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# Therapeutic Approach to Focal and Segmental Glomerulosclerosis (FSGS) Recurrence in Kidney Transplant Recipients

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## 1. Introduction

Primary focal and segmental glomerulosclerosis (FSGS) is the most frequently acquired disease leading to end stage renal disease (ESRD) in children (NAPRTCS 2004, annual report)[1-6]. The recurrence of FSGS after kidney transplantation is frequent (20-40%) and is associated with poor graft survival[7-13]. The pathophysiology of primary FSGS remains uncertain, but secretion of a circulating factor is suspected to play a key role in excessive glomerular permeability. Excepted for the recurrence of FSGS with a previous allograft, this event is almost unpredictable and characterized by early nephrotic range proteinuria. Some studies have identified risk factors for recurrent FSGS in children, including rapid progression to ESRD, young age of onset of FSGS and, of course loss of a previous graft from recurrent disease but none of these studies can clearly separate the patients who will or will not be affected by recurrence. The treatment of recurrence remains controversial, and most reports relate to use of plasma exchange (PE) in uncontrolled trials with relatively small groups of patients and conflicting results. PE and protein immunoadsorption can markedly reduce urinary protein excretion and induce complete remission in some cases, but they usually fail to achieve sustained remission[14-16]. Steroids and cyclosporine are also associated with inconstant remission and act through different ways. More recent therapeutic approach seems promising and need to be evaluated in large trials. This review summarizes the various therapeutic approaches to FSGS recurrence.

## 2. Pathogenesis of FSGS recurrence

To better understand the therapeutic approaches to FSGS recurrence, we might briefly comment on its pathogenesis. The pathophysiology of this disease remains largely unclear and is thought to involve at least three types of cells (T-cells, B-cells and podocyte) and a circulating factor. In 1974, to explain what would later be called idiopathic nephrotic syndrome (INS), Shalhoub proposed the hypothesis (Shalhoub hypothesis) of T-cell dysfunction resulting in the secretion of *"circulating chemical mediator toxic to an*

*immunologically innocent glomerular basement membrane"*[17]. Although knowledge of the pathogenesis of this disease has improved in recent years, novel therapeutics have not ameliorated the rate of its recurrence. T-cell disorder is still suspected based on much evidence for Th2 cytokine bias in INS. Sahali et al. were the first to report that T-cells from INS patients are driven toward a Th2 phenotype[18]. By screening a cDNA library from T-cells of patients with relapsing INS they found that overexpression of truncated c-maf–inducing protein (Tc-mip) induced c-maf, transactivated the IL-4 gene, and downregulated IFNγ expression, characteristic of Th2 commitment[19]. These data were also supported by the observation of increased expression of cytoplasmic IL-13 mRNA in T-cells from patients with relapsing INS as compared to those in remission and control patients[20]. Furthermore, overexpression of IL-13 in Wistar rats led to minimal change disease confirming the potential role for Th2 predominance in pathophysiology of INS[21]. More recently, the expression level of soluble ST2 protein (sST2), a marker of Th2 cells that is predicted to be regulated by c-maf, was investigated in a population of patient with FSGS recurrence after transplantation[22]. The level of sST2 were increased after transplantation in patients with recurrence compared to the control group; however this protein was unable to induce podocyte injury *in vitro* suggesting that it could be a marker of recurrence but might not be implicated in the pathogenesis of recurrence. Using a humanized mouse model, Sellier-Leclerc et al showed that CD34+ stem cells, unlike CD34- peripheral blood mononuclear cells, from patients with INS induced albuminuria, suggesting the involvement of immature differentiating cells rather than mature peripheral T-cells in the pathogenesis of the disease[23]. Thus, there is evidence for T-cell dysfunction in INS, but treatments targeting T-cells (calcineurin inhibitors, anti-CD3 or anti-CD52) are not completely effective in preventing or treating FSGS recurrence. Furthermore, there is recent evidence for B-cell participation from a report of remission obtained with rituximab (anti-CD20)[24]. Indeed, it is accepted that primary FSGS is the consequence of a complex interaction between T- and B-cells leading to the secretion of a circulating factor targeting podocyte. The presence of a circulating vascular permeability factor implicated in the physiopathology of this disease is highlighted by (i) the early recurrence of nephrotic syndrome after transplantation[25], (ii) the fact that serum from patients with recurrent FSGS infused in rats can induce albuminuria[26], (iii) the occurrence of a transient nephrotic syndrome in newborn infants of women with FSGS[27], and (iv) the efficiency of plasma exchange and/or immunoadsorption at inducing remission[15]. The biochemical characteristics of this factor, however, are still unknown. Its molecular weight is suspected to be between 30-100 kDa, and Dantal et al. suggested that it could be a part of a complex with immunoglobulins[28]. Recently, Savin et al. found that this circulating factor had a high affinity for galactose and that all its activity was eliminated by galactose affinity columns[29]. The third player in this complex disease is the podocyte. Podocytes are a post-mitotic cell, arrested in G2/M phase of the cell cycle, and do not proliferate. It has been postulated that the circulating factor and/or immune cells directly interact with podocytes, and could induce the redistribution of the protein of the slit diaphragm, the loss of nephrin and/or podocin and the effacement of the foot processes, a hallmark of podocyte injury[30]. It has been suggested that foot processes effacement, if reversed, can lead to the restoration of glomerular architecture, which is typically observed in steroid-sensitive minimal change disease. The failure of repair mechanisms promotes podocyte detachment, apoptosis, podocyte depletion and FSGS. A special situation is collapsing glomerulopathy, a specific variant of FSGS. Findings in human suggest that

podocytes may undergo a proliferative state and phenotypic changes in collapsing glomerulopathy[31, 32]. Importantly, evidence suggests that, in addition to podocytes, parietal epithelial cells also participate in the collapsing glomerulopathy phenotype[33]. Recently, Reiser et al. described the expression of the co-stimulatory molecule B7.1 on podocytes[34]. The significance of the presence of this molecule is not clearly understood and remains speculative.

## 3. Treatment of FSGS recurrence

Despite the introduction of new immunosuppressive regimens, discovery of cyclosporine, and use of induction therapies, the incidence of FSGS recurrence has remained unchanged[35-37]. In the case of recurrence treatments are not standardized, and show inconstant results. Most reports concern children and involve a small number of patients[15, 38-46]. Cyclosporine (CsA) has shown some degree of efficacy in pediatric subjects[43, 44]. Indeed, intravenous CsA after FSGS recurrence was associated with a drastic decrease of proteinuria in 82% of patients, although PE was added in some resistant cases[43]. A few reports have studied the use of tacrolimus to prevent or to treat recurrence. The results of these studies are almost inconstant[47, 48]. Due to the presence of a circulating permeability factor, most transplant teams test the efficacy of PE, which substitutes the plasma of the patient with either plasma from healthy pooled donors, albumin or colloidal substance. This treatment usually induces a reduction in proteinuria and, in some cases complete remission. Determining when to begin PEs, their frequency, duration and optimal stop time are challenging to determine, and most remissions are PE-dependant. Others supporting approaches have also been used, such as anti-human immunoglobulin affinity immunoadsorption and tryptophan immunoadsorption[28, 49].

We recently conducted a non-randomized pilot trial of intensive and prolonged multiple treatment of FSGS recurrence in adult kidney transplant recipients[50]. As this complex disease involves systemic immune dysregulation targeting podocyte, we used a strategy of concomitant high dose steroids and intravenous CsA not only for their immunosuppressive properties, but also for their podocyte cytoskeleton stabilization properties, and with PE sessions. Glucocorticoid receptors are present on podocytes, have anti apoptotic properties *in vitro* [51] and could stabilize the actin cytoskeleton[52]. CsA acts directly on podocytes by blocking calcineurin-mediated dephosphorylation of synaptopodin and stabilizes actin cytoskeleton[53]. We decided to add PE sessions based on the presence of the circulating factor and an increased five-year allograft survival rate in our own experience. Indeed, from January 1994 to December 2004, we observed that the five-year allograft survival rate was 55% in cases of FSGS recurrence (R group), compared to 93% in cases without recurrence (NR group) (p<0.01). In the R group, patients who benefited from PE had an increased five-year allograft survival rate (91%) similar to the NR group, whereas patients not treated with PE had a five-year allograft survival rate of only 40% (p<0.01).

The details of our therapeutic strategy consisted of high dose of oral steroids (1 mg/kg/d) for the first 4 weeks followed by tapering according to the following sequence: 0.75 mg/kg/d for 2 weeks, 0.5 mg/kg/d for two weeks, 0.25 mg/kg/d for two weeks and 0.2 mg/kg/d or a maximal daily dose of 10 mg thereafter. We used 14 days of intravenous CsA (2 mg/kg, targeting a blood level between 200 and 400 ng/ml) followed by oral treatment, targeting C2 levels between 1,200 and 1,400 ng/ml. PEs were performed with 5% albumin replacement (three sessions per week for three weeks, followed by two sessions per week

for three weeks, one session per week until month 3, two sessions per month until month 5, and once per month until month 9). Once remission was obtained, an angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker were introduced. Rescue with rituximab therapy was anticipated in case of failure. The primary endpoint was the induction of a complete (<0.3 g per 24H) and sustained (>12 months) remission of proteinuria. The treatment was started after 3 days of nephrotic-range proteinuria without spontaneous improvement. Of 286 kidney transplant procedures performed between September 2005 and March 2007 at our institution, 18 were performed in patients with primary FSGS. After transplantation these individuals were carefully monitored for proteinuria and ten (56%, eight men, two women) exhibited recurrence. The mean age at the onset of primary FSGS in native kidneys was $19.1 \pm 14.8$ years, leading to ESRD $8.1 \pm 8.6$ years later. The mean duration of hemodialysis was $2.8 \pm 2.4$ years. For nine of the patients, this transplant was their first; the remaining patient had received two previous kidney transplants, both of which had been quickly lost due to recurrence. After kidney transplantation, all patients received an immunosuppressive regimen including prednisone, mycophenolate mofetil, oral CsA (n=10) or tacrolimus (n=8), along with an induction of either basiliximab (n=12) or antithymocyte globulin (Thymoglobulin®, n=6). Proteinuria occurred immediately after transplantation in six patients (60%) and early post-transplant in the remaining four (range 4-55 days). Recurrence was associated with massive proteinuria (mean $12 \pm 11$ g/day). We began PE within the first ten days of diagnosis in all patients, while high-dose steroids and intravenous CsA were initiated at the time of diagnosis. Complete proteinuria remission was achieved in all patients at a mean of $22.9 \pm 6.6$ days post-diagnosis. Three months after diagnosis, all patients were still in complete remission (mean proteinuria $0.16 \pm 0.09$ g/day) and all but one patient remained in remission at one year (mean proteinuria $0.19 \pm 0.29$ g/d). In the nine patients with complete remission, PE was tapered gradually until month 9 and then stopped. During early follow-up (mean $15.8 \pm 3.3$ months), none of these nine patients relapsed. At one year post-transplant, mean serum creatinine was $121 \pm 29\mu mol/l$ and the measured iohexol glomerular filtration rate was $68.5 \pm 18ml/min$. The patient who failed to obtain sustained remission of proteinuria was the individual who had undergone a third kidney transplant. In this patient, proteinuria recurred when the frequency of PE was tapered to less than once per week. Rituximab infusion was attempted, and after two doses circulating B-cells were completely depleted (CD19 < $1/mm^3$). Proteinuria was maintained in the range 1-2 g/day with PE administered twice per month.

Long term follow-up ($34.2 \pm 6.7$ months) of this cohort revealed that all these patients were still in complete remission with a mean proteinuria level of $0.11 \pm 0.07$ g/day and a mean serum creatinine of $122.6 \pm 18$ $\mu mol/l$. The patient in partial remission went into complete remission by maintaining PE (two times per month). During the follow-up, none of these patients developed diabetes, cancer or severe infectious disease. Indeed, long-term follow-up of our cohort revealed that intensive treatment of FSGS induces not only an excellent short term response but also a complete and sustained remission of proteinuria without significant immunosuppressive regimen-associated adverse effects.

We then considered whether the treatment administered in case of FSGS recurrence impacted the pathological features of FSGS during the post-transplant course. To address this question, we retrospectively studied 77 patients from January 1984 to December 2007, including both children and adults with primary FSGS who underwent renal transplantation[54]. Of these, 42 patients experienced a recurrence of nephrotic-range

proteinuria. After kidney transplantation, recurrence of proteinuria occurred immediately in 32 of the 42 cases (children, $n$ = 28; adults, $n$ = 4), early in 9 of the 42 cases (children, $n$ = 4; adults, $n$ = 5) and late in 1 of the 42 case (adult, $n$ = 1). Briefly, at time of recurrence, day 6 to day 60 days after transplantation, no glomerular lesion was observed in 32 of 33 biopsies and we considered them as minimal change disease. Only one patient had already developed a FSGS lesion. At month 3, FSGS lesions were observed in 11 of 39 cases, and at month 12, they were observed in 14 of 37 cases. Interestingly, 17 of the 42 patients went into complete and sustained remission, and none of them developed FSGS. On the other hand, patients who never achieved complete and sustained remission developed FSGS lesions. These data suggest continuing intensive treatments if no FSGS lesion are observed on transplant biopsies.

## 4. Other available treatments

### 4.1 Preemptive PE

A few studies of preemptive PE have been reported that show inconstant efficacy and lack a control group. In 2005, Gohh et al conducted a prospective study to test whether pre-transplant PE could prevent recurrence of primary FSGS in high risk patients[55]. A high risk of FSGS recurrence was defined by a rapid evolution toward ESRD (n= 4) or prior allograft loss due to recurrence (n= 6). Patients were subjected to a course of eight PE sessions over 2 weeks in the immediate peri-operative period. Recipients of living donor kidneys initiated PE treatments 1 week before transplantation and completed their course at the end of the first post-operative week. Recipients of cadaver kidneys underwent an initial PE within 24 h of implantation. FSGS recurred in 3 of 10 patients, each of whom had lost prior transplants to recurrent FSGS. Two of these progressed to ESRD and the third had significant renal dysfunction. The authors conclude that PE may decrease incidence of FSGS recurrence in this particular population (rate of recurrence expected without PE: 60%). This therapeutic approach is difficult to organize in case of deceased donors, which is the major group of donors in many countries including our own. Furthermore, PE session before or soon after transplantation, may increase the risk of major bleeding despite the finding that no adverse event were reported in the previous study. This approach would also lead to excessive treatment in 50% of patients.

### 4.2 Rituximab

In 2006, Pescovitz et al reported complete remission after infusion of rituximab in a young transplant recipient[24]. After kidney transplantation this child rapidly developed FSGS recurrence resistant to PE and CsA and at month 5 developed a post-transplantation lymphoproliferative disease (PTLD). After six infusions of rituximab to treat the PTLD, proteinuria disappeared suggesting a possible interaction between B- and T-cells that leads to the secretion of permeability factor. Since that report, many transplant teams have tested the ability of rituximab to treat FSGS recurrence with inconstant results[56-59]. In fact, rituximab seems to induce remission in about 50% of cases, but some questions remain unsolved. When should the infusion begin: as an induction therapy or at time of recurrence? How many infusions should be administered, given that depletion of circulating B-cells does not always correlate with lymphoid organ depletion[60]? What are the long term side effects of this treatment? To date, no consensus has emerged, and double-blind studies are needed to determine the therapeutic potential of rituximab.

### 4.3 Anti-CTLA4

The co-stimulation molecule B7.1 is normally expressed on antigen presenting cells and B-cells. Recently, Reiser et al found that B7.1 is also expressed on podocyte and could be upregulated in many proteinuric states[34]. Again, the significance of the presence of this molecule is not clearly understood and remains speculative. To date, no published studies have evaluated blockade of this co-stimulation pathway for the treatment of FSGS recurrence.

### 4.4 Anti-TNFα

TNFα mRNA was found to be upregulated in macrophages preceding the development of nephrotic syndrome in Buffalo/Mna rats[61]. Furthermore, a high level of TNFα mRNA was detected in mononuclear cells from patients with FSGS[62]. Anti-TNFα therapy was recently tested in a child with resistant FSGS recurrence[63] and induced transient complete remission, but every relapse was sensitive to anti-TNFα infusion.

### 4.5 Retinoic acid, Roscovitine and cyclin dependant kinase inhibitor

Collapsing glomerulopathy recurrence is a situation in which podocytes can proliferate. Using *in vitro* and *in vivo* mouse models, retinoic acids were found to be efficient at reducing podocyte proliferation and proteinuria[64]. An on going study is evaluating treatment of collapsing glomerulopathy in native kidneys using retinoic acid (NCT00098020).

### 4.6 Galactose

Recently, Savin et al. found that the circulating factor has a high affinity for galactose, and that its activity can be removed by use of galactose affinity columns[29]. This group and one another reported a significant reduction in proteinuria following administration of galactose along with others therapeutics[29, 65]. A clinical trial (NCT00098020) is recruiting patients to treat primary FSGS in native kidney with galactose. Galactose has an excellent safety profile and could be an interesting therapeutic candidate.

## 5. Conclusion

Primary FSGS remains mysterious with a poorly understood pathogenesis. Recurrence is still frequent and associated with a poor allograft prognosis. We clearly must increase our knowledge of the pathogenesis of this disease to better identify specific risk factors for recurrence and design more specific therapeutic strategies. Our pilot study, although limited by a small population size, provides very encouraging results. Combined and intensive therapy showed a markedly beneficial effect on early proteinuria recurrence in this cohort of adult kidney transplant recipients. These preliminary results require confirmation on a larger scale with extensive follow-up. We have also described patients who went into complete and sustained remission and did not develop FSGS; patients who never achieved complete and sustained remission developed FSGS lesions. New therapeutics such as rituximab, anti-TNFα, galactose and retinoic acid should be evaluated in randomized double-blind studies. A better understanding of the molecular function of podocytes give hope that new therapeutics will be available in the next future.

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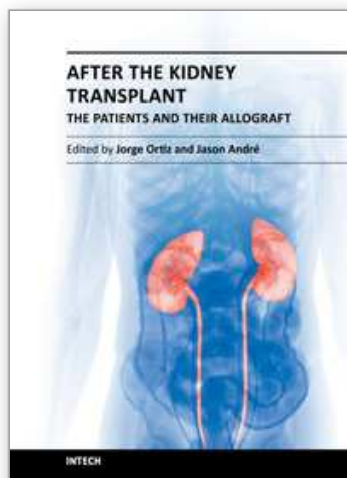
**After the Kidney Transplant - The Patients and Their Allograft**

Edited by Prof. Jorge Ortiz

There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipientâ€™s tolerance of the allograft and the infection risk of a suppressed immune system. These potential long term complications of kidney transplantation are relatively well known, but there are many other complications that patients and families do not consider when preparing themselves for a kidney transplant. Although the benefits of attempting a kidney transplant far outweigh downfalls of the long term sequelae, kidney transplantation is by no means a benign procedure. It is the hope of these authors that the reader will leave with a sense of understanding towards the kidney recipients.

**How to reference**

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