

Optimal management of primary focal segmental glomerulosclerosis in adults

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Abstract: Focal segmental glomerulosclerosis (FSGS) is a frequent glomerular kidney disease that is revealed by proteinuria or even nephrotic syndrome. A diagnosis can be established from a kidney biopsy that shows focal and segmental glomerulosclerosis. This histopathological lesion may be caused by a primary podocyte injury (idiopathic FSGS) but is also associated with other pathologies (secondary FSGS). The first-line treatment for idiopathic FSGS with nephrotic syndrome is a prolonged course of corticosteroids. However, steroid resistance or steroid dependence is frequent, and despite intensified immunosuppressive treatment, FSGS can lead to end-stage renal failure. In addition, in some cases, FSGS can recur on a graft after kidney transplantation: an unidentified circulating factor may be implicated. Understanding of its physiopathology is unclear, and it remains an important challenge for the scientific community to identify a specific diagnostic biomarker and to develop specific therapeutics. This study reviews the treatment of primary FSGS and the recurrence of FSGS after kidney transplantation in adults.

Keywords: glomerulosclerosis, kidney transplantation, circulating factor, treatment

Introduction

Epidemiology and clinical presentation

Focal segmental glomerulosclerosis (FSGS) is a frequent glomerular kidney disease. It can occur in up to 35% of biopsies from adults with idiopathic nephrotic syndrome and in 19% of native kidney biopsies.^{1,2} Biopsies may reveal FSGS in >50% of Black patients with idiopathic nephrotic syndrome,¹ and in the United States, a number of studies have demonstrated its increasing incidence over time.²⁻⁵ The main clinical presentations of FSGS are nephrotic-range proteinuria (78%), hypertension (3%–63%), microscopic hematuria (29%–94%), renal failure (48%–59%), and an increase in serum creatinine (>1.3 mg/dL).⁶

Definition and pathologic classification

“Glomerulosclerosis” describes a lesion that leads to obliteration of the capillary lumina by the matrix component. Sclerosis can be focal (involving some, but not all glomeruli) or segmental (affecting only a portion of glomerular tuft). Segmental granular deposition of immunoglobulin M and C3 may be present on immunofluorescence microscopy, and wrinkling, retraction, and foot process effacement are visible in electron microscopy.

Glomerulosclerosis has a wide spectrum of morphological appearances. A classification proposed by D’Agati et al⁷ includes five types of lesions: FSGS not otherwise

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specified (NOS), collapsing variant, tip variant, cellular variant, and perihilar variant. Patients with collapsing variant FSGS have the worst outcomes with less frequent remission of proteinuria and quicker evolution to end-stage renal failure, whereas those with tip variant FSGS do much better and more frequently respond to various immunosuppressive treatments. Lesions can change with the subtype and usually evolve into an NOS phenotype as the kidney approaches end-stage renal disease.

Causes of focal and segmental glomerulosclerosis

FSGS is associated with podocyte injuries that can be caused by several triggers. The response is effacement of the foot processes, which are actin-based structures, and the destruction of the slit diaphragm, which is a set of transmembrane proteins that spread from adjacent interdigitating foot processes to form a zipper-like scaffold. The slit diaphragm is composed of cell adhesion molecules that are connected to the actin cytoskeleton and its associated proteins (including synaptopodin, vinculin, and dynamin). These changes in podocyte phenotype are closely correlated with a loss of function in glomerular permeability and the characteristic clinical hallmark of proteinuria that occurs in FSGS; for example, the large GTPase dynamin, which plays a key role in the maintenance of kidney barrier filtration, is implicated in regulating the actin cytoskeleton via direct dynamin-actin interactions^{8,9} and regulates focal adhesion maturation in podocytes via a parallel signaling pathway to RhoA.¹⁰ Moreover, Notch signaling, which is implicated in the development of glomerular disease,¹¹ promotes dynamin-dependent, raft-independent endocytosis of nephrin.¹²

FSGS may be genetic or familial with genetic mutations of proteins involved in the formation of the slit diaphragm and/or the organization of the actin cytoskeleton (e.g., nephrin, podocin, and CD2AP). FSGS has also been reported to be promoted by viruses (e.g., human immunodeficiency virus [HIV], parvovirus B19, and cytomegalovirus), by drugs (e.g., intravenous [IV] heroin and interferon), or by glomerular capillary pressure elevation, as observed in people with obesity or cyanotic congenital heart disease (Table 1). Finally, FSGS may be primary or idiopathic. In this case, FSGS can be recurrent after kidney transplantation. The origin of primary FSGS is unknown, and a circulating permeability factor involved in primary FSGS has been suggested, but not identified. Several molecules have been reported, and the most recent is the soluble urokinase plasminogen activator receptor (suPAR). The cleavage of

Table 1 Different causes of FSGS

Viral diseases:	HIV, parvovirus B19, hepatitis C
Drugs:	Anabolic steroids, intravenous bisphosphonate, lithium, interferon α , and heroin
Genetic mutation:	α -Actinin 4, TRPC6, NPHS1, NPHS2, WT1, SCARB2, INF2, CD2AP, and APOL1
Adaptive/structural changes in the glomerulus:	Reflux nephropathy, low nephron mass, unilateral kidney agenesis, surgical kidney ablation, kidney dysplasia, chronic allograft nephropathy, chronic damage with other glomerular diseases, diabetes, obesity, and sickle-cell disease

Abbreviations: FSGS, focal segmental glomerulosclerosis; HIV, human immunodeficiency virus; WT1, Wilms tumor protein.

the urokinase plasminogen activator surface (uPAR) into fragments yields various circulating suPAR fragments. In mice that lack uPAR, treatment with or overexpression of suPAR has been linked to increased $\alpha v \beta 3$ integrin signaling in podocytes, with resulting foot process effacement and proteinuria. These effects were prevented by the treatment with the uPAR-specific antibody.¹³ suPAR plasma level increases in some inflammatory conditions and in 70% of the patients with primary FSGS,¹³ but suPAR is also increased in secondary FSGS,¹⁴ in all kidney transplant patients independently of nephropathy.¹⁵ Moreover, the level of suPAR is correlated with glomerular filtration and not with the primary kidney disease.¹⁶ Other possible biomarkers of FSGS, such as vasodilator-stimulated phosphoprotein,¹⁷ protein tyrosine phosphatase receptor-O-antibodies,¹⁸ and cardiotrophin-like cytokine-1, have been reported.¹⁹

Moreover, apolipoprotein A-1-1b (Apo-1b), a high-molecular-weight form of apolipoprotein A-1, was found in 93% of those with recurrent FSGS compared with <5% of those without recurrence who had received a transplant for familial FSGS or proteinuria unrelated to FSGS. Moreover, urinary Apo-1b had a sensitivity of 92.8% and a specificity of 98.1% for identifying an FSGS relapse.²⁰

MicroRNA also seems to be implicated in FSGS. Overexpression of miRNA-193A in transgenic mice led to foot process effacement, FSGS, and dedifferentiation of podocytes with a loss of expression of Wilms tumor protein (WT1), podocalyxin, and nephrin.²¹ In cultured podocytes, the overexpression of miRNA-193A caused injury and was rescued by WT1 overexpression. The levels of miRNA-193A were increased in patients with idiopathic FSGS and in some patients with HIV-associated FSGS, but not in those with genetic causes of FSGS.²¹ Patients with FSGS had higher expression of miRNA-193A compared with the expression

found in patients with minimal change disease. Additional miRNAs, for example, miR-30, have been implicated in podocyte injury.²²

Finally, some antibodies are associated with recurrent FSGS after kidney transplantation. The two most recently discovered are anti-CD40 and the anti-angiotensin II type-1 receptor. Pretransplant elevation of anti-CD40 is associated with recurrent FSGS risk after transplantation. Moreover, the injection of anti-CD40/rFSGS antibodies enhanced suPAR-mediated proteinuria in wild-type mice.²³ The anti-angiotensin II type-1 receptor has been reported to be associated with de novo FSGS after kidney transplantation. Treatment with plasmapheresis, IV immunoglobulin, and angiotensin receptor blockers (losartan) resulted in undetectable AT1 receptor antibodies and the resolution of the proteinuria and histologic glomerular injuries.²⁴

The variety of disease processes associated with FSGS reflect the nonspecific nature of this lesion, and, despite research that has provided some insights into its pathophysiology, the mechanisms by which many of these processes lead to podocyte damage and an FSGS lesion remain unknown. Consequently, idiopathic FSGS, which is poorly understood, is difficult to treat and may lead (in some cases) to end-stage renal disease. The present study reviews the treatments for idiopathic FSGS in adults and recurrent FSGS after kidney transplantation, with a particular focus on immunosuppressive therapy.

Treatment of idiopathic FSGS

Conservative management

Regardless of the clinical form of FSGS, conservative treatment is recommended even though no randomized trials have been conducted. The largest retrospective study conducted so far has demonstrated significantly lower kidney survival in nephrotic patients than in non-nephrotic patients.²⁵ The recommendation to control blood pressure and proteinuria by using angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers in patients with FSGS has been extrapolated from studies that have shown improvement in proteinuria and long-term kidney function in other proteinuria-related kidney diseases.²⁶

In FSGS, blood pressure should be <130/80 mmHg with the objective of achieving 125/75 mmHg for patients with proteinuria >1 g/day. Monitoring the adverse effects from inhibiting the renin-angiotensin system, notably hyperkalemia and reduced glomerular filtration rate, is necessary during the treatment.²⁶ Modification in lifestyle (e.g., salt restriction, weight normalization, regular exercise, and smok-

ing cessation) should be an integral part of the therapy for blood pressure control. Adequate dietary protein should be ensured (0.8–1 g/kg daily). The treatment of hyperlipidemia should follow the usual guidelines. Dietary restriction of fats and cholesterol alone has only modest effects. Statins are well tolerated and effective in correcting the lipid profile, although not proven to reduce cardiovascular events in nephrotic syndrome. Care is needed with calcineurin inhibitors as they increase the risk of myalgia.²⁷

Treatment of initial nephrotic syndrome in patients with FSGS

Oral corticosteroids are the main treatment for FSGS (Figure 1). This strategy is the first-line therapy for patients with proteinuria within nephrotic range; however, evidence for this approach is based on nonrandomized and often retrospective studies conducted with different designs, different populations, different corticosteroid dosages, and different follow-up periods and frequently includes the use of additional immunosuppressive treatments.^{28–33} Altogether, the cumulative remission rate with steroid therapy ranges between 40% and 60%.

The largest study that used steroids as a monotherapy is retrospective and describes 30 patients treated with oral steroids (1 mg/kg/day for 8 weeks, then tapered by 5–10 mg/day every 1–2 weeks) compared with 23 patients who received pulses of methylprednisolone followed by oral prednisone (0.5 mg/kg/day for 8 weeks, followed by stepwise decreases);²⁸ the median treatment duration was 16 weeks. Only 15% achieved partial remission in both steroid treatment groups. The duration of treatment is important: of the 27 patients who received steroids for <16 weeks, only 15% achieved complete remission compared with 61% who achieved complete remission and 11% who achieved partial remission when treated for >16 weeks.

Thus, the recommendation is initial steroid therapy using oral prednisone at a dose of 1 mg/kg/day, with a maximum dose of 80 mg/day for 4–16 weeks depending upon the response, followed by slowly tapering the dose.²⁷ Several comparative studies have reported that a longer duration of steroid treatment (3–7 months) after an initial 4–8 weeks of daily steroid treatment, followed by an alternate-day protocol, significantly reduced relapse rate compared with the 8-week protocol.^{34,35}

Some patients may have contraindications (i.e., uncontrolled diabetes, obesity, psychosis, or prior prolonged steroid use) or secondary effects related to steroids, which means that steroid therapy needs to be reduced or avoided. In order to reduce steroid use, an association of prednisolone

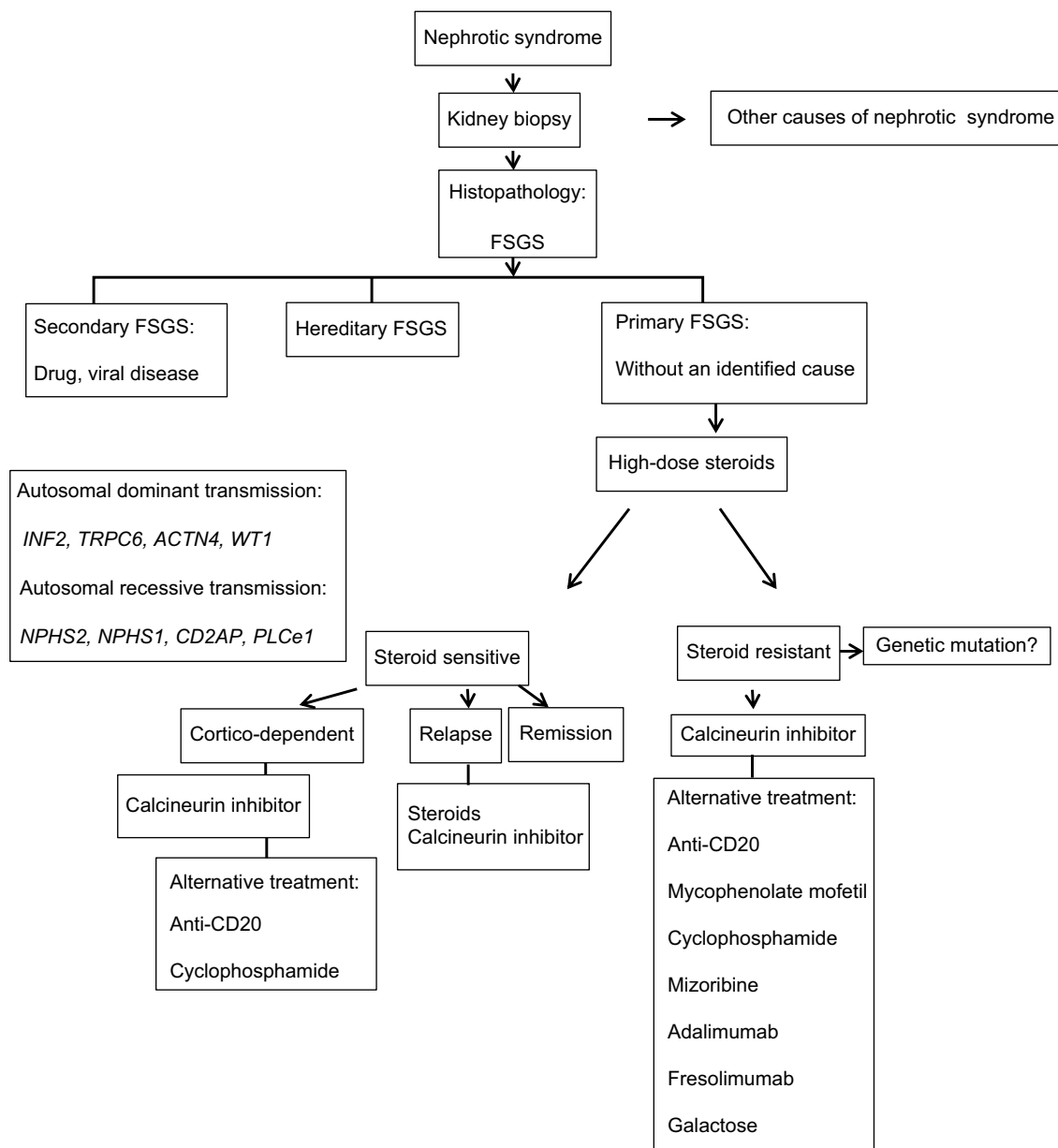


Figure 1 Algorithm for the management of primary FSGS.

Abbreviation: *ACTN4*, α -Actinin 4; *CD2AP*, CD2-associated protein; FSGS, focal segmental glomerulosclerosis; *WT1*, Wilms tumor protein.

with azathioprine and prednisolone with cyclosporine as a first-line therapy achieved remission in 80% and 88% of 20 nephrotic FSGS patients, respectively.³⁶ Tacrolimus (trough level of ~5.5 ng/mL) has also been used as a first-line therapy.³⁷ Another strategy to reduce patients' exposure to steroids is using mycophenolate mofetil (MMF). A retrospective study compared MMF (2 g/day for 6 months) plus prednisolone with a conventional therapy (prednisone 1 mg/kg/day for 3–6 months followed by a stepwise decrease) in 33 patients for an initial episode of FSGS. The remission rates were similar in both the groups: 69% in the MMF group and 71% in the conventional group. Relapse rates

and infectious complications also occurred at similar rates in both the groups.³⁸

Treatment of relapses of nephrotic syndrome in patients with FSGS

A relapse after remission of FSGS is common. In the largest prospective cohort of adults with FSGS, 52% of those who experienced a partial remission and 36% of those who achieved complete remission had a relapse during the follow-up period.⁶ The time from remission to relapse was shorter in the partial remission group.⁶ A repeat course of steroids is then recommended if the initial therapy was well tolerated

(Figure 1). Cyclosporine can be used and is associated with longer remission. Indeed, cyclosporine can reduce the relapse rate by 80%.³⁹ However, these patients then tend to become cyclosporine-dependent, just as they do with steroids. The remission rate is higher when the posology of cyclosporine is between 4 and 6 mg/kg/day with a trough level of 60–80 ng/mL.^{27,40} However, there are questions regarding the prolonged use of cyclosporine because patients may then develop a renal lesion because of cyclosporine toxicity.

Cyclophosphamide can also reduce the risk of a relapse in steroid-dependent nephrotic syndrome.²⁷ The combination of cyclophosphamide with steroids increases the duration of remission in patients with a relapse when compared to cyclophosphamide alone.²⁷

Treatment of steroid-dependent nephrotic syndrome in patients with FSGS

Patients with FSGS are considered to be steroid-dependent if they experience two relapses during tapering or within 2 weeks of completing steroid therapy. The goal is to then obtain remission while discontinuing or decreasing steroid dose in the hope of avoiding long-term adverse events from a high-dose therapy. A calcineurin inhibitor, such as cyclosporine or tacrolimus, may then be recommended (Figure 1). The antiproteinuric effects of calcineurin inhibitors are via the stabilization of the podocyte actin skeleton rather than by their immunomodulatory effects on T cells.⁴¹ This strategy requires close monitoring of trough levels and kidney function.⁴²

The use of tacrolimus with prednisone has been described in two small prospective studies.^{43,44} A Chinese trial compared the association of tacrolimus with prednisone to the association of IV cyclophosphamide with prednisone given to 33 adults with steroid-dependent or steroid-resistant FSGS: they reported 6- and 12-month cumulative remission rates of 67% and 73%, respectively, in the tacrolimus–prednisone group compared with 56% and 67%, respectively, in the cyclophosphamide–prednisone group.⁴⁴

Two alternative treatments may be proposed as second-line therapies, although few data are available on their efficacy: they are alkylating agents and monoclonal antibodies against CD20. Alkylating agents, given as oral cyclophosphamide, are associated with higher remission rates and a longer time of remission than calcineurin inhibitors. The doses recommended, in different studies that have included patients with FSGS and other etiologies of nephrotic syndrome, range between 2 and 2.5 mg/kg/day.⁴⁵ Rituximab is

associated with a lower relapse rate and the need for lower doses of other immunosuppressive medications in adults with a steroid-dependent minimal change disease.⁴⁶ The role of rituximab in the physiopathology of FSGS is still debated: it may interact with a podocyte antigen or may control, directly or indirectly, immunity by depleting B cells.

Treatment of steroid-resistant nephrotic syndrome (SRNS) in patients with FSGS

Steroid-resistant FSGS occurs in 40%–60% of cases: it is defined as persistent nephrotic-range proteinuria, despite receipt of prednisone at 1 mg/kg/day (or 2 mg/kg every other day) for >4 months. Few randomized and observational studies have evaluated different immunosuppressive strategies; the evaluation of the different therapeutics is difficult and confounding because treatments are very heterogeneous.

Calcineurin inhibitors have been proposed, and tacrolimus and cyclosporine seem to have similar efficacies to treat SRNS; however, few studies have compared these two calcineurin inhibitors. Cyclosporine can bring about remission in ~60% of patients who are steroid-resistant.^{47,48} Tacrolimus at doses of 0.1–0.2 mg/kg/day, divided into two doses, was effective and well tolerated in patients with SRNS and resulted in complete remission in 81% of cases. However, in these present studies,^{47,48} the patients also received other multiple immunosuppressive agents.

The recommended target trough level in patients with SRNS is between 5 and 7 ng/mL.^{27,49} Remission rates, in studies where tacrolimus has been given to patients who are dependent on or resistant to corticoids, were between 48% and 100%.^{37,44,50–52} Any difference between cyclosporine and tacrolimus regarding nephrotoxicity has not been proven. Side effects include tremor, arterial hypertension, and diabetes mellitus.

An alternative treatment for patients with FSGS and SRNS, after an initial treatment of prednisone for 4 weeks, is administering an IV pulse of methylprednisolone at 30 mg/kg per dose, with a maximum of 1 g every day for 2 weeks.⁵³ Two-thirds of nonresponders of initial steroid treatment eventually became responders after a 2-week course of methylprednisolone.⁵⁴ The “Mendoza protocol” combined high doses of methylprednisolone as a pulse therapy and oral prednisolone, with or without an alkylating agent, administered for a total of 82 weeks.^{54,55} In that study, 65% of patients achieved complete remission and 25% progressed to chronic kidney disease.⁵⁵ Prolonged steroid treatment for nephrotic syndrome causes significant side effects, including growth impairment, obesity, hypertension, cataracts, osteoporosis,

immune suppression, diabetes mellitus, psychosis, hirsutism, and striae.

Cyclophosphamide is also a potential option for steroid-resistant patients; it may also decrease progression to renal failure. Cyclophosphamide can be given in monthly IV pulses at a dose of 500 mg/m² for 6 months for infrequently relapsing syndrome.⁵⁶ Cyclophosphamide should not be given to children.

Additional therapies for the treatment of idiopathic FSGS

Additional emerging therapies can help the management of steroid-dependent, steroid-resistant, or relapsing FSGS but have not been validated in controlled studies. These are described as follows.

MMF

MMF can inhibit purine synthesis in lymphocytes and has been developed to control the immune system. However, the widespread use of MMF is not recommended,²⁷ although MMF can reduce the combined rate of complete and partial remission by 67% in patients with SRNS, and in association with tacrolimus and steroids, it can increase remission rate to 75%.⁵³ MMF has fewer side effects than calcineurin inhibitors and is not nephrotoxic. Thus, MMF can be an alternative agent for patients who have adverse effects from calcineurin inhibitors.²⁷ A multicenter, open-label, randomized comparison of cyclosporine versus oral dexamethasone plus MMF has underlined the interest in MMF for this pathology as well as the difficulty of conducting this type of study.⁵⁷ The posology is 1,200 mg/m²/day, divided into two doses. Calculation of areas under the concentration–time curve are essential when using this drug. Common side effects from MMF include metabolic acidosis, infection, diarrhea, abdominal pain, and hyperlipidemia.

Rituximab

Rituximab is a humanized monoclonal antibody that targets the CD20 surface antigen on B-lymphocytes, selectively depleting these cells. Furthermore, rituximab seems to have a direct protective effect on podocytes.⁵⁸ The use of rituximab in steroid-resistant FSGS has been documented in case reports and small uncontrolled case series, both in native kidneys and recurrence of FSGS after kidney transplantation in adults and children. Rituximab is administered as two or four IV injections at a dose of 375 mg/m² weekly or biweekly. Rituximab may be used as an effective steroid-sparing agent for children with steroid-dependent nephrotic syndrome.^{59,60}

or SRNS.^{61,62} However, some patients may become rituximab-dependent or may develop autoantibodies against rituximab after repetitive infusions.

Mizoribine

Mizoribine inhibits inosine monophosphate synthetase and guanosine monophosphate synthetase, resulting in the inhibition of DNA synthesis and cell division. A Japanese case series reported successful treatment with a combined therapy of mizoribine, tacrolimus, and plasmapheresis given to children with refractory nephrotic syndrome.^{63,64} Mizoribine can be administered at a dose of 3 mg/kg once daily before breakfast.⁶³

Adalimumab

Adalimumab is a human monoclonal antibody directed against tumor necrosis factor- α . Adalimumab reduced proteinuria by >50% in four of ten patients with resistant FSGS. Adalimumab was well tolerated with no serious side effects.⁶⁵

Fresolimumab

Fresolimumab is a recombinant, fully human monoclonal antibody that inhibits the activity of all isoforms of transforming growth factor β . Fresolimumab achieved one case of complete remission and two cases of partial remission of proteinuria among a total of 16 patients with resistant FSGS.⁶⁶

Low-density lipoprotein (LDL) apheresis

LDL apheresis, using an absorptive column, which has been used to treat familial hypercholesterolemia, has been shown to be effective in a small series of patients with resistant FSGS.⁶⁷

Synthetic adrenocorticotropin (ACTH) analog

Many decades ago, injections of ACTH were used as a therapeutic agent for children with nephrotic syndrome.⁶⁸ A recent case series described using a natural ACTH injection in 24 adults with FSGS (six patients with steroid dependent nephrotic syndrome and 15 with SRNS). The median prescription was 80 units injected subcutaneously twice weekly. Five partial and two complete remissions were reported, with two relapses observed during the follow-up period (66 months).⁶⁸

Treatment of recurrent focal glomerulosclerosis after kidney transplantation

The recurrence rate of FSGS is ~30% after a first kidney transplantation and 85%–100% after a second kidney

transplantation.⁶⁹ Its physiopathology is still unclear, but a circulating factor may be implicated, despite it still being unidentified. Several candidates have been proposed but need to be confirmed. Improvements in the understanding of the pathophysiology of recurrent FSGS after kidney transplantation may help to develop urine or plasma biomarkers to diagnose recurrent disease and, thus, to develop specific treatments.

Some risk factors for recurrence have been identified after graft failure caused by recurrent FSGS: younger age (particularly children aged 6–15 years), non-Black race, rapid progression of disease in native kidneys (within 3 years of diagnosis), and severity of proteinuria.^{70,71} The recurrence of FSGS occurs rapidly after kidney transplantation at only a few hours to several days. A diagnosis of recurrence needs to be made rapidly before the development of irreversible kidney damage. The appearance of massive proteinuria, which is the first symptom, prompts a kidney biopsy to eliminate rejection and to indicate rapid commencement of intensive therapy. At that time, a kidney biopsy is usually assessed by using a regular microscopy and immunofluorescence staining that is negative. A foot process fusion can only be observed by electronic microscopy. Glomerulosclerosis appears later. Currently, the management of FSGS recurrence remains difficult, and treatment decisions are often based on case series. Data from controlled trials that compare the efficacy of various approaches are lacking. Immunosuppressive treatments are intense and unspecific, and the prognosis of this disease is usually poor, often with graft loss.^{72,73}

Curative treatment of recurrent FSGS after kidney transplantation

Plasmapheresis

One of the most commonly used therapies for recurrent FSGS is plasmapheresis to rapidly remove the circulating factors. Plasmapheresis must be started immediately after diagnosis of recurrence to improve the prognosis. Remission rates vary within different studies but are ~70% in children and ~63% in adults.⁷⁴ Usually, 1.5 plasma exchange volumes using 4% or 5% albumin are done 3–4 times weekly to achieve a total of 8–12 plasma exchanges until remission is achieved. In some cases, weaning or the use of intensive protocols for several months has been conducted.⁷⁵

Prophylactic plasmapheresis therapy during the perioperative period has been proposed; however, the results are controversial.^{75–77} Immunoabsorption with a protein-A column is an interesting strategy because the circulating factor, even though unidentified, is known to have the capability of

binding to protein-A columns.^{19,78} No prospective randomized clinical trials have yet compared the efficacies of plasmapheresis and immunoabsorption, although the outcomes from these two methods seem to be similar. Therefore, the choice between these two methods depends on their availability and the preference of the physician. However, immunoabsorption reduces the risk of developing transfusion-related acute lung injury and of inducing viral transmission through plasma exchange. It is important to begin plasma exchange as soon as possible because removal or replacement of the FSGS-causing circulating factor(s) should be instituted before irreversible damage is inflicted to the graft. Intense immunosuppression is also associated with this approach.

Calcineurin inhibitors

Higher IV doses of cyclosporine have been associated with reduced proteinuria.⁷⁹ The rationale behind maintaining high cyclosporine levels in the blood is the lipophilic characteristics of cyclosporine. This drug is incorporated into peripheral lymphocytes via LDL receptors that bind onto the surface of the cells. High levels of LDL cholesterol in the blood are often encountered in patients with nephrotic syndrome, which then reduces the amount of free drug availability. Thus, because hypercholesterolemia inhibits the effect of cyclosporine on lymphocytes, the presence of high levels of cyclosporine in the blood may overcome this effect.⁸⁰ Blood should contain ~250–350ng/mL of cyclosporine.⁸⁰ In some cases, a high dose of oral cyclosporine may be effective, whereas other groups recommended IV infusion.⁸¹ However, high doses of cyclosporine for long periods may cause side effects. Tacrolimus has been proposed as a replacement for cyclosporine⁸² at a trough level of 12 ng/mL: it could be combined with high-dose methylprednisolone and/or rituximab, in addition to providing immediate and intense plasmapheresis.

Alternative treatments for recurrent FSGS after kidney transplantation

Rituximab

Rituximab, in addition to binding to CD20, partially prevented the downregulation of the sphingomyelin phosphodiesterase acid-like 3b protein and acid sphingomyelinase in podocytes treated with the sera from patients with recurrent FSGS.⁶¹ Based on data from the existing studies, it was found that rituximab could be a useful treatment for some cases of recurrent FSGS. However, randomized case-control studies are required to strengthen these results. Most patients described in the literature have usually been treated with multiple medications, making it difficult to parse out the treatment effects of

specific drugs, including rituximab. However, its beneficial effect has been demonstrated in several studies.⁶² The typical rituximab regimen is 2–6 doses (at 375 mg/m²/dose), given once every 1–2 weeks.^{83,84} In one study, rituximab seemed to show efficacy after a single low dose of 100 mg/m².⁸⁵ After rituximab infusion, plasmapheresis should not be performed for the following 72 h to prevent removal of the antibody.

Galactose

Oral galactose, a monosaccharide sugar, has been reported to decrease in vitro glomeruli permeability to albumin when exposed to the sera from patients with recurrent FSGS after kidney transplantation.⁸⁶ Case reports describe patients with recurrent FSGS after transplantation whose proteinuria improved after oral galactose therapy at a dose of 0.2 g/kg twice daily.^{87–89} A pilot study that included seven children with SRNS (n=4 with FSGS, n=2 with recurrent FSGS after kidney transplant, and n=1 with minimal change disease) who had received oral galactose for 16 weeks reported decreased glomerular permeability in vitro, although there was no significant difference in proteinuria.⁸⁷ This effect needs to be confirmed.

Abatacept

Abatacept (cytotoxic T-lymphocyte-associated antigen 4-immunglobulin fusion protein) is an inhibitor of the T-cell costimulatory molecule, B7-1 (CD80).⁹⁰ Some research on podocytes has identified B7-1 as an important factor during podocyte injury. This led to the identification of B7.1 (CD80) as a new therapeutic target in renal disease. However, the role of B7-1 in podocyte injury in patients with recurrent FSGS after renal transplantation is controversial. One study found B7-1 expression on podocytes and decreased proteinuria in five patients with rituximab-resistant recurrent FSGS and in one patient with steroid-resistant FSGS treated with abatacept, a B7.1-blocking fusion protein.⁹⁰ More recently, another study did not find these results: no proteinuria remission was observed in nine patients with recurrent FSGS after kidney transplantation who had been treated prospectively with abatacept or belatacept. Moreover, in this study, B7-1 expression was not found on podocytes.⁹¹ Currently, abatacept is no longer considered as a treatment for FSGS due to the lack of convincing data.

Cyclophosphamide

The current use of cyclophosphamide in recurrent FSGS is infrequent due to its contradictory results and concerns about long-term toxicity.⁷³

Infusion of allogeneic mesenchymal stem cells

Infusion of allogeneic mesenchymal stem cells has been used successfully to stabilize kidney function in children with recurrent FSGS and to prevent renal dysfunction.^{92,93} However, more investigations are warranted to provide a rationale for stem-cell-based treatments.

Blockade of the renin–angiotensin system

Despite evidence that activation of the renin–angiotensin system is crucially involved in the progression of recurrent FSGS,⁹⁴ only a few case reports have addressed the beneficial effect of blocking the renin–angiotensin system to reduce proteinuria in recurrent FSGS.^{77,95,96}

Preventive treatments for the recurrence of FSGS after kidney transplantation

Patients who have lost a previous allograft because of the recurrence of FSGS have a particularly high risk of recurrence.^{97,98} In order to eliminate the circulating factors, preemptive plasmapheresis/immunoabsorption may be considered: that is, 3–5 sessions prior to transplantation followed by 3–5 sessions immediately at post-transplantation. An additional single dose of rituximab (375 mg/m²), plus immunosuppression with corticosteroids, calcineurin inhibitors, and MMF for 2 weeks prior to kidney transplantation, has been shown to prevent recurrence.^{99,100}

Conclusion

The management of idiopathic FSGS remains a challenge for nephrologists. Controlled trials concerning therapeutic strategies are lacking. Understanding of the physiopathology of FSGS should be increased in order to conduct and develop specific diagnostic tests and treatments that can improve the prognosis of patients with this disease.

Disclosure

The authors report no conflicts of interest in this work.

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