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## RECENT PROGRESS IN THE PATHOPHYSIOLOGY AND TREATMENT OF FSGS RECURRENCE

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### Abstract

Focal segmental glomerulosclerosis (FSGS) is a glomerular disease characterized by proteinuria, frequent progression to end-stage renal disease, and recurrence after kidney transplantation in ~25% of patients, which negatively impacts long-term allograft survival. Experimental studies suggest that abnormalities in T and, possibly, B cells may represent one initial pathogenic trigger, leading to podocyte injury and progressive loss. New data also support the existence of circulating permeability factors able to damage the podocytes, but no single molecule has been consistently identified as the causal pathogenic element in FSGS recurrence. Unfortunately, major progress from mechanistic studies has not translated into substantial advancements in patient treatment, with plasmapheresis (PP) and high doses of cyclosporine (CsA) remaining the mainstays of therapy. Despite consistent experimental and clinical evidence that treatment of proteinuria slows renal function decline in proteinuric nephropathies, maximal use of antiproteinuric agents such as renin angiotensin system antagonists is not routine in the management of FSGS recurrence. More recently, encouraging results have been reported with anti-CD20 depleting antibody rituximab, but further studies are needed to establish its safety/efficacy profile.

### Index words

kidney transplant; FSGS; glomerulonephritis; permeability factor; proteinuria

### INTRODUCTION

Gallon *et al.* recently reported the case of a 27-year-old patient with end stage renal disease (ESRD) caused by primary focal segmental glomerulosclerosis (FSGS) who developed severe nephrotic syndrome shortly after receiving a kidney transplant from his 24-year-old sister (1). A graft biopsy obtained on day 6 showed FSGS recurrence, revealing signs of podocyte foot-process effacement and loss of the interdigitating arrangements. Severe hypoalbuminemia and rapidly deteriorating graft function, together with the development of an intra-abdominal hematoma, led to renal allograft removal on post-transplant day 14. After consulting with the hospital ethics committee and internal review board, the removed kidney

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### DISCLOSURE

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was transplanted into a 66-year-old man with ESRD secondary to type 2 diabetic nephropathy. Immediately after retransplantation, the graft regained function, proteinuria decreased, and glomerular lesions regressed, as shown by allograft biopsies performed on days 8 and 25 after retransplantation (1).

This intriguing case emphasizes the role of host factors in initiating recurrent FSGS, and prompts us to review the status of our understanding of the pathophysiology of FSGS recurrence and the currently available therapeutic options for this problematic disorder.

## FSGS RECURRENCE IN KIDNEY TRANSPLANT PATIENTS

The global incidence of FSGS has been estimated at 8 cases/million/yr (2). Further there appears to have been a tripling of FSGS incidence, expressed as a fraction of the kidney biopsy population (3). There is a major effect of race/ethnicity, with African descent individuals at increased risk (4). In the USA, the lifetime risk for FSGS has been estimated at 0.2% for European Americans and 0.7% for African Americans (5). Progression to ESRD occurs in 40–60% of FSGS patients within 10 to 20 years from diagnosis, which makes of FSGS the most common primary glomerular disease in dialysis patients in the USA (6).

Five forms of FSGS are currently recognized: genetic, adaptive (post-adaptive), virus-associated, drug-induced, and primary (idiopathic) (7). Genetic FSGS has been associated with mutations in over 20 genes, encoded in the nuclear or mitochondrial genome, and encoding a range of molecules, including those of the slit diaphragm and actin cytoskeleton, which appear to be critical for podocyte function. Adaptive FSGS arises due to a mismatch between physiological load (in part dependent upon body size but also other determinants of glomerular blood flow) and glomerular filtration surface (in part dependent on nephron number), and this mismatch leads to podocyte stress, followed by podocyte detachment and loss. Virus-associated FSGS - including, amongst the others, parvovirus B19 and HIV-associated FSGS may occur via direct viral infection of the podocyte, circulating viral proteins, or as a consequence of the inflammatory cytokines released by other infected cells that interact with podocyte receptors. Drug-induced FSGS is due to a short list of medication including those that act on the podocyte (pamidronate, interferon-alpha) and those that damage the tubulointerstitium (e.g. lithium, cyclosporine, tenofovir). Importantly, only primary FSGS generally recurs following kidney transplant.

Primary FSGS patients are thought to display immune and/or cytokine abnormalities that lead to podocyte injury. This provides the rationale for the use of glucocorticoids as initial treatment. However, 20% of patients are resistant to steroids and other immunosuppressants (cyclosporine, tacrolimus, mycophenolate mofetil, or cyclophosphamide) and often progress to ESRD. Unfortunately, up to 50% of patients develop recurrence of proteinuria after kidney transplantation, which can occur within hours to days after grafting, and this increases the risk of renal dysfunction and early graft loss (8). The first three cases of FSGS recurrence were reported by Hoyler et al. in 1972 (9). As described in this initial paper, diffuse podocyte foot process effacement by electron microscopy is usually the only finding in early graft biopsies and may already appear after reperfusion, anticipating proteinuria onset (10). Severity of foot process effacement correlates with the extent of proteinuria, which supports the central role of podocytes in the pathophysiology of this disease (10). Compared to patients with recurrence of other glomerulonephritides, those with FSGS recurrence have a two-fold higher risk of losing the graft over 10 years (11). Risk factors for recurrent FSGS include younger age (especially in children <6 at FSGS onset), nonblack race, a rapid progression to ESRD in the native kidney (<3 years), heavy proteinuria in the period before transplantation, and the loss of previous allografts to recurrence (12).

## PATHOPHYSIOLOGY OF FSGS RECURRENCE: INSIGHTS FROM BUFFALO RATS

The Buffalo/Mna rats develop spontaneous proteinuria associated with renal histological features of FSGS. As with their human counterparts, treatment of these rats with glucocorticoids, cyclosporine, or cyclophosphamide is associated with proteinuria reduction. Of even higher interest, when a kidney from a healthy MHC-compatible LEW.1W rat is transplanted into a nephrectomized Buffalo/Mna recipient, FSGS recurs (13). Importantly, detailed sequential analyses of renal histology, infiltrating cell populations and cytokine transcripts excluded the presence of acute or chronic rejection processes in the transplanted kidney and confirmed that primary FSGS and post-transplantation recurrence represent the same entity (14), making Buffalo/Mna rats a suitable model for study FSGS recurrence. Intriguingly, when Buffalo/Mna kidneys are transplanted into normal LEW.1W rats, proteinuria and renal lesions regress, which closely reproduces the case described in the initial vignette (13).

Studies performed in Buffalo/Mna rats showed that the most represented cell lineage in the kidney infiltrate before and during the development of the disease was monocytes/macrophages (15), together with Th2 lymphocytes (15). Importantly, treatment with the deoxyspergualin derivative LF15-0195 was associated with the formation of regulatory T cells that, in turn, were able to reduce proteinuria in the initial kidney disease and to prevent its recurrence after transplant. Taken together, these findings support the importance of T cells in the pathogenesis of FSGS.

In addition to these immune abnormalities, genetic analyses have shown that the development of the proteinuria in Buffalo/MNa rats is associated with an abnormality in the actin cytoskeleton, which suggests the existence an inherited direct podocyte defect (16–18). This finding is consistent with the rare possibility of FSGS recurrence in patients with heterozygous mutations in *NPHS2* gene encoding podocin that should be theoretically corrected by the graft (19, 20). Though anti-podocin antibodies have not been found in patients with disease recurrence and mechanisms at the basis of this phenomenon are still obscure, it could be hypothesized that inherited abnormalities in the kidney elicit, in predisposed individuals, an immune response, which could further accelerate glomerulosclerosis.

## CIRCULATING FACTORS

The frequent occurrence of proteinuria relapse in the immediate phases after transplantation suggests that podocyte injury is probably caused by a circulating permeability factor, initially thought to be released by T cells. Moreover, the rapid recovery of allograft function after retransplantation into a patient without FSGS further supports this hypothesis. However, despite mounting *in vitro* and *in vivo* observations supporting the existence of permeability factor(s), their identification has proven frustratingly elusive.

Many cytokines and other mediators able to increase glomerular albumin permeability *in vitro* have been found increased in sera of patients with FSGS. This group includes cardiotrophin-like cytokine 1 (CLC-1), a member of the interleukin-6 family, decreases nephrin expression in cultured podocytes and its blockade reverses the permeability effect of sera from FSGS patients (21). However, data on its potential role in the pathogenesis of FSGS are still preliminary.

At present the strongest evidence for a permeability factor relates to soluble urokinase receptor (suPAR), the soluble form of the urokinase type plasminogen activator receptor

(uPAR) (22, 23). In mice, circulating suPAR activated podocyte  $\beta 3$  integrin (ITG $\beta 3$ ), causing foot process effacement, proteinuria and FSGS-like glomerulopathy. Intriguingly, the proteinuric effects of suPAR are blocked *in vitro* by a specific antagonising antibody. Moreover, creating a point mutation in suPAR gene in mice blocked its ability to activate  $\beta 3$  integrin and to produce proteinuria.

This solid experimental evidence of a causative role of suPAR in FSGS, however, is not supported by similarly convincing clinical data. Though serum levels of suPAR in FSGS patients reported by Wei *et al.* were, on average, significantly higher than in patients with other glomerulopathies, a wide overlap was present amongst different renal diseases (22). High serum levels of suPAR were predictive of FSGS recurrence in transplanted kidneys, and lowering the levels of suPAR by plasmapheresis was associated with disease remission. However, serum levels of suPAR above the suggested threshold of 3000 pg/mL were found in patients without recurrent FSGS (22). Further, plasma suPAR levels are elevated in a wide range of inflammatory conditions, including chronic infections (including tuberculosis and malaria), bacterial pneumonia, bacterial and viral central nervous system infections, sepsis, and various cancers (24). These conditions are not frequently associated with nephrotic proteinuria, casting doubt upon a simple model that relates suPAR plasma levels to podocyte injury and nephrotic proteinuria. HIV infection has been also associated with high suPAR levels, but no evidence has linked suPAR with HIV-associated FSGS.

Therefore, the role of suPAR in human FSGS pathogenesis is unclear and probably less straightforward than initially proposed. The role of suPAR as a potential permeability factor in FSGS was challenged by data showing that, in a single center cohort of 23 patients, serum suPAR levels were not different amongst idiopathic FSGS, secondary FSGS, and minimal change disease (MCD), nor did they predict responsiveness to steroid therapy in patients with idiopathic FSGS or MCD (25). Conversely, an inverse correlation was found between serum suPAR levels and estimated GFR, independently from glomerular disease. These findings raised additional doubts on the potential use of serum suPAR as a marker of primary FSGS. This report has stimulated a reply that points out the critical role of careful phenotyping in FSGS studies (26).

Altogether, despite strong clues in support of its existence, research on the circulating factor has been inconclusive so far, possibly because not a single factor is responsible for all the cases of FSGS. Conversely, in harmony with the protean nature of the disease, multiple factors may act in the same patients together or at different stages of the disease.

## PROGRESSION OF FSGS INJURY

Data from experimental and clinical studies converge to support the hypothesis that FSGS is the result of various insults directed to or inherent within the podocyte. Podocyte injury leads to effacement of the foot processes, which is the major structural correlate of nephrotic proteinuria. This change in podocyte shape is the result of cytoskeleton rearrangement, a process that is partially reversible by glucocorticoid and calcineurin inhibitor therapy (7).

In rats with podocytes transgenic for the human diphtheria toxin receptor, Wharram *et al.* were able to induce precise levels of podocyte depletion by titrating the dose of administered toxin (27). The animals showed dose-dependent structural alterations characteristic of FSGS disease. Podocyte depletion of <20% induced transient proteinuria and mesangial expansion, loss of 20% to 40% of podocytes resulted in persistent proteinuria and focal glomerulosclerosis, but no progressive renal function decline, and >40% podocyte loss caused progressive glomerular failure, indicating the existence of a threshold for disease progression (27) In a chimeric model in which only a subpopulation of podocytes express toxin receptor, podocyte injury and dedifferentiation were shown to spread to neighboring

toxin-resistant podocytes that escaped the initial insult (28). Consistently, podocytes are shed into the urine for months after a brief toxin exposure (29). Mechanisms underlying the local propagation of podocyte injury are still ill defined; one possibility is that podocyte loss requires that neighboring podocytes must undergo hypertrophy to cover a larger area of the capillary loop and that hypertrophy, beyond a certain threshold, places stress on the podocyte. Recently, Fukuda *et al.* (30) showed that in rats with impaired mammalian target of rapamycin (mTOR) signaling (a key determinant of a cell hypertrophic response to nutrients and growth factors), weight gain was associated with accelerated development of glomerular hypertrophy, development of FSGS lesions, and renal failure. This phenomenon was even more striking when renal mass was reduced by uni-nephrectomy. Thus, the process of podocyte hypertrophy is essential in renal compensation, although it may come at a cost.

As a consequence of podocyte loss, unremitting proteinuria may be associated with upregulation of transforming growth factor- $\beta$  and other soluble factors, and downregulation of vascular endothelial growth factor and other soluble factors, which mediates progressive glomerular scarring (31). Additional, non mutually exclusive mechanisms include loss of pro-survival factors such as nephrin signaling or enhanced angiotensin II, shear stress, or cell death gap junction signaling (32) (Figure 1).

Therefore, a mismatch between nephron number and metabolic demand represents an important element for progression of FSGS. This could be particularly relevant in kidney transplant patients, where nephron mass provided with a single graft is reduced by the ischemia-reperfusion injury and immunosuppressive agent nephrotoxicity (especially calcineurin and mTOR inhibitors), which could at least partially account for the accelerated loss of renal function in FSGS recurrence compared to primary disease. Thus, recurrent FSGS patients may have components of both primary FSGS and adaptive FSGS from relatively early stages of the disease evolution.

## TREATMENT OF FSGS RECURRENCE

The management of patients with recurrent FSGS is challenging, with none of the multiple approaches providing consistent efficacy. Most reports consist of single cases and the few prospective studies are uncontrolled or with limited follow-up periods. Therefore, while experimental studies have provided major advancements in our understanding the pathophysiology of FSGS, treatment of affected patients is still largely empirical.

### Plasmapheresis and plasma absorption

Starting from animal experiments showing the potential existence of a circulating permeability factor in a patient with FSGS recurrence, Zimmerman reported in 1985 the first successful use of plasmapheresis (PP) (33). Since that original description, many case reports and case series supported the use of PP for the treatment of recurrent FSGS (34). Otsuba *et al.* retrospectively reviewed 5 recurrent FSGS patients treated with PP and 11 who were not treated; while outcomes were marginally better in those who received plasma exchange, the results did not reach statistical significance (35). A systematic review of the literature showed that PP was effective in promoting partial or complete remission of proteinuria in 70% of children and 63% of adults with recurrent FSGS (8). However, most studies were flawed by a retrospective, uncontrolled, design and by a short-term follow-up.

Few prospective studies of plasma exchange are available and none have involved a control group, either a non-treated control group or an alternative therapy. Gohh *et al.* prospectively treated 10 patients deemed to be at high risk for recurrent FSGS with 8 plasma exchanges during the perioperative period; only 3 patients experienced recurrent FSGS, which the

authors suggested was less than would have been predicted in the absence of the intervention (36). Interpreting the retrospective literature is complicated by publication bias of cases with positive outcomes that may lead to overestimation of treatment efficacy and by the fact that other therapies in addition to PP were part of the treatment regimen.

Cases and series have suggested that plasma absorption with protein A is effective at reducing proteinuria, and some authors have advocated the use of plasma absorption as an adjunctive treatment to PP, but data in support of this hypothesis are still limited (37, 38). According to a retrospective study of 11 patients with recurrent FSGS, double diffusion PP was able to reduce proteinuria in 7 cases, but its potential benefit over traditional PP needs further evaluation (35).

Despite the absence of good controlled trials, PP is still widely employed to treat recurrent FSGS in kidney transplant recipients. In light of the still limited evidence on the role of permeability factor(s) in the pathogenesis of FSGS, this treatment should probably be considered more critically.

### Calcineurin inhibitors

A few small studies have tested the hypothesis that calcineurin inhibitors prevent or treat FSGS recurrence by inhibiting T cells. More recently, the antiproteinuric effect of cyclosporine has been attributed also to the inhibition of calcineurin-mediated dephosphorylation of synaptopodin, a protein critical for stabilizing the actin cytoskeleton in podocytes (39). Though the use of standard oral doses of cyclosporine used to prevent acute rejection has not been associated with reduced incidence of FSGS, higher intravenous doses have been associated with proteinuria reduction (Table 1). The rationale behind maintaining a high cyclosporine blood level is to overcome the effect of high serum cholesterol often seen in patients with nephrotic syndrome due to recurrent FSGS. Indeed, due to the lipophilic nature of cyclosporine, hypercholesterolemia reduces the fraction of the active free drug. In a prospective cohort study, 17 patients with FSGS were treated with intravenous cyclosporine (3 mg/kg/d, converting to the oral route in 3–4 weeks to maintain trough levels between 250 and 350 ng/mL) (40). Fourteen patients had a prompt remission of proteinuria that, in some cases, persisted for years. Other reports showed encouraging results of cyclosporine in treating FSGS recurrence (41–43), but the long-term safety/efficacy of such a therapy remains to be established, especially in light of the severe toxicities associated with high doses of calcineurin inhibitors.

### Rituximab

Rituximab, a chimeric monoclonal antibody targeting the CD20 antigen of B-cells, was approved by the US Food and Drug Administration in 1997 for the treatment of relapsing or refractory non-Hodgkin's lymphoma. In 2006, a child with post-transplant recurrent FSGS achieved remission of nephrotic syndrome after receiving six intravenous rituximab administrations to treat a post-transplant lymphoproliferative disease (44). Depletion of a circulating autoantibody or interference with the presentation of B-cell antigens were mechanisms suggested to explain the efficacy of rituximab in this patient. Moreover, recent evidence has been provided that rituximab can directly bind to molecules other than CD20, such as SMPDL-3b, expressed in human podocytes. Intriguingly, *in vitro* exposure of podocytes to sera of FSGS patients down-regulates SMPDL-3b (a protein implicated in actin remodeling), which can be prevented by rituximab (45).

A recent systematic review of the 39 reported cases (19 pediatric) of FSGS recurrence treated with rituximab showed that complete or partial remission occurred in 64% of patients (46). Multivariate analysis revealed that normal serum albumin at FSGS recurrence and

lower age at transplant were associated with response. Intriguingly, fewer number of rituximab infusions was associated with a higher frequency of response. This is in line with what reported in membranous nephropathy, where a single rituximab dose is enough to achieve proteinuria remission (47). Therefore, though rituximab is generally well tolerated, its dosing should be titrated to the minimal level required to obtain B-cell depletion, especially in consideration of the increased risk of opportunistic infections in immunosuppressed transplant patients (48). According to some reports, combined use of PP and rituximab may potentiate the efficacy of both treatments (49) (Table 2). Intriguingly, this treatment strategy is made more appealing by its efficacy in reducing the anti-HLA antibody titer, another major risk factor for long-term graft loss.

### Renin angiotensin system inhibitors

Despite experimental and clinical evidence that activation of the renin angiotensin system (RAS) is involved in FSGS progression, only a few cases have been reported on the use of RAS inhibitors in patients with FSGS recurrence. Recently, Freiburger *et al.* (50) reported the case of a patient with FSGS recurrence after transplant that safely achieved proteinuria remission with intensified RAS inhibition through the use of triple RAS therapy: ACE inhibitor, an angiotensin II receptor antagonist and a renin inhibitor. Of note, previous treatment with PP and rituximab obtained only transient proteinuria reduction. This finding is in line with retrospective studies showing a beneficial effect of RAS inhibitors in reducing proteinuria and improving graft or patient survival in subjects with chronic rejection. Consistent evidence of the nephroprotective effects of RAS inhibitors should therefore encourage their wider use in transplant patients with proteinuria, including those with nephrotic syndrome associated with FSGS recurrence. Though these drugs have a good safety profile, serum creatinine and potassium levels should be carefully monitored, at least during the up-titration phase.

## MANAGEMENT OF FSGS RECURRENCE

In renal transplant recipients with FSGS recurrence, proteinuria should be monitored strictly and treatment should be instituted as soon as the diagnosis of FSGS recurrence is made. Urinary protein excretion should be measured frequently during the early post-transplant phase, when the risk of recurrence is the highest. Ideally, proteinuria should be evaluated on a daily basis during the first one or two weeks after transplant, then the frequency of measurements should be progressively tapered up to once every week or every two weeks (month 3), then to once a month (month 6) and every two months thereafter. Due to the potential late onset of disease recurrence, proteinuria should be evaluated at least every 6 months after the first transplant year. Measurement of urinary protein/creatinine ratio is the preferred way to assess proteinuria, at least during the first months after transplant. Urinary dipstick represents an alternative and more practical screening strategy to identify those patients who require a quantitative measurement of urinary proteins. Once proteinuria is found, a graft biopsy should be performed to confirm that diagnosis. Early graft biopsies may show normal-appearing glomeruli by light microscopy but diffuse foot process effacement by electron microscopy.

Lack of any treatment with proven benefit makes the management of FSGS disease extremely challenging. Despite the mixed results available, a course of PP treatment should be attempted in every patient. Initial schedule should be 2–3 changes per week, using 5% albumin as replacement fluid, and then titrated according to patient response (8). Rituximab should be also administered early, starting with a single 375mg/m<sup>2</sup> dose (48). Evidence also exists suggesting that rituximab induction may reduce the rate of FSGS recurrence (45).

Because of the reported association between sirolimus and FSGS, conversion from mTOR to calcineurin inhibitors is recommended (51). The use of high CsA doses should be decided case by case and its potential benefits in proteinuria reduction have to be carefully weighed against the drug-related toxicities, including nephrotoxicity. For patients with a contraindication to CsA, tacrolimus should be used. All patients with FSGS recurrence should receive the maximal tolerated dose of RAS inhibitors to reduce proteinuria and protect the kidney from progressive scarring.

To assess response to treatment, proteinuria should be monitored frequently after any change in the drug regimen or dosing, since most of the aforementioned therapies, when effective, reduce proteinuria rapidly. In case of disease remission, patients should be followed-up in the long-term with proteinuria evaluations every three to six months.

## OUTLOOK

Recurrence of FSGS after transplant is frequent and associated with accelerated graft loss. Despite the remarkable progress made in unraveling the pathogenesis of FSGS, outcomes of affected patients have not significantly improved in the last several decades. More recently, studies investigating the immune abnormalities associated with FSGS and the pathophysiology of progressive podocyte loss are opening new avenues for the identification of novel, hypothesis-driven therapies. Investigations on rare, genetic forms of FSGS could provide important clues about more common cases that are not genetically determined. Hopefully, these achievements will translate into more powerful and selective therapies for FSGS patients.

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## List of abbreviations

<b>ACE</b>	Angiotensin converting enzyme
<b>CLC-1</b>	Cardiotrophin-like cytokine 1
<b>CsA</b>	Cyclosporin
<b>ESRD</b>	End stage renal disease
<b>FSGS</b>	Focal segmental glomerulosclerosis
<b>HLA</b>	Human Leukocyte antigen
<b>ITG<math>\beta</math>3</b>	podocyte $\beta$ 3 integrin
<b>MCD</b>	Minimal change disease
<b>mTOR</b>	Mammalian target of rapamycin
<b>PP</b>	Plasmapheresis
<b>RAS</b>	Renin angiotensin system
<b>suPAR</b>	Soluble form of the urokinase type plasminogen activator receptor

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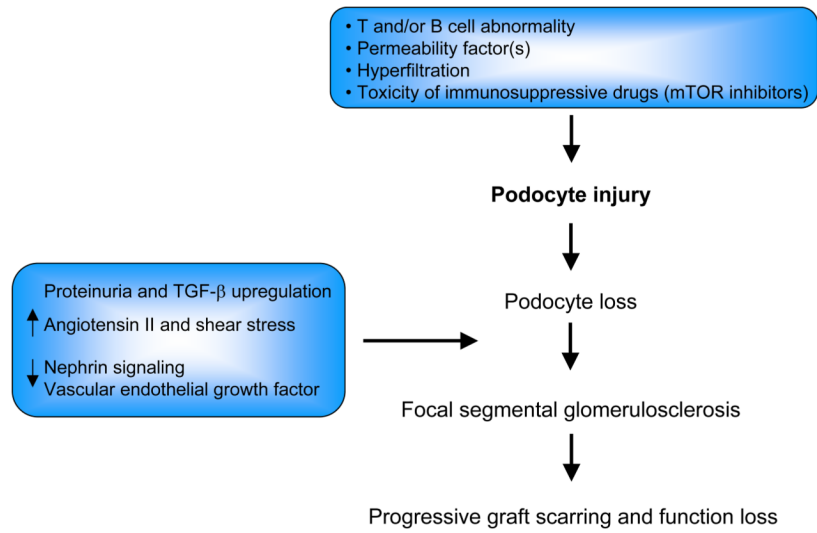


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**Figure 1.**  
Proposed pathogenic mechanism(s) of FSGS recurrence after transplant.

Table 1

Studies on cyclosporine effect on recurrent FSGS.

Reference	Study Design	Treatments	Incidence of FSGS recurrence/ <sup>o</sup> Remission Rate
<b>Prevention</b>			
Banfi G, et al. (52)	Retrospective	- Steroids + AZA (n=6) - Steroids + CsA (n=19)	2 (33%) 10 (55%)
Schwartz A, et al. (43)	Retrospective	- Steroids + AZA (n=7) - Steroids + CsA (n=8)	1 (14%) 2 (25%)
Ingulli E Tejani A (53)	Retrospective	- Steroids + AZA (n=22) - Steroids + CsA (n=18)	4 (18%) 2 (11%)
<b>Treatment<sup>o</sup></b>			
Ingulli E, et al. (42)	Case report	Progressive up-titration of oral CsA doses	1 Complete and 1 partial remission
Salomon R, et al. (40)	Retrospective	I.v. CsA (n=16). trough levels: 250–350ng/mL	Complete remission: 13 (81%) Partial remission: 2 (13%)
Raafat RH, et al. (41)	Retrospective	Oral CsA doses were up-titrated until proteinuria reduction or serum creatinine elevation (n=16)	Complete remission: 11 (65%) Partial remission: 2 (12%)
Canaud G, et al. (72)	Prospective cohort	I.v. CsA, combined with high-dose steroids and intensive plasmapheresis (n=10)	Complete remission: 9 (90%) 5/19 (27%) [Incidence of complete remission in a control historical cohort:

AZA: azathioprine; CsA: cyclosporine.

Table 2

Cases of rituximab therapy in FSGS recurrence.

Reference	Gender, age (y)	Background treatment	Rituximab dose	Follow-up (m)*	Remission	Adverse effects
<b>Adults</b>						
Hristea et al.(54)	1M (22)	Basiliximab induction, Tac, MMF, steroids, PP	375mg/m <sup>2</sup> ×2	24	Y	No
Gossman et al.(55)	1F (48)	Thymoglobulin induction, Tac, MMF, steroids, PP	375mg/m <sup>2</sup> ×2	12	Y	No
Meyer et al. (56)	1F (29)	Steroids, Tac, MMF, immunoadsorption	375mg/m <sup>2</sup> ×3	12	Y	No
Kamar et al. (57)	2M (25, 47)	MMF, steroids, CsA, PP	375mg/m <sup>2</sup> ×2	10	-Y (M 27) -No (M 47)	No
Yabu et al. (58)	3F (41, 43, 47) 1M (41)	FSGS refractory or dependent on PP	1000mg × 2 375mg/m <sup>2</sup> ×4-6		-Y (1M) -No (3W)	No
El-Firjani, et al. (59)	1F (48)	Thymoglobulin induction, Tac, MMF, steroids, PP	375mg/m <sup>2</sup> ×6		No	No
Apeland T, et al. (60)	1M (18)	MMF, Tac, steroids, PP	375mg/m <sup>2</sup> ×3	36	Y	No
Freiberger V, et al. (50)	1F (29)	MMF, Tac, steroids, PP	375mg/m <sup>2</sup> ×1	12	No	No
<b>Children</b>						
Grenda R, et al. (61)	1M (5)	CsA, MMF, steroids, PP	375mg/m <sup>2</sup> ×2	8	Y	No
Sethna C, et al. (62)	2F (13, 17) 2M (13, 18)	Thymoglobulin induction, steroids, Tac, MMF, PP	375mg/m <sup>2</sup> ×4	22.5	3Y, 1 No	No
Prytula, et al. (63)	14 cases	N/A	375mg/m <sup>2</sup> ×1-5	5-84	6Y, 3 partial, 5No	2 acute reactions, infection
Stewart, et al. (64)	1F (16)	Thymoglobulin induction, steroids, Tac, MMF, PP	375mg/m <sup>2</sup> ×6	12	Y	No
Nozu et al. (65)	1M (12)	CyA, steroids	375mg/m <sup>2</sup> ×4	36	Y	No
Pescovitz et al. (44)	1M (7)	Tac, MMF, steroids, PP	375mg/m <sup>2</sup> ×6	8	Y	No
Nakayama et al. (66)	2F (10, 12)	CyA, steroids, cyclophosphamide Mizoribin	375mg/m <sup>2</sup> ×3	8 2	Y	No
Marks and McGraw (67)	2M (6, 10)	Steroids, Tac, AZA, cyclophosphamide, CyA, PP	375mg/m <sup>2</sup> ×2-4		No	No
Bayrakci, U. S.(68)	1M (14)	Daclizumab induction, steroids, CyA, MMF, PP	375mg/m <sup>2</sup> ×4	8	Y	No
Hickson LJ, et al. (69)	1F (19) 3M (5, 6,13)	Tac, PP	375mg/m <sup>2</sup> ×2-4	7-30	Y	No

Reference	Gender, age (y)	Background treatment	Rituximab dose	Follow-up (m) <sup>*</sup>	Remission	Adverse effects
Rodriguez-Ferrero M, et al. (70)	1M (6), 2F(17, 22)	Steroids, MMF, Tac (n=2), Everolimus (n=1), PP	375mg/m <sup>2</sup> ×4	1	Significant proteinuria reduction	No
Dello Strogolo, et al. (71)	7 cases (7.3–26.9 years)	Steroids, Tac (n=5), CsA (n=2), MMF, PP, ACE inhibitors	375mg/m <sup>2</sup> ×1–4	2–9	3Y, 2 partial, 2No	2 acute reactions
<b>Fornoni, et al. (45)</b>	<b>41 cases (&lt;25years)</b>	Untreated (n=14), Rituximab to prevent recurrence (n=27)	375mg/m <sup>2</sup> ×1	12	Untreated=9 <sup>o</sup> Rituximab=7 <sup>o</sup>	

ACE: Angiotensin converting enzyme; CsA: Cyclosporine A; MMF: mycophenolate mofetil; PP: Plasmapheresis; RAS: Renin angiotensin system; Tac: tacrolimus.

<sup>\*</sup> after rituximab administration.

<sup>o</sup> Cases of FSGS recurrence.