ORIGINAL ARTICLE

Response to plasma exchange and graft survival in recurrent focal and segmental glomerulosclerosis after transplantation: does the time of recurrence matter? A retrospective study

Caroline Dudreuilh[1,2], Christelle Barbet[1,2], Philippe Gatault[1,2], Sophie Ferlicot[3], Yvon Lebranchu[1,2], Nolwenn Rabot[1,2], Severine Beaudreuil[4,5], Antoine Dürrbach[4,5] & Matthias Büchler[1,2]

1 Department of Nephrology - Hypertension, Dialysis, Transplantation, CHRU, Tours, France
2 EA4245 Dendritic Cells, Immunomodulation and Grafts, François-Rabelais University, Tours, France
3 Department of Pathology, Bicetre University Hospital, Le Kremlin Bicêtre, France
4 Nephrology Department, Hopitaux Universitaires Paris-Sud, APHP, Le Kremlin-Bicetre, France
5 UMR 1197, University Paris Sud, INSERM, Paris-Saclay University, Villejuif, France

Correspondence
Caroline Dudreuilh MD, Department of Nephrology - Hypertension, Dialysis, Transplantation, CHRU, Tours, France.
Tel: +33247478930
fax: +33234378901
e-mail: caroline.dudreuilh@kcl.ac.uk

SUMMARY

Recurrence of primary focal and segmental glomerulosclerosis following kidney transplantation (rFSGS) is a frequent and severe disease. We studied the time to recurrence of FSGS and its impact on the response to plasma exchange (PE) and graft survival. Between 1990 and 2013, 2730 kidney transplants were performed, including 52 patients with a primary diagnosis of FSGS. Of these patients with primary FSGS, 34 (67%) developed rFSGS. We retrospectively divided these patients into two groups depending on the time to recurrence: early (up to three months after transplantation, $n = 26$) or late (more than three months after transplantation, $n = 8$). Survival did not significantly differ between the two groups. In cases of late recurrence, PE was started later and was performed less frequently, and remission was achieved after more PE sessions and longer PE treatment than for the early group ($P = 0.01$). In early recurrence, resistance to PE at 40 days was associated with no long-term response to PE. PE should be performed as soon as possible after rFSGS. Patients with late rFSGS need to be offered the same treatment regime as those with early rFSGS.

Transplant International 2021; 34: 302–312

Key words
kidney transplantation, plasma exchange, primary focal and segmental glomerulosclerosis, recurrence

Received: 15 June 2020; Revision requested: 10 July 2020; Accepted: 30 November 2020; Published online: 31 December 2020

Introduction

Focal and segmental glomerulosclerosis (FSGS) is a histopathological glomerular lesion of podocytes that is responsible for 40% of the cases of nephrotic syndrome (NS) in adults [1–3]. The primitive or idiopathic form leads to end-stage renal disease (ESRD) in 50% of patients with NS at diagnosis and may recur after transplantation [4]. Because of its recurrence after renal transplantation and the rapid reduction of proteinuria after PE or immunoadsorption (IA), it has been suggested that the disease is related to a soluble factor that has yet to be identified [1,3]. Other forms of FSGS are related to conditions including genetic mutation of proteins involved in podocyte physiology, infection and glomerular hyper-filtration (nephrotic reduction), and also as a side effect of certain medications [1–3].

The treatment of idiopathic forms of FSGS is based on corticosteroids. In the absence of remission of NS

doi:10.1111/tri.13796

(due to corticosteroid resistance), FSGS management is based on immunosuppressive therapies such as calcineurin inhibitors (CNIs), cyclophosphamide, mycophenolate mofetil or rituximab [1–10]. PE or IA is rarely used to treat primary FSGS in native kidneys [1–3]. Corticosteroid-resistant forms of FSGS have a poor prognosis and lead to ESRD in three to seven years [1–3].

FSGS recurs after kidney transplantation in 10–50% of patients [1–3,7–9] associated with abundant proteinuria. The recurrence of FSGS (rFSGS) is associated with poor graft survival; around 60% renal survival versus 80% in the non-rFSGS kidney transplant population at five years [1–3,7–9]. The time to rFSGS varies and can be immediate or much later post-transplantation. However, no study has compared patients' outcomes depending on time of recurrence, and it is not known if time to recurrence is associated with differences in prognosis and/or treatment efficacy.

The treatment of post-transplantation rFSGS is not well defined and remains controversial due to a lack of randomized trials. Furthermore, the majority of previous studies are retrospective, with a small number of patients and a short follow-up period [1–3,11]. The most common treatment consists of PE or IA to remove the soluble permeability factor, alongside steroids and CNIs (intravenous cyclosporine or tacrolimus), with high trough level targets [12–18]. CNIs may act through their modulation of the activation of T lymphocytes (potential secretors of the soluble permeability factor) and/or via a direct impact on podocyte survival (via the stabilization of their actin cytoskeleton) [19]. Any benefits of adjuvant treatment remain unclear and controversial [1,20]. Several studies have investigated treatments such as rituximab [21–24], belatacept or abatacept (CTLA4-Ig) [25–27] and ofatumumab [28]. There is evidence that, besides their primary target, some of these treatments could directly target podocytes [21–28]. However, the results of these studies remain controversial and have yet to be confirmed. Additionally, predictor factors of treatment response remain unknown.

In this bi-centric retrospective study, we collected clinical, biological and histopathological characteristics of patients who developed rFSGS after transplantation. We specifically focused on how therapeutic management was dependent on the time category of rFSGS. Additionally, we analysed the efficacy of PE/IA for treatment of rFSGS and the impact of delayed recurrence on renal graft survival.

Patients and methods

Inclusion criteria

From all patients who received a kidney allograft between 1990 and 2013 in the nephrology department of either Tours or Kremlin-Bicêtre hospital in France, we selected those with primary FSGS and those with recurrent FSGS after transplantation. The exclusion criterion was a high proteinuria of another origin, including a history of secondary FSGS. A diagnosis of primary FSGS was confirmed by reviewing patients' notes, including biopsies of the native kidney where available, to exclude any other cause of FSGS. We decided to exclude one of the patients who presented a malignancy at the same time as a diagnosis of rFSGS and therefore received a very delayed treatment for rFSGS. The study was conducted in accordance with the ethical guidelines from the two hospitals. No institutional review board approval was necessary at the time of the study (before loi Jarde) as it was a retrospective study involving no intervention. All studies were performed in accordance with the Declaration of Helsinki.

Clinical and biological characteristics

We recorded clinical, biological and histological characteristics at the time of FSGS diagnosis in the native kidney (e.g. age, gender, immunosuppressive treatment, evolution to ESRD) on the day of transplantation (e.g. duration of dialysis, proteinuria) and at the time of diagnosis of rFSGS (e.g. serum creatinine level, proteinuria, angiotensin-converting enzyme inhibitor [ACEi] treatment, immunosuppressive regimen).

rFSGS was defined as the rapid occurrence of nephrotic-range proteinuria (>3 g/24 h) after kidney transplantation that was not attributable to the native kidney [29]. Biopsy excluded another origin for the NS in most cases (see below). If patients were not anuric at time of transplantation, rFSGS was diagnosed with a combination of a significant increase in proteinuria, associated with an increase in the urine output attributable to the transplanted kidney, and a kidney biopsy with evocative lesions of FSGS.

Complete remission was defined as the absence of proteinuria (proteinuria < 0.3 g/24 h) and partial remission as at least a 50% reduction in the level of proteinuria recorded at the time of recurrence [1]. Persistent remission was defined as sustained remission with a reduction in or lack of proteinuria for over 12 months. A second rFSGS following the same

transplantation was defined by nephrotic proteinuria occurring more than three months after initially successful PE/IA. Resistance to treatment was defined as persistent nephrotic proteinuria, a less than 50% reduction in proteinuria and/or a decrease in kidney function despite treatment. Secondary resistance was defined as resistance in patients who initially responded to PE/IA (partial or complete) during their first rFSGS episode, but who displayed an absence of response to PE/IA following a second recurrence.

Patients were classified depending on the post-transplant time in an adapted version of the classification by Cameron et al. [10] as either an early (within three months of transplantation) or late recurrence (more than three months after transplantation); termed E-rFSGS, and L-rFSGS, respectively. Renal graft survival referred to death-censored kidney transplant survival.

Renal biopsy

We retrospectively reviewed the available pathology reports for the native and transplanted kidneys to confirm the diagnosis of primary FSGS or minimal change disease and excluded any differential diagnosis (acute or chronic rejection, recurrence of other primitive disease). We performed light microscopy (LM) of biopsy tissue following haematoxylin phloxine and safran (HPS), periodic acid–Schiff (PAS) and Masson's trichrome and argentic (Marinozzi) staining or following immunofluorescent staining of frozen tissue sections with anti-IgA, -IgG, -IgM, -C3 and -C1q antibodies. As in previous reports [24,27], interstitial fibrosis and tubular atrophy of the renal parenchyma on kidney biopsy were semi-quantitatively scored from 0 to 3 for absent, mild (1–25%), moderate (25–50%) and severe (>50%) disease. Available biopsy samples were retrospectively analysed by two independent observers to determine the FSGS variants according to the Columbia classification by LM [30–33]: 'collapsing' (COLL), 'cellular' (CELL), 'perihilar' (PH), 'tip lesion' (TIP) and 'not otherwise specified' (NOS).

FSGS treatment

We recorded all treatments that were started in the presence of rFSGS, including immunosuppressive treatments and PE/IA. The PE technique was based on either centrifugation (Kremlin-Bicêtre hospital) or plasma filtration (Tours hospital). Second-line therapy was recorded (rituximab, belatacept, cyclophosphamide). PE for a second recurrence after the same kidney transplantation was not studied. PE dependence was defined as an increasing proteinuria following spacing between PE sessions, regardless of the frequency of PE, leading to re-starting of the original PE regime. Unless otherwise specified, in this manuscript the term PE will refer to PE and IA, as the number of patients receiving IA was too small to make a proper comparison between the two techniques.

In our study, PE or IA was continued until complete or partial remission and then rapidly decreased before cessation of treatment and proteinuria follow-up [18]. For patients with no significant decrease in proteinuria (resistance), the overall PE/IA treatment period was variable but long enough to consider the disease resistant to PE/IA. In these cases, discontinuation was mostly due to either treatment complication(s) (infection, vascular access) or in accordance with the patient's wishes [1–4].

Statistical analysis

Data are expressed as percentage (%) or mean ± standard deviation (SD) for normally distributed variables and as median (range) for non-normally distributed variables. Qualitative data were compared by chi-squared or Fisher's exact test dependent on the sample size. Quantitative data were compared by the Mann–Whitney test. Kaplan–Meier curves were used to estimate the predictive value of PE on patient survival and graft survival (death was censored). A log-rank test was used to compare survival curves. End of follow-up was defined by death or day of last visit. Statistical analyses were performed using XLSTAT. Data were considered statistically significant at $P < 0.05$.

Results

Patient characteristics and FSGS recurrence

Between 1990 and 2013, among 2730 renal allograft recipients, 52 patients had a history of primary FSGS. After transplantation, 34/52 patients (67.3%) showed massive proteinuria, which was considered as primary FSGS recurrence (Fig. 1). Clinical characteristics at primary FSGS diagnosis and on the day of transplantation for rFSGS patients are shown in Table 1. The population was young, with a mean age of 35 ± 12.6 years (mean ± SD) at the time of transplantation. Fifty-seven per cent were male, and 85% were receiving their first transplant from a deceased donor. Median delay between diagnosis and ESRD was five years (range 0–27),

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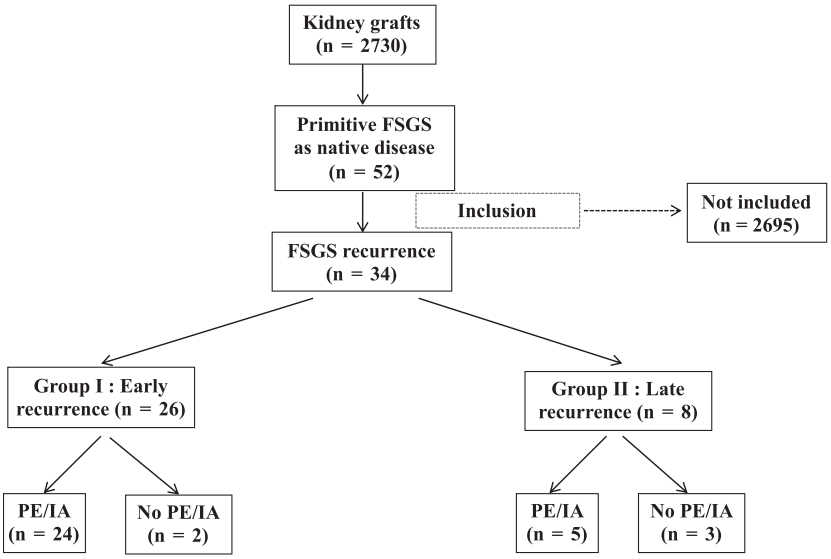

Figure 1 Flow of participants in the study. FSGS, focal and segmental glomerulosclerosis; PE, plasma exchange.

and 41% started dialysis within three years of primary diagnosis. After transplantation, the median delay between transplantation and FSGS recurrence was 11 days (0–6808). For nonanuric patients (n = 11, all in the early group), mean (SD) 24-hour proteinuria before transplantation was 9.1 ± 9.1 g/24 h and 16/34 (47%) of patients were receiving an ACEi or angiotensin II receptor blocker (ARB) before transplantation (Table 1).

Overall, 26 patients (76%) showed an early recurrence and eight (24%) a late recurrence (Table 1). The characteristics of these two groups were similar except that patients with E-rFSGS were younger than those in the other group at the time of FSGS diagnosis (P = 0.005). Patients with L-rFSGS were all aged over 16 years when primary FSGS was diagnosed. Patients with E-rFSGS displayed a more symptomatic disease on native kidneys with almost all having a nephrotic-range proteinuria (96%) compared to patients in the L-rFSGS group (P = 0.01). At time of recurrence, patients in the L-rFSGS group were receiving more frequently an antiproteinuric treatment (ACEi or ARB) (P = 0.037) (Table 2).

At diagnosis on native kidneys, 31/34 patients (91%) underwent a native kidney biopsy; only eight patients had biopsies available for retrospective variant analysis. Four (50%) had a 'NOS' variant, and four (50%) a 'TIP' variant. At the time of recurrence, 29/34 patients (85%) underwent a kidney biopsy. FSGS lesions on transplant kidney biopsies were more frequent with L-rFSGS than with E-rFSGS (P = 0.006). Only five patients had biopsy slides available to compare the FSGS variant before transplantation and after recurrence.

Treatment of FSGS recurrence

Median delay between diagnosis and PE/IA was 5.5 days (range 5–155). In 29/34 patients (86%), first-line treatment included PE (n = 26) or IA (n = 3) (Table 3) and five patients did not receive any PE/IA (two out of 26 patients with E-rFSGS and three out of eight patients with L-rFSGS). PE/IA was maintained for a median of 3.3 (0.1–83) months. The mean number of PE/IA sessions was 26 ± 19 (SD) per patient. In addition, 10/34 patients (29%) received intravenous CsA + PE/IA + corticosteroid pulses + substitutive intravenous immunoglobulin (IVIg). The other patients received oral CNI. Three patients had second-line treatment with belatacept because of CNI intolerance. In total, 11/34 patients (32%) received rituximab (R) as first or second-line treatment. Moreover, PE/IA was started later in patients with L-rFSGS (median of 44 days after diagnosis [range 3–155]) than in the other group (P = 0.022).

Overall, 13/29 patients (45%) receiving PE/IA showed partial or complete remission. The mean number of PE/IA sessions to induce partial remission was significantly higher in L-rFSGS patients than in E-rFSGS patients (15 ± 9 vs. 6 ± 5; P = 0.06). After transplantation, IVIg was less frequently used for patients with L-rFSGS than E-rFSGS (25% vs 69%; P = 0.042), and patients with L-rFSGS never received cyclophosphamide.

Table 1. Characteristics of total population by delay of focal and segmental glomerulosclerosis (FSGS) recurrence after transplantation

General characteristics	Total (*n* = 34)	Early recurrence (within 3 months)	Late recurrence (after 3 months)	*P*
n (%)	34 (100%)	26 (76)	8 (24)	
Sex male/female	20 (57) / 14 (43)	15 (58) / 11 (42)	5 (62) / 3 (38)	1
Native kidney				
Age a diagnosis (y)	25 ± 15	21 ± 13	39 ± 13	**0.005**
Age at diagnosis < 16y	10 (29)	10 (38)	0 (0)	**0.07**
Nephrotic-range proteinuria at diagnosis*	23/25 (92)	22 (96)	1 (33)	**0.01**
Kidney biopsy (if available)	31 (91)	25 (96)	6 (75)	1
FSGS / MCD / other†	23 (74) / 5 (16) / 3 (10)	19 (73) / 5 (19) / 0 (0)	4 (67) / 0 (0) / 2 (33)	ns
Mesangial hypercellularity	1/20 (5)	1 (4)	0 (0)	ns
Tubular atrophy and interstitial fibrosis	10/32 (31)	7 (27)	3 (50)	0.34
ESRD < 3 years (%)	14 (41)	9 (35)	5 (63)	0.23
Evolution to ESRD, median (min–max) (y)	5 (0–27)	4.8 (0–27.5)	2.2 (0–14.8)	0.22
Transplantation				
First/second transplant	29/5 (85/15)	22/4 (85/15)	7/1 (87/13)	ns
Recurrence on a previous transplant	3/5 (15)	3 (60)	0 (0)	ns
Dialysis duration before transplant, median (min–max) (y)	2.7 (0.8–7.7)	2.3 (0.8–13)	3.8 (1.1–5.9)	0.74
Living donor	4 (12)	3 (12)	1 (13)	ns
Induction treatment: ALS / anti-IL2R / none‡	16 (47) / 16 (47) / 2 (6)	11 (42) / 14 (54) / 1(4)	5(63) / 2(25) / 1(12)	ns
Anuric at transplant, n (%)	21 (62)	14 (54)	7 (88)	
Proteinuria, mean ± SD (g/24 h)§	9.1 ± 9.1	9.1 ± 9.1	All were anuric	ns

Data are n (%) unless indicated. *P* in bold are statistically significant.

*Nephrotic-range proteinuria defined by proteinuria > 3 g/24 h or > 50 mg/kg/24 h in children, when available.

†Other: other identified cause of kidney disease except FSGS or minimal change disease (MCD).

‡No induction treatment (protocols) hr, hours; y, years; ESRD, end-stage renal disease; ALS, anti-lymphocyte serum; anti-IL2R, anti-interleukin 2 receptor.

§Nonanuric patients had pretransplant proteinuria checked.

Evolution and response to PE

Median follow-up for all patients was 5.2 years (range 0.1–22.8) (Table 4). Eleven patients had a one-year follow-up, four received a two-year follow-up, and 19 received a five-year follow-up or more. In total, among the 290 patients who received PE or IA, five (17%) and 11 (38%) achieved complete or partial remission, respectively. Thirteen patients (45%) were resistant to PE/IA. During follow-up, 6/347 patients (18%) received a second transplant; four showed rFSGS on the second transplant (data not shown).

For patients receiving PE/IA, the remission rate was comparable in the two groups. Time to remission tended to be longer in patients with L-rFSGS than in those with E-rFSGS (49 [range 30–78] vs 11 [2–35] days; $P = 0.012$). The number of PE/IA sessions needed to achieve partial remission was higher in patients with L-rFSGS (15 ± 9) than in the other group ($P = 0.06$). Complete remission was never observed with L-rFSGS. We observed mostly partial remission in the whole cohort but the response to PE/IA (resistance, partial or complete remission) did not differ between the groups (Table 4).

Within the E-rFSGS group, all patients had partial remission within the first 40 days of initiation of treatment. In the L-rFSGS group, this delay in remission had to be increased to at least 80 days, as patients responded to treatment at 30, 49 and 80 days, respectively.

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Table 2. Characteristics of total population at recurrence of FSGS

General characteristics	Total (n = 34)	Early recurrence (within 3 months) (n = 26)	Late recurrence (after 3 months) (n = 8)	P
Recurrence delay, median (min–max) (days)	11 (0–6808)	4 (0–64)	1857 (94–6808)	
Albumin level, mean ± SD (g/dl)	31.7 ± 7.1	31.3 ± 7.5	32.7 ± 6.6	ns
Proteinuria, mean ± SD (g/24 h)	10 ± 10.9	11.4 ± 12.1	5.8 ± 4.1	0.1
ACEi/ARB at time of recurrence	7 (21)	3 (12)	4 (50)	**0.037**
Kidney biopsy	29 (85)	21 (81)	8 (100)	ns
FSGS / MCD / Other*	15 (52) / 6 (21) / 8 (27)	7 (33) / 6 (29) / 8 (38)	8 (100) / 0 / 0	**0.006**
TAIF†	11 (46)	5/17 (29)	6/7 (86)	**0.04**
Variant if available: TIP / CELL / COLL / PH / NOS (n)	4/0/0/1/6	4/0/0/1/2	0/0/0/0/4	ns
Immunosuppressive treatment at time of recurrence				
Cyclosporine A	13 (38)	12 (46)	1 (12)	0.12
Tacrolimus	21 (62)	14 (54)	7 (88)	**0.12**
T0 Tacrolimus, mean ± SD (ng/mL)	10.5 ± 4.5	12.2 ± 4.5	7.6 ± 2.8	ns
T0 CsA, mean ± SD (ng/mL)	159 ± 115	164 ± 132	138.5 ± 0	ns

Data are n (%) unless indicated. P in bold are statistically significant.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; FSGS, focal and segmental glomerulosclerosis; MCD, minimal change disease; TIP, tip lesion; CELL, variant with hyper cellularity; NOS, not otherwise specified; COLL, collapsing; PH, perihilar; SD, standard deviation; T0 CsA: cyclosporine A trough level; T0 Tacrolimus: tacrolimus trough level.

*Other: other identified cause of kidney disease except FSGS or minimal change disease (MCD).

†TAI: tubular atrophy and interstitial fibrosis. The information was only available for 24 patients. TAIF was Grade 1 for 4 patients in each group and > 1 in the remaining 3 patients.

Patient and renal survival

Patient survival did not differ between the two groups as one patient died during follow-up in the E-rFSGS group, compared to none in L-rFSGS (P = ns). Graft failure leading to haemodialysis tended to occur more frequently in patients with E-rFSGS compared to patients with L-rFSGS (Table 4). Death-censored graft survival by recurrence time did not differ significantly between the two groups at one year (P = 0.21) (Fig. 2). For patients receiving PE/IA, graft survival did not differ, regardless of whether they had received rituximab after a 12-year follow-up (P = 0.14) (data not shown). There was no difference in terms of outcome, in univariate analysis, with the following treatments: belatacept (P = 0.44) and cyclophosphamide (P = 0.86) (data not shown).

Discussion

To our knowledge, this is the largest series of patients with post-transplantation rFSGS to be studied by time to recurrence, with a focus on therapeutic management. The pattern of resistance to PE/IA could be predicted by resistance at 40 days post-transplantation in the E-rFSGS group. Therefore, discontinuing PE after 40 days could be discussed with E-rFSGS patients. Patients with L-rFSGS, which is rarer, could potentially benefit from the same aggressive treatment regime but with a greater length of treatment (80 days) and an increased number of PE sessions.

Overall, we found that 52/2730 patients had a diagnosis of primary FSGS prior to transplantation. This figure could be considered low in comparison to big registry studies [2–3]. However, our figure may be more accurate as all diagnoses of FSGS were reviewed to confirm the primary status of the disease. Patients with E-rFSGS were younger at FSGS diagnosis on their native kidneys than those with L-rFSGS. Similarly, patients who were older when they developed primary FSGS were more likely to develop a late recurrence and require extended observation. To our knowledge, this is the first time that the age at diagnosis has been associated with the time to recurrence of rFSGS.

Some patients did not have a kidney biopsy at the time of rFSGS. These patients were all previously anuric and demonstrated a heavy proteinuria at day one post-transplantation, classifying as E-rFSGS. Some patients displayed minimal change disease (MCD) at time of diagnosis, and electron microscopy was not performed

Table 3. Treatment of FSGS recurrence

Recurrence treatment	Total (*n* = 34)	Early recurrence (within 3 months) (*n* = 26)	Late recurrence (after 3 months) (*n* = 8)	*P*
First-line treatment				
PE (including IA)	29 (85)	24 (92) incl. 2 (8)	5 (63) incl. 0 (0)	**0.07**
Delay to first PE after recurrence, median (min–max) (days)	5 (0–155)	5 (1–32)	44 (3–155)	**0.022**
PE duration, median (min–max) (months)	3.3 (0.1–83)	3.5 (0.183)	2 (1–2.7)	0.09
Total no. of PEs, mean ± SD	26 ± 19	28 ± 20	16 ± 9	0.34
No. of PEs for PR, mean ± SD	7 ± 6	6 ± 5	15 ± 9	**0.06**
PE discontinuation	24 (83)	20 (83)	4 (80)	ns
Cause: remission / resistance	11 (44) / 13 (56)	10 (50) / 10 (50)	1 (25) / 3 (75)	ns
Associated cause: vascular access / other (allergy, thrombosis, infection*)	3 (13) / 2 (13)	3 (15) / 2 (10)	0 (0) / 0 (0)	ns
Other treatment				
IVIg	20 (59)	18 (69)	2 (25)	**0.042**
Cyclophosphamide	6 (18)	6 (23)	0 (0)	**0.29**
Rituximab	3/34 (9)	3 (12)	0 (0)	ns
PE/IA + CsA IV + IVIg + bolus CS	10 (29)	9 (35)	1 (13)	0.38
Second-line treatment	15 (44)			
Rituximab	8 (53)	7 (27)	1 (13)	ns
Belatacept	3 (20)	1 (4)	2 (25)	ns
Other†	6 (40)	4 (15)	2 (25)	ns

Data are n (%) unless indicated. *P* in bold are statistically significant.

PE, plasma exchange; IA, immunoadsorption; incl., including; SD, standard deviation; PR, partial remission; CsA, cyclosporine A; FK, tacrolimus; IV, intravenous; CS, corticosteroids; IVIg, intravenous immunoglobulin.

*Some patients discontinued for multiple reasons.

†Other: treatment with galactose, retinoic acid, eculizumab.

routinely at the time of study. However, this did not delay the diagnosis of rFSGS as the clinical picture was evident in those patients (heavy proteinuria in a previously anuric patient) with MCD on kidney biopsy. Histological variants were present for only a small proportion of patients as both hospitals are expert transplant referral centres and the patients were not diagnosed on-site. We could not draw any conclusions on histological variants in the native kidney at time of recurrence as the information was only available in a small number of patients.

To determine whether the time to recurrence might affect patient management, patients were classified into two groups according to time of rFSGS. Recurrence was early for 76% and late for 24%. In comparison, Canaud et al. [18] observed proportions of 100% for E-rFSGS, with no L-rFSGS during the 16-month inclusion period in their prospective study. We found that five recurrences occurred beyond 16 months, which may explain this discrepancy in group distribution.

All patients who developed L-rFSGS were diagnosed with primary FSGS as adults. They were more frequently receiving an ACEi or ARB at the time of recurrence. All L-rFSGS patients exhibited FSGS lesions on kidney biopsy at the time of recurrence, but the presence of these lesions may be explained by the delay between initial symptoms and the time of the biopsy. Several studies have demonstrated that biopsies performed early after the occurrence of proteinuria show only minimal lesions [1,7,10]. In contrast, biopsies performed later after the occurrence of nephrotic-range proteinuria more often show typical FSGS lesions.

The difference in treatments between groups could be explained by the fact that late proteinuria after transplantation is often managed with nephroprotective agents such as an ACEi or ARB [34]. Less 'aggressive' treatments were received by patients with L-rFSGS: PE/IA was started less frequently and later after proteinuria. The number of PE/IA sessions required to achieve remission was higher than in the other group. This finding may be explained by the presence of fixed lesions. IVIg was also given less frequently, and none of these patients received cyclophosphamide.

Table 4. Evolution and response to Plasma exchange (PE) or Immunoadsorption (IA)

Evolution	Total (n = 34)	Early recurrence (within 3 months) (n = 26)	Late recurrence (after 3 months) (n = 8)	P
General population				
Follow-up after treatment median, (min–max) (years)	5.2 (0.1–22.8)	7.3 (0.1–22.8)	1.1 (0.4–7.4)	**0.014**
Recurrence after remission during same transplantation	3 (9)	3 (12)	0 (0)	ns
Haemodialysis during follow-up	14 (41)	11 (42)	2 (25)	**0.44**
Time before haemodialysis, median (min–max) (years)	2.8 (0.5–11.8)	1.7 (0.5–11.8)	2.8 (2.8–2.9)	0.92
Proteinuria at last follow-up, mean ± SD	2.6 ± 3.2	2.7 ± 3.6	2.4 ± 2	ns
Evolution with PE/IA at last follow-up	n = 29	n = 24	n = 5	
Remission	16/29 (55)	14/24 (58)	2/5 (40)	ns
Time to remission, mean ± SD (days)	36.5 ± 73.2	14.3 ± 11.2	52.3 ± 24.2	**0.012**
Complete remission	5/16 (31)	5/14 (36)	0 (0)	ns
Partial remission	11/16 (69)	9/14 (64)	2/5 (40)	ns
Resistance	13/29 (45)	10/24 (42)	3/5 (60)	ns

Data are n (%) unless indicated. P in bold are statistically significant.

IA, immunoadsorption; PE, plasma exchange; SD, standard deviation.

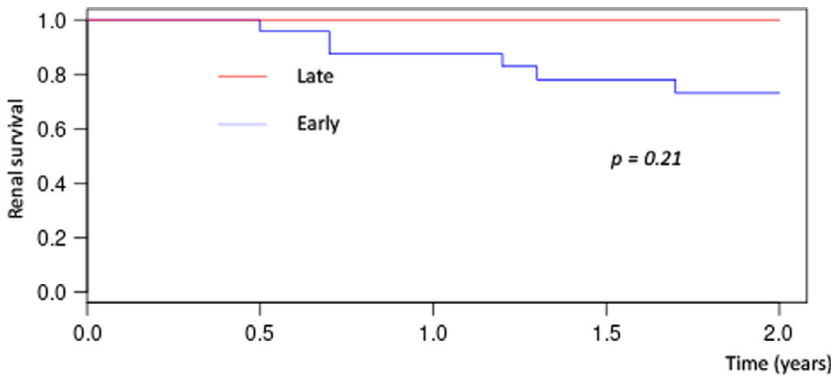

Figure 2 Death-censored renal graft survival by recurrence delay.

L-rFSGS is not a well-recognized entity, and some would argue that it does not fit with the usual 'permeability factor' physiopathology and is a difficult diagnosis, therefore doubting the usefulness of PE in this context. However, we do believe that L-rFSGS is a distinct entity and the originality of our work lies in further describing this entity and its outcomes. In our hands, patients who were offered PE were patients with a primary diagnosis of FSGS on native kidneys, who developed sudden heavy proteinuria with a kidney biopsy showing FSGS, without any features of other chronic kidney disease. In this case, rFSGS was the most likely diagnosis. Patients were treated with a high increase of steroids and higher CNI target levels, and only in the absence of any significant improvement were they treated with PE/IA.

Two patients out of five who underwent PE for L-rFSGS developed partial remission, and 2/3 patients who did not receive PE went into remission. These patients received an increase in steroids and in their CNI dose, which could explain this remission. No patients in the L-rFSGS group displayed a complication of PE. We believe that patients with L-rFSGS could benefit from the same treatment as the E-rFSGS even if the pathophysiology remains unclear.

Renal survival at one year was similar to that observed in the literature [1–3,18]. A total of 15 patients in the E-FSGS group and two in the L-FSGS group reached five years of follow-up. At five years, the transplant survival rate was only 50%, but only 10% had received the recommended treatment of IvIg, IV Cyclosporine, PE/IA and IV corticosteroids [20].

Remarkably, evolution to ESRD was slower (median 2.8 years [range 0.5–11.8]) than in previous studies (314 days in [1]) in all groups, regardless of the response to treatment and degree of proteinuria.

Therapeutic management of patients with rFSGS involves PE/IA, which is especially efficient when started immediately after recurrence. Remission is observed in most cases after 8–12 PE/IA sessions with a renal survival rate of 80% at five years [14–18]. Our data are consistent with the literature. The median time to PE/IA onset in our study was five days (range 1–155 days) [14–18]. The patient with delayed therapy (155 days) belonged to the L-rFSGS group, with a rFSGS 2.5 years after transplantation. PE/IA was started in this patient because of no improvement of proteinuria after increasing steroids and CNI. She went into partial remission under PE. The mean number of PE/IA sessions required to achieve remission was higher in our study (75 ± 6) than in other reports [14–18]. Complete remission, if present, was achieved in 36.5 ± 73.2 days. However, in the only existing controlled trial of ten patients, treatment was started within ten days of diagnosis and complete remission was observed at 23 ± 7 days [18].

The cut-off for PE/IA dependence differed for each individual, and the response to PE/IA depended on the time to recurrence. E-rFSGS patients who responded to this therapy had a quick response to PE, with a median remission at 11 days. We found that five recurrences occurred beyond 16 months, which may explain this discrepancy in group distribution.

All patients who responded in this group responded within 40 days of the initiation of treatment. All patients who were resistant did not develop remission after 40 days of treatment. Patients with L-rFSGS needed a median of 49 days (range 30–78 days) to respond to treatment with only a partial response. In addition, nine patients in the overall population who were resistant to PE/IA at month one remained resistant at month three. Therefore, the benefit of further PE/IA beyond month three for patients resistant to PE/IA treatment is still to be questioned.

In our study, we demonstrated that PE/IA can take up to 35 days to be effective in patients with I-rFSGS or E-rFSGS, but this was increased to 78 days with L-rFSGS. Therefore, treatment with PE/IA needs to be continued for at least 80 days after recurrence in patients with L-rFSGS in order to see an improvement. However, because PE and IA are aggressive treatments with potentially adverse effects (six early discontinuations in our study due to serious adverse effects such as bleeding, infection and intolerance to plasma), discussing discontinuation of PE/IA for patients who exhibit resistance seems reasonable after 40 days of treatment for E-rFSGS. For patients with L-rFSGS, the decision point to consider stopping ineffective PE/IA treatment may need to be increased. Clinicians should bear in mind that L-rFSGS can be associated with a late response to PE. However, these results need to be confirmed, ideally in future prospective studies with greater numbers. Any benefits of adjuvant treatment remain unclear, and several studies have investigated nonspecific treatments such as rituximab [21–24] or abatacept and belatacept [25–27].

In our study, additional treatment with rituximab did not improve renal survival in patients with rFSGS. However, it was used as a second-line therapy in patients with resistance to PE/IA in eight out of 11 patients who received Rituximab (72%). At this time, lesions may have already been established, which could explain its lack of efficacy. In a recent study, 13 out of 19 patients who received rituximab as first or second-line therapy achieved total or partial remission after rFSGS, with a kidney graft survival of 77.4% at five years [24]. However, the fact that no patient had late recurrence may explain the efficacy of rituximab in this cohort.

Our study was a retrospective study; as rFSGS is a rare disease, it is difficult to investigate prospectively.

The evolution did not differ between the two study groups, potentially because of the small number of patients and differences in follow-up time. Patients in the L-rFSGS group were followed for a shorter period compared to E-rFSGS. However, as this study was retrospective, and in a population showing a rare disease, we could not standardize the length of follow-up. To properly compare the groups, we decided to set up a cut-off for the survival curves at one year, which was met by 22 patients and six patients in E-rFSGS and L-rFSGS respectively.

Our study represents the largest cohort of patients with post-transplantation rFSGS used to investigate therapeutic management. The recurrence period could be incorporated into the therapeutic decision-making process. In patients with recurrence of FSGS after three months (late recurrence), the same treatment including plasmapheresis and/or immunoadsorption should be considered as in the early recurrence of FSGS.

Authorship

CD, CB, AD and MB: have participated in research design. All the authors participated in writing and correcting the manuscript. All the authors participated in the performance of the research. CD, CB, PG, AD and MB: participated in data analysis.

Transplant International 2021; 34: 302–312

Funding

The authors declare that no funding was received for this study.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. *N Engl J Med* 2011; **365**: 2398.
2. Allen PJ, Chadban SJ, Craig JC, *et al.* Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes. *Kidney Int* 2017; **92**: 461.
3. Rosenberg AZ, Kopp JB. Focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2017; **12**: 502.
4. Kitiyakara C, Eggers P, Kopp JB. Twenty-one-year trend in ESRD due to focal segmental glomerulosclerosis in the United States. *Am J Kidney Dis* 2004; **44**: 815.
5. Munyentwali H, Bouachi K, Audard V, *et al.* Rituximab is an efficient and safe treatment in adults with steroid-dependent minimal change disease. *Kidney Int* 2013; **83**: 511.
6. Guigonis V, Dallocchio A, Baudouin V, *et al.* Rituximab treatment for severe steroid- or cyclosporine-dependent nephrotic syndrome: a multicentric series of 22 cases. *Pediatr Nephrol* 2008; **23**: 1269.
7. Canaud G, Dion D, Zuber J, *et al.* Recurrence of nephrotic syndrome after transplantation in a mixed population of children and adults: course of glomerular lesions and value of the Columbia classification of histological variants of focal and segmental glomerulosclerosis (FSGS). *Nephrol Dial Transplant* 2010; **25**: 1321.
8. IJpelaar DHT, Farris AB, Goemaere N, *et al.* Fidelity and evolution of recurrent FSGS in renal allografts. *J Am Soc Nephrol* 2008; **19**: 2219.
9. Shimizu A, Higo S, Fujita E, Mii A, Kaneko T. Focal segmental glomerulosclerosis after renal transplantation. *Clin Transplant* 2011; **25**: 6.
10. Cameron JS, Senguttuvan P, Hartley B, *et al.* Focal segmental glomerulosclerosis in fifty-nine renal allografts from a single centre; analysis of risk factors for recurrence. *Transplant Proc* 1989; **21**: 2117.
11. Pardon A, Audard V, Caillard S, *et al.* Risk factors and outcome of focal and segmental glomerulosclerosis recurrence in adult renal transplant recipients. *Nephrol Dial Transplant* 2006; **21**: 1053.
12. 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**: 7.
13. Banfi G, Colturi C, Montagnino G, Ponticelli C. The recurrence of focal segmental glomerulosclerosis in kidney transplant patients treated with cyclosporine. *Transplantation* 1990; **50**: 594.
14. Hickson LJ, Gera M, Amer H, *et al.* Kidney transplantation for primary focal segmental glomerulosclerosis: outcomes and response to therapy for recurrence. *Transplantation* 2009; **87**: 1232.
15. Deegens JKJ, Andresdottir MB, Croockewit S, Wetzels JFM. Plasma exchange improves graft survival in patients with recurrent focal glomerulosclerosis after renal transplant. *Transpl Int* 2004; **17**: 151.
16. Kandus A, Ponikvar R, Buturović-Ponikvar J, *et al.* Plasmapheresis and immunoadsorption for treatment and prophylaxis of recurrent focal segmental glomerulosclerosis in adult recipients of deceased donor renal grafts. *Ther Apher Dial* 2013; **17**: 438.
17. Keith DS. Therapeutic apheresis rescue mission: recurrent focal segmental glomerulosclerosis in renal allografts. *Semin Dial* 2012; **25**: 190.
18. Canaud G, Zuber J, Sberro R, *et al.* Intensive and prolonged treatment of focal and segmental glomerulosclerosis recurrence in adult kidney transplant recipients: a pilot study. *Am J Transplant* 2009; **9**: 1081.
19. 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**: 931.
20. Sannomiya A, Murakami T, Koyama I, Nitta K, Nakajima I, Fuchinoue S. Preoperative low-density lipoprotein apheresis for preventing recurrence of focal segmental glomerulosclerosis after kidney transplantation. *J Transplant* 2018; **2018**: 8926786.
21. Sethna C, Benchimol C, Hotchkiss H, *et al.* Treatment of recurrent focal segmental glomerulosclerosis in pediatric kidney transplant recipients: effect of rituximab. *J Transplant* 2011; **2011**: 1.
22. Audard V, Kamar N, Sahali D, *et al.* Rituximab therapy prevents focal and segmental glomerulosclerosis recurrence after a second renal transplantation. *Transpl Int* 2012; **25**: 62.
23. Garrouste C, Canaud G, Büchler M, *et al.* Rituximab for recurrence of primary focal segmental glomerulosclerosis after kidney transplantation: clinical outcomes. *Transplantation* 2017; **101**: 649.
24. Alasfar S, Matar D, Montgomery RA, *et al.* Rituximab and therapeutic plasma exchange in recurrent focal segmental glomerulosclerosis post kidney transplantation. *Transplantation* 2018; **102**: 115.
25. Benigni A, Gagliardini E, Remuzzi G. Abatacept in B7-1-positive proteinuric kidney disease. *N Engl J Med* 2014; **370**: 1261.
26. Yu C-C, Fornoni A, Weins A, *et al.* Abatacept in B7-1-positive proteinuric kidney disease. *N Engl J Med* 2013; **369**: 2416.
27. Delville M, Baye E, Durrbach A, *et al.* B7–1 blockade does not improve post-transplant nephrotic syndrome caused by recurrent FSGS. *J Am Soc Nephrol* 2016; **27**: 2520.
28. Kienzl-Wagner K, Rosales A, Scheidl S, *et al.* Successful management of recurrent focal segmental glomerulosclerosis. *Am J Transplant* 2018; **18**: 2818.
29. Amer H, Fidler ME, Myslak M, *et al.* Proteinuria after kidney transplantation, relationship to allograft histology and survival. *Am J Transplant* 2007; **7**: 2748.
30. Mackensen-Haen S, Bader R, Grund KE, Bohle A. Correlations between renal cortical interstitial fibrosis, atrophy of the proximal tubules and impairment of the glomerular filtration rate. *Clin Nephrol* 1981; **15**: 167.
31. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis* 2004; **43**: 368.

32. D'Agati VD, Alster JM, Jennette JC, *et al*. Association of histologic variants in FSGS clinical trial with presenting features and outcomes. *Clin J Am Soc Nephrol* 2013; **8**: 399.
33. Thomas DB, Franceschini N, Hogan SL, *et al*. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. *Kidney Int* 2006; **69**: 920.
34. Heeg JE, de Jong PE, van der Hem GK, de Zeeuw D. Reduction of proteinuria by angiotensin converting enzyme inhibition. *Kidney Int* 1987; **32**: 78.
35. Fornoni A, Sageshima J, Wei C, *et al*. Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. *Sci Transl Med* 2011; **3**: 85ra46.