Nephrol 2000, 20(3): 309-17.
96. Halloran, P.F. *Immunosuppressive drugs for kidney transplantation.* N Engl J Med 2004, 351(26): 2715-29.
97. Zietse, R., Wenting, G.J., Kramer, P. et al. *Effects of cyclosporin A on glomerular barrier function in the nephrotic syndrome.* Clin Sci 1992, 82(6): 641-50.
98. Schrijver, G., Assmann, K.J., Wetzels, J.F. et al. *Cyclosporin A reduces albuminuria in experimental anti-GBM nephritis independently from changes in GFR.* Nephrol Dial Transplant 1995, 10(7): 1149-54.
99. Ambalavanan, S., Fauvel, J.P., Sibley, R.K. et al. *Mechanism of the antiproteinuric effect of cyclosporine in membranous nephropathy.* J Am Soc Nephrol 1996, 7(2): 290-8.
100. Chen, D., Jefferson, B., Harvey, S.J. et al. *Cyclosporine a slows the progressive renal disease of alport syndrome (X-linked hereditary nephritis): Results from a canine model.* J Am Soc Nephrol 2003, 14(3): 690-8.
101. Charbit, M., Gubler, M.C., Dechaux, M. et al. *Cyclosporin therapy in patients with Alport syndrome.* Pediatr Nephrol 2007, 22(1): 57-63.
102. Sharma, R., Savin, V.J. *Cyclosporine prevents the increase in glomerular albumin permeability caused by serum from patients with focal segmental glomerular sclerosis.* Transplantation 1996, 61(3): 381-3.
103. Sharma, R., Sharma, M., Ge, X. et al. *Cyclosporine protects glomeruli from FSGS factor via an increase in glomerular cAMP.* Transplantation 1996, 62(12): 1916-20.
104. Faul, C., Donnelly, M., Merscher-Gomez, S. et al. *The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A.* Nat Med 2008, 14(9): 931-8.
105. Cattran, D.C., Appel, G.B., Hebert, L.A. et al. *A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. North America Nephrotic Syndrome Study Group.* Kidney Int 1999, 56(6): 2220-6.
106. Ponticelli, C., Rizzoni, G., Edefonti, A. et al. *A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome.* Kidney Int 1993, 43(6): 1377-84.
107. Meyrier, A., Noel, L., Auriche, P. et al. *Long-term renal tolerance of cyclosporin A treatment in adult idiopathic nephrotic syndrome. Collaborative Group of the Societe de Nephrologie.* Kidney Int 1994, 45(5): 1446-56.
108. Segarra, A., Vila, J., Pou, L. et al. *Combined therapy of tacrolimus and corticosteroids in cyclosporin-resistant or -dependent idiopathic focal glomerulosclerosis: A preliminary uncontrolled study with prospective follow-up.* Nephrol Dial Transplant 2002, 17(4): 655-62.
109. McCauley, J., Shapiro, R., Ellis, D. et al. *Pilot trial of FK 506 in the management of steroid-resistant nephrotic syndrome.* Nephrol Dial Transplant 1993, 8(11): 1286-90.
110. Duncan, N., Dhaygude, A., Owen, J. et al. *Treatment of focal and segmental glomerulosclerosis in adults with tacrolimus monotherapy.* Nephrol Dial Transplant 2004, 19(12): 3062-7.
111. Fervenza, F.C., Fitzpatrick, P.M., Mertz, J. et al. *Acute rapamycin nephrotoxicity in native kidneys of patients with chronic glomerulopathies.* Nephrol Dial Transplant 2004, 19(5): 1288-92.
112. Lawsin, L., Light, J.A. *Severe acute renal failure after exposure to sirolimus-tacrolimus in two living donor kidney recipients.* Transplantation 2003, 75(1): 157-60.
113. Letavernier, E., Bruneval, P., Mandet, C. et al. *High sirolimus levels may induce focal segmental glomerulosclerosis de novo.* Clin J Am Soc Nephrol 2007, 2(2): 326-33.
114. Cattran, D.C., Wang, M.M., Appel, G. et al. *Mycophenolate mofetil in the treatment of focal segmental glomerulosclerosis.* Clin Nephrol 2004, 62(6): 405-11.
115. Choi, M.J., Eustace, J.A., Gimenez, L.F. et al. *Mycophenolate mofetil treatment for primary glomerular diseases.* Kidney Int 2002, 61(3): 1098-114.
116. Pescovitz, M.D., Book, B.K., Sidner, R.A. *Resolution of recurrent focal segmental glomerulosclerosis proteinuria after rituximab treatment.* N Engl J Med 2006, 354(18): 1961-3.
117. Benz, K., Dotsch, J., Rascher, W. et al. *Change of the course of steroid-dependent nephrotic syndrome after rituximab therapy.* Pediatr Nephrol 2004, 19(7): 794-7.
118. Peters, H.P., van de Kar, N.C., Wetzels, J.F. *Rituximab in minimal change nephropathy and focal segmental glomerulosclerosis: Report of four cases and review of the literature.* Neth J Med 2008, 66(10): 408-15.
119. Fernandez-Fresnedo, G., Segarra, A., Gonzalez, E. et al. *Rituximab treatment of adult patients with steroid-resistant focal segmental glomerulosclerosis.* Clin J Am Soc Nephrol 2009, 4(8): 1317-23.
120. Cho, M.E., Smith, D.C., Branton, M.H. et al. *Pirfenidone slows renal function decline in patients with focal segmental glomerulosclerosis.* Clin J Am Soc Nephrol 2007, 2(5): 906-13.
121. Shihab, F.S. *Do we have a pill for renal fibrosis?* Clin J Am Soc Nephrol 2007, 2(5): 876-8.