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Long-term outcome of renal transplantation in adults with focal segmental glomerulosclerosis

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Summary

Little information is available about the long-term results of kidney transplantation in adults with focal segmental glomerulosclerosis (FSGS). The outcomes of 52 renal transplants performed between 1988 and 2008 in 47 adults with FSGS were compared with those of 104 matched controls (median follow-up 93.4 vs. 109.4 months respectively). At 15 years, patient survival was 100% and graft survival 56% in FSGS patients vs. 88.3% and 64% respectively in controls (P = NS). FSGS recurred in 12 out of 52 grafts (23%) and led to graft failure in seven within 10 months (median). In the other five cases, proteinuria remitted and grafts are functioning 106 months (median) after transplantation. A second recurrence developed in five out of eight re-transplanted patients (62.5%) who lost their first graft because of recurrence; only one graft was lost. Patients with recurrence were more frequently male subjects (83% vs. 40%, $P = 0.02$), younger at diagnosis of FSGS (16.3 ± 6.8 vs. 24.1 ± 11.5 years, $P = 0.03$) and of younger age at transplantation (28.4 ± 7.8 vs. 35.8 ± 12.2 years, $P = 0.05$). Treatment with plasmapheresis plus ACE inhibitors achieved either complete or partial remission in 80% of the cases. Long-term patient and renal allograft survivals of adults with FSGS were comparable to those of controls. Recurrence was more frequent in young patients and in patients who lost a previous graft from recurrence. Graft loss resulting from a second recurrence is lower than expected.

Introduction

Focal segmental glomerulosclerosis (FSGS) is a frequent cause of end-stage renal disease (ESRD) in children and adults. As with other progressive renal diseases, kidney transplantation should represent the treatment of choice also for patients with FSGS. However, some physicians are reluctant to accept patients with FSGS for kidney transplantation, being concerned that recurrence of the original disease on the transplanted kidney, perhaps caused by circulating factors [1,2], can lead to an early graft failure. Actually, the available studies reported that 14–57% of transplanted children had a recurrence of FSGS [3–10] and about half of them eventually lost their allograft [11]. The North American Pediatric Renal Transplant Cooperative Study [12] reported a mean graft survival of <6 years in adolescents with FSGS transplanted either from living related or deceased donors. The United Network for Organ Sharing (UNOS) database [13] also showed a reduced graft survival rate for Caucasian children with FSGS when compared with other primary renal diseases.

Only a few articles have reported the outcome of renal transplantation in adults with FSGS, [14–16]. The reported risk of recurrence ranged from 34% to 48%, and again recurrence was associated with a poor graft survival.

In 1990, we reported the outcome of 24 adults with FSGS who received 25 renal transplants in our Unit from

June 1969 to June 1988 [14]. In this article, we have re-evaluated the experience in our Unit of patients with FSGS transplanted during the period between July 1988 and July 2008. The aims of this single-center retrospective analysis were (i) to evaluate the long-term patient and renal allograft survival of FSGS with those of well-matched controls, (ii) to compare the long-term renal and patient survival and the complications in these two groups, and (iii) to evaluate if the rate, the outcome and the predictors of recurrence in renal transplant recipients with FSGS have changed during the last 20 years in comparison to that reported in the previous 20 years in our Unit.

Subjects and methods

Patients

Of 1300 renal transplants (1034 from deceased and 266 from living donors) performed in our Unit between the period July 1988 and July 2008, 52 (4%) were performed on 47 adults (>18 years) with ESRD resulting from biopsy-proven primary FSGS (five patients received two renal transplants). Five patients who lost the first graft because of recurrence before this study (included in the article of Banfi *et al.* [14]), were re-transplanted after 1988. Nine patients received a graft from a living donor. Thirteen patients with secondary forms of FSGS were excluded from the study.

Patients who received a renal transplant in the same period (±3 months before or after transplantation of patients with FSGS), matched for age (±5 years), gender and source of the donor (deceased/living) were chosen as controls. Of 104 controls, 13 were carriers of autosomal dominant polycystic kidney disease, 22 had congenital urinary tract abnormalities, 44 had glomerular diseases (IgA glomerulonephritis 13 patients, membranoproliferative glomerulonephritis 9, lupus nephritis 4, Henoch-Schonlein purpura 4, crescentic glomerulonephritis 1, AA amyloidosis 1, AL amyloidosis 1, chronic nonbiopsied glomerulonephritis 11); six patients had hypertensive nephrosclerosis, one had chronic pyelonephritis, one post-partum bilateral cortical necrosis, one hemolytic uremic syndrome, three had nephronophthisis, four had Alport's syndrome, and eight patients had renal failure of unknown origin. All FSGS patients and controls were Caucasian.

Zero allograft biopsies were not performed in FSGS patients and in controls.

Definitions

Recurrence was suspected by the discovery of proteinuria and confirmed by graft biopsy. Recurrence was defined by the presence of segmental or focal glomerulosclerosis on light microscopy or diffuse effacement of epithelial foot processes on electron microscopy.

Acute rejection was diagnosed on the basis of a double-checked increase of 20% or more in plasma creatinine over the baseline which could not be explained by other causes. In patients who underwent graft biopsy, the rejection and the chronic histologic lesions were scored retrospectively according to the recently revised Banff classification [17]:

Unspecific sclerosing lesions were defined as: interstitial fibrosis with tubular atrophy and glomerular and arteriolar sclerosis, without evidence of any specific etiology.

Chronic rejection was defined by the presence of chronic allograft arteriopathy and/or chronic transplant glomerulopathy.

Severe infections: those requiring hospitalization

Arterial hypertension: supine diastolic blood pressure >90 mmHg and/or systolic blood pressure >140 mmHg in three consecutive measurements.

Plasmapheresis (PLX) was performed with a Bellco Lynda machine (Mirandola, Italy) with one plasma volume exchange per session and 5% albumin replacement: three sessions per week during the first 3 weeks followed by two sessions per week during 3 weeks and then tailored to the response.

Immunosuppression

Fifteen grafts (29%) in the FSGS group and 25 (24%) in the control group were given prednisone and cyclosporine (CsA), two patients (2.8%) in FSGS group and seven in the control group (6.7%) received CsA alone. Eighteen FSGS patients (35%) and 40 (38%) controls received a triple therapy with prednisone, CsA and azathioprine or mycophenolate mofetil (MMF). Thirteen FSGS patients (25%) and 29 controls (28%) received prednisone tacrolimus and MMF. Four FSGS patients (7.6%) and two controls (1.9%) received sirolimus plus CsA and prednisone. One patient in the control group received prednisone, sirolimus and MMF.

Acute cellular rejections were treated with intravenous methylprednisolone pulse (MPP) therapy, and acute vascular rejections with anti-thymocyte globulins.

Treatment of recurrences of FSGS

In patients at first renal transplant, the treatment for recurrence consisted of ACE inhibitors (enalapril), with the exception of one patient intolerant to these drugs who received MPP therapy. ACE-inhibitor was started at 10 mg day and progressively increased to 20 mg twice a day if tolerated. In nonresponsive patients, PLX was associated. In patients who lost their first renal transplant because of

recurrence, the treatment of the second recurrence consisted of ACE inhibitors associated with PLX, with the exception of one patient who developed severe allergic reaction to PLX and who was treated with ACE inhibitors alone. This approach was the result of the experience acquired during the management of these patients.

Statistical analysis

The statistical package S-Plus was used to analyse sample data. Means ± SDs and median and interquartile (IQ) range (25°–75° percentile) were used for descriptive analysis. *t*-Test and nonparametric Wilcoxon test were used to look at differences between the two groups of patients. Cross-tabulated data were analysed by chi-squared test, or by Fisher test when the expected cell count was <5. Survival curves were drawn using the Kaplan–Meier estimate and compared using the log-rank test.

Results

Diagnosis of FSGS was made at a median of 113 months (71.5–201.7) before transplantation. FSGS patients had been on dialysis for 40.9 months (20.2–55.9) before transplantation. No significant difference was seen in the main demographic characteristics between FSGS patients and controls. (Table 1).

Patient and graft survival

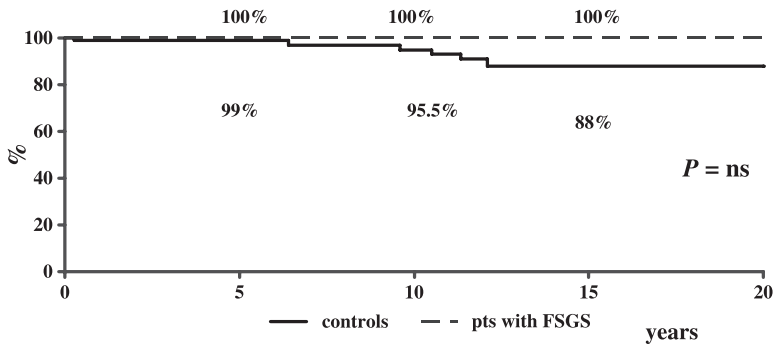
The actuarial 10- and 15-year patient survival were both 100 % in FSGS patients and 95.5% and 88.3% respectively in controls (P = NS) (Fig. 1). In the control group, six patients died, two from sepsis, the other four from cardiac infarct, cerebral thrombosis, non-Hodgkin lymphoma, and cancer respectively. In all these patients, death occurred while their grafts were still functioning with the last serum creatinine ranging between 0.7 and 3.5 mg/dl.

The actuarial 10- and 15-year graft survival were 60% and 56% in FSGS patients, and 81% and 64% in the control group (P = NS) (Fig. 2). In FSGS patients, 17 grafts were lost (32%), because of recurrence of FSGS in seven patients, chronic rejection in six, primary nonfunction in one patient, acute arterial graft thrombosis in one patient, nonadherence to therapy in one patient, and unspecific

	FSGS	Controls	*P*-value
Age (years) at transplant (mean ± SD)	34.1 ± 11.7	34.3 ± 11.6	NS
Gender (male/female)	31/21	62/42	NS
Living/deceased donors	9/43	18/86	NS
Length of dialysis, months Median (25°,75° percentile)	40.9 (20.2–55.9)	39.1 (16.1–55.2)	NS
CAPD/HD/pre-emptive transplant	2/49/1	18/84/2	NS
HCV positive/negative	6/46	10/94	NS
Follow-up post-transplant Median (25°,75° percentile)	93.4 (52.2–163.1)	109.4 (55.4–173.2)	NS
Nadir serum creatinine (mg/dl)	1.49 ± 0.63	1.37 ± 0.67	NS

FSGS, focal segmental glomerulosclerosis; CAPD, continuous ambulatory peritoneal dialysis; HD, hemodialysis.

Table 1. Demographic characteristics of renal transplant recipients with FSGS and controls.



FSGS	52	37	16	10	3
Controls	104	75	46	25	3

Figure 1 Kaplan–Meier estimates of patient survival in renal transplanted patients with focal segmental glomerulosclerosis (dashed line)and in controls (solid line). The numbers below the graphs are numbers of patients at risk at basal, at 5, 10, 15 and 20 years.

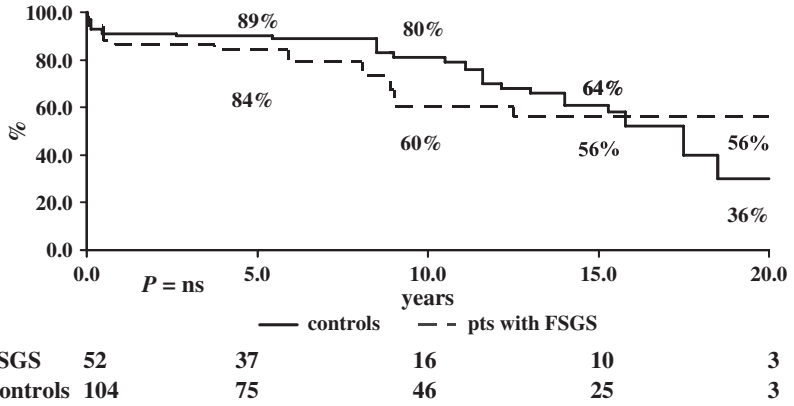


Figure 2 Kaplan–Meier estimates of renal survival probability censored for death in renal transplanted patients with focal segmental glomerulosclerosis (dashed line) and in controls (solid line). The numbers below the graphs are numbers of patients at risk at basal, at 5, 10, 15 and 20 years.

chronic lesions in one patient. Twenty-six graft failures occurred in the control group (25%). Causes of graft failure were chronic rejection in eight patients, unspecific sclerosing lesions in seven, primary nonfunctioning kidney in four, recurrence of primary glomerular disease in four, acute vascular rejection in one, acute arterial graft thrombosis in one, and irreversible acute cellular rejection in one. The actuarial 10- and 15-year graft survival censored by death was not significantly different between the two groups (P = NS, data not shown)

Post-transplant complications

The number of delayed graft functions, of acute and chronic rejections, the number of unspecific chronic lesions and of severe infections were not significantly different between FSGS patients and controls.

In addition to the 13 controls who received a graft biopsy early after transplant resulting from acute rejection (reported in Table 2), 30 other controls were submitted to graft biopsy during a median follow-up of 63.4 months (36,93) after renal transplant resulting from proteinuria in 15 cases (associated with an increase in serum creatinine in 10) and to a worsening of renal function alone in the other 15. In seven out of these 30 biopsies (23%) FSGS was observed. In these cases, focal glomerulosclerosis was the accompanying feature of: calcineurin-inhibitor toxicity in two (proteinuria 0.08 and 0.8 g/24 h), chronic rejection in two (proteinuria 0.4 and 1.8 g/24 h), unspecific chronic lesions in one (proteinuria 0.12 g/24 h), transplant glomerulopathy in one (proteinuria 7.6 g/day), and recurrence of membranoproliferative glomerulonephritis in the last case (proteinuria 7 g/day). In another patient, who developed proteinuria (2 g/24 h) after a shift from tacrolimus to sirolimus because of a parathyroid cancer, graft biopsy was not performed. Altogether 16 controls out of 104 (15.4%) developed proteinuria during the follow-up.

One of the 11 patients with nonbiopsied glomerulonephritis developed proteinuria (4 g/day) associated with rapidly progressive renal insufficiency 142 months after renal transplant. Graft biopsy showed a crescentic glomerulonephritis. None of the other 10 controls with a nonbiopsied glomerulonephritis developed proteinuria during a median follow-up of 77.7 months.

Considering FSGS grafts still functioning at the end of the follow-up (35 out of 52), the mean levels of serum creatinine and daily proteinuria were respectively 1.57 ± 0.96 mg/dl and 0.27 ± 0.34 g/24 h, not different from those of controls with functioning grafts (78 out of 104), i.e. serum creatinine 1.53 ± 0.5 mg/dl, and proteinuria 0.46 ± 0.54 g/day (P: NS).

Table 2. Main complications after kidney transplantation.

	FSGS 52 grafts	Controls 104 grafts	*P*-value
Delayed graft function ≥ 3 days	0	8	NS
Acute rejections	23 (44)	39 (37.5)	NS
Vascular rejections	7	4	
Cellular rejections	5	9	
Clinical acute rejections	11	26	
Chronic rejection	6 (11.5)	11 (10.5)	NS
Unspecific sclerosing lesions	6 (11.5)	15 (14.4)	NS
Arterial hypertension,	49 (94)	98 (94)	NS
No. patients with severe infections	26 (46)	40 (38.5)	NS

Values in parentheses are percentages.
FSGS, focal segmental glomerulosclerosis.

Outcome of transplant patients with recurrence of FSGS

In 12 out of 52 grafts (23%) of the present series, a biopsy-proven recurrence of FSGS was diagnosed in comparison to 46% recurrences (12 out of 25 grafts) observed in our Unit between 1969 and 1988 (P = 0.05) (Table 3).

Three out of 12 recurrent grafts were living related grafts. Nephrotic proteinuria developed within 1–9 days after renal transplant in nine cases, around 4 weeks in two cases, and after 11 months in the last one. Renal

Table 3. Patients with recurrence of focal segmental glomerulosclerosis in renal transplantation.

							Outcome after therapy				At last observation		
Patients	Donor	Gender	Time of recurrence	Time of biopsy (days)	S.creat mg/dl	U.Prot g/24 h	Therapy	PLX-months	S.creat mg/dl	U.Prot g/24 h	Follow-up months	S.Creat mg/dl	U.prot g/24 h
1 I	Living	M	3 Days	19	2	4.42	PLX+ACE	40	1.5	1.1	93	ESRD	4.38
2 I	Deceased	F	35 Days	75	1	6	ACE	0	1.1	0.1	240	1.9	1.66
3 I	Living	F	2 Days	47	1.6	6.75	ACE	0	2.2	1.8	99	ESRD	
4 I	Deceased	M	2 Days	28	9.5	5.8	PLX+ACE	3	3.1	14	6	ESRD	
5 II	Deceased	M	30 Days	3	2	4.5	MP+ PLX+Cy	3	2.5	2	10	ESRD	
6 II	Deceased	M	2 Days	6	1.1	4.75	PLX+ACE	9	1	1.29	73	2	0.29
7 II	Deceased	M	11 Months	6	1.46	4.32	PLX+ACE	10	1.1	0	199	1.26	0.04
8 I	Living	M	4 Days	2	1.6	7.72	MP	0	5.2	24	1	ESRD	
8 II	Deceased	M	9 Days	7	2.2	7.57	PLX+ACE	19	1.1	0.154	59	1	0.02
9 I	Deceased	M	7 Days	35	1.18	4.5	MP+ ACE	0	1.8	2.8	45	ESRD	
10 I	Deceased	M	1 Day	12	11.2	8.11	MP+ACE	0	11	9	1	ESRD	
11 II	Deceased	M	6 Days	6	1.1	1.6	ACE	0	1.2	0.6	109	1.15	0.27

I, first renal transplant; II, second renal transplant; S. creat, serum creatinine; U. Prot, urinary protein; PLX, plasmapheresis; ACE, ACE inhibitor; Cy, cyclophosphamide; ESRD, end-stage renal disease; MPP, methylprednisolone pulses; time of biopsy, time of transplant biopsy; number of days from clinical diagnosis from recurrence to graft biopsy.

biopsy was performed in median 9.5 days (range 2–75 days) after the onset of proteinuria. Segmental glomerulosclerosis on light microscopy was found in eight biopsies while in the other four cases glomeruli had normal appearance at light microscopy but diffuse effacement of epithelial foot processes on electron microscopy.

These 12 recurrences of FSGS occurred in 11 patients (patient number 8, received two grafts during this study period). Of them, six received a first renal transplant, one received a first and a second graft and four a second graft. One out of the seven first grafts (number 2) achieved full remission of proteinuria under ACE inhibitors. Fifteen years after renal transplantation mild impairment of graft function occurred followed by the development of proteinuria of around 1 g/day. A follow-up graft biopsy was performed that showed chronic rejection. The graft is still functioning after a mean follow-up of 240 months. Recurrence led to graft failure in the other six cases: in number 8 and 10, the graft ceased to function within 1 month after transplant, another graft (number 4) was lost 6 months after transplant in spite of PLX and ACE inhibitors. The last three grafts (number 1, 3, 9), all treated with ACE inhibitors associated with MPP in one and with PLX in another, achieved partial and transient remission of nephrotic syndrome and lost the function respectively 45, 93 and 99 months after transplantation. Patient 1, and patient 9 received a follow-up graft biopsy 56 months and 22 months respectively after the first biopsy. In patient 1, the second graft biopsy performed with a serum creatinine of 2 mg/dl and a proteinuria of 3 g/24 h, showed the progression of glomerulosclerosis and of tubulointerstitial lesions. In patient 9, whose basal graft biopsy showed effacement of epithelial foot processes only, the follow-up biopsy demonstrated a full-blown picture of FSGS (serum creatinine 3.7 mg/dl, proteinuria 8.22 g/24 h).

Three out of these six patients who lost the first graft because of recurrence of FSGS were re-transplanted. In one (number 8), FSGS recurred again but proteinuria remitted with PLX and ACE inhibitors. Fifty-nine months after the second transplant, the patient has normal renal function and no proteinuria. The other two grafts are still functioning 27 and 79 months respectively after the second transplant with no signs of recurrence of FSGS. At the last observation, serum creatinine was 1.4 and.1.9 mg/dl and proteinuria 0.14 and 0.20 g/24 h respectively. In the last four patients (numbers 5, 6, 7, 11) who received a second graft after having lost the first from recurrence before the commencement of this study, (included in the previous article) [14], the disease recurred again. One patient (number 5) was treated with PLX, MPP, and cyclophosphamide, but the graft was lost 10 months after transplantation. Seven months after the basal graft biopsy, this patient received a second biopsy that showed progression of glomerulosclerosis and of tubulointerstitial lesions. In the other three patients, proteinuria remitted under treatment with ACE inhibitors and angiotensin receptor blockers (ARBs) associated with PLX in two patients. Their grafts are still functioning at 199, 109 and 73 months after transplantation. Patient 7 who, at basal graft biopsy had a lesion of segmental sclerosis in one out of the 12 glomeruli was submitted to a second biopsy 32 months later when he was on complete remission (serum creatinine 1.1 mg/dl, protienuria 0.23 g/24 h). The second graft biopsy was normal at light and electron microscopy.

Table 4. Comparison of time to recurrence and of survival between the first and the second allograft in patients with recurrent FSGS in the second allograft.

	First renal allograft			Second renal allograft		
Patients	Time of recurrence (days)	Follow-up (months)	Outcome	Time of recurrence	Follow-up (months)	Outcome
5	1	4	ESRD	30 Days	10	ESRD
6	1	18	ESRD	2 Days	73	Functioning graft
7	4	28	ESRD	11 Months	199	Functioning graft
11	2	12	ESRD	6 Days	109	Functioning graft
8	4	1	ESRD	9 Days	59	Functioning graft

ESRD, end-stage renal disease.
Patients 5, 6, 7, 11 received their first allograft during the period of our previous study; patient 8 received both allografts during this study period.

The comparison of time to recurrence and survival between the first and the second allograft in patients with recurrent FSGS in the second allograft is reported in Table 4.

Altogether, in this series, seven out of the 12 grafts with recurrence of FSGS (58%) were lost, a percentage similar to the 50% observed in our previous study [14]. However in the previous study, all recurrent grafts were lost within 28 months, while in this series three out of seven grafts were still functioning 4–8 years after transplantation. The other five grafts achieved remission of nephrotic syndrome and are still functioning after a median follow-up of 106 months (range 59–240 months), while none of the recurrent grafts still functioning at the end of our previous study had achieved remission of nephrotic syndrome.

The percentage of recurrence in patients with first graft was 15% while in those with second graft was 62.5% ($P = 0.01$). Only one of the five second grafts with recurrence (20%) was lost because of recurrence. In our previous study, only one patient received a second allograft because of the loss of the first resulting from recurrence. FSGS recurred in this second graft too and the graft was lost.

Patients who developed a recurrence of FSGS were more frequently males ($P = 0.02$), younger at diagnosis of the original disease ($P = 0.03$), and younger at renal transplant ($P = 0.05$) than patients who did not develop recurrence. The duration of the original disease in the native kidney was shorter in patients who developed FSGS recurrence than in those who did not (Table 5). In our previous study, no predictors of recurrence were found although recurrent patients tended to be younger at the onset of the disease and to have a shorter duration of FSGS, when compared with those without recurrence.

Treatment with PLX led to partial (one patient) or complete (three patients) remission of nephrotic syndrome and the maintenance of graft function in 80% of patients in comparison to 33% in nontreated patients (P = NS). PLX was started within 1 week from the onset of proteinuria in three patients and within 2 weeks in two other patients and was continued with variable frequency for 3–40 months. Five out of the 10 grafts that received ACE inhibitors and/or ARB were lost as well as the other two recurrent grafts not treated with these drugs. Four out of the five patients treated with PLX plus ACE inhibitors (80%) went into complete or partial remission and maintained graft function in comparison with two out of the seven not treated (28%; P = NS).

Discussion

There is little information about the long-term outcome of adults with FSGS submitted to renal transplantation. In this series, the actuarial 15-year patient survival in patients with FSGS was 100%, confirming the findings of previous articles that reported excellent patients' survival, although with shorter follow-ups [18]. There are not many studies that have reported data on graft survival in adults with FSGS. Pardon *et al.* [16] reported a graft survival of 73% at 5 years in 33 transplanted adults with FSGS, but no comparison with a control group was made. In 27 adults followed for a mean of 70 months. Choi *et al.* [15] reported a 10-year graft survival of 41% in patients who received a graft from donors younger than 40 years, while none of the grafts from donors older than 40 years was functioning at 10 years. In this series, the actuarial 15-year graft survival was 56% in FSGS patients and 64% in controls. No difference was seen in the number of acute and chronic rejections and the risk of developing severe infections between patients with FSGS and controls. These data underline the fact that patients affected by FSGS can obtain a good graft survival even in the long term. A potential drawback of our control group is the absence of patients with diabetic- or ischemic nephropathy, diseases that represent some of the most prevalent causes of renal transplantation in adults in

Table 5. Demographic, clinical and laboratory characteristics of patients with FSGS who relapsed and those who did not.

	Grafts with recurrent FSGS: 12	Nonrecurrent grafts: 40	*P*-value
Age at diagnosis of FSGS of the recipient (years) mean ± SD	16.3 ± 6.8	24.1 ± 11.5	0.03
Age at tx (years) mean ± SD	28.4 ± 7.8	35.8 ± 12.2	0.05
Age of donors (years) mean ± SD	32.4 ± 13.5	40 ± 17.8	NS
Gender of the recipient (male/female)	10/2	16/24	0.02
Months between diagnosis of FSGS and ESRD (months) Median (25°,75° percentile)	37.5 (30.1–58.4)	56.2 (32.9–113)	0.1
Duration of dialysis (months) Median (25°,75° percentile)	45 (26.2–132.8)	39.2 (17.3–50.3)	0.04
Type of dialysis HD/CAPD/pre-emptive transplant	11/1/0	30/9/1	NS
Follow-up post-tx (months) Median (25°,75° percentile)	66 (8.9–101.1)	98.7 (98.7–163.7)	0.003
Deceased/living donors	9/3	34/6	NS
HCV positive (yes/no)	3/9	3/37	NS
Induction with Basiliximab	3	13	NS
Calcineurin inhibitors therapy	12	40	NS
Triple immunosuppression	6	27	NS
Nadir serum creat. mg/dl mean ± SD	1.4 ± 0.47	1.51 ± 0.67	NS
Arterial hypertension	12	37	NS
Acute rejection	3	20	NS
Chronic rejection grafts	1	5	NS
Unspecific sclerosing lesions	1	5	NS
No. patients with infections	4	22	NS
Final Serum creat. mg/dl mean ± SD	1.4 ± 0.37	1.6 ± 1.02	NS
Final Proteinuria g/24 h mean ± SD	0.46 ± 0.68	0.68 ± 1.4	NS
No. lost kidney	7 (58%)	10 (25%)	0.07

FSGS, focal segmental glomerulosclerosis; tx, transplant; ESRD, end-stage renal disease; CAPD, continuous ambulatory peritoneal dialysis; creat, creatinina; HD, hemodialysis.

some, though not in our patient population. Indeed, as we matched our controls for (the) age of FSGS patients, the age range of uremic patients with diabetic- or ischemic nephropathy was not included.

Recurrence of FSGS is a frequent complication in transplanted children and adults, and can lead to the loss of graft in about 50% of the patients [11]. In our previous experience [14], recurrence occurred in 12 out of 25 transplants performed between 1969 and 1988 (46%). In this series of 52 renal transplants performed 20 years later, the rate of recurrence was much lower, 23% after a mean follow-up of 103 months. As in our previous experience, the recurrences occured extremely early post-transplant, this could highlight the fact that there is likely a circulating permeability factor responsible for this process [2]. Of note, five of these 12 patients with recurrence had previously lost a first graft from recurrence, a condition considered as the greatest risk factor for recurrence in a second transplant [19–21]. If we exclude these five re-transplanted patients, the rate of recurrence on the first grafts would be only 15%. As we did not exclude any patients from transplantation on the basis of the presence of FSGS, it is possible to speculate that the more potent immunosuppression, (with more than 60% of patients receiving triple-drug therapy), may have played a role in reducing the rate of recurrence of FSGS in recent years. In this context, it is worth noting that a number of pediatric centers reported the possibility of preventing or reversing proteinuria through the use of high-dose CsA, either administered by mouth or intravenously [3,22,23]. The larger use in recent years of ACE inhibitors and/or ARB may have also been a factor in preventing proteinuria, at least in milder cases [19].

In this series, 58% of patients with recurrence lost their grafts, a percentage similar to the 50% observed in our previous study [14]. However in our previous study, recurrent grafts were lost within 28 months while in this series, three out of seven grafts were still functioning 4–8 years after transplantation. This difference can be accounted for by the more frequent use of ACE inhibitors, ARB, and/or PLX in this series. Therapy with PLX has been advocated for induction of remission of proteinuria in grafts with recurrence of FSGS with the aim of removing still unidentified circulating factors which may influence glomerular basement membrane permeability [1,2,24–26]. PLX has been employed alone or in association with ACE inhibitors [19] and with intensified immunosuppression such as cyclophosphamide [22] or high dose cyclosporine

[23,27,28]. A number of investigators concluded that PLX was ineffective or of transient benefit [1,29,30]. However, better results were obtained when treatment with PLX was given early on [31] and/or for prolonged periods [24,32]. In a review of the literature Bosch and Wendler [33] found that proteinuria could be improved and renal function stabilized in 58% of adults with recurrent FSGS. When PLX was used in a prophylactic manner immediately prior to transplantation, this decreased the incidence of recurrence to 26% in treated patients vs. 54% in controls. In this series, the use of PLX and ACE inhibitors led to a complete or partial remission of nephrotic syndrome and improved graft survival in 80% of treated patients. Treatment with PLX was started on all patients within 1 or 2 weeks after the onset of proteinuria and was continued for a minimum of 3 months and up to 40 months in one patient. We do not have any direct experience with the use of rituximab which has been recently used in recurrent FSGS with controversial results [34,35].

In this study, male gender, and younger age, both at diagnosis of the original disease and at transplant, emerged as significant risk factors for recurrence of FSGS in the graft. Young age at the onset of the disease has been associated with a higher risk of recurrence in children [3,9,36,37] but this association has never been documented in adults. In pediatric studies, a number of investigators found that the shorter the interval between the diagnosis of the original disease in the native kidney and the development of ESRD, the higher the risk of recurrence [7,19,21,37,38]. We found that the duration of the original disease from diagnosis to the development of ESRD was shorter in recurrent than in nonrecurrent patients, but the difference was not significant. In contrast to other studies [15,16], we did not find any significant differences in the age of donors between patients who developed and those who did not develop recurrences of FSGS. On the basis of these results which show a low rate of recurrence and good graft survival in the long term in transplant patients with FSGS, we do not feel justified in excluding any patients with FSGS from transplantation. However, it is our opinion that a course of prophylactic pre- and post-transplant PLX particularly in young males with rapid progression to ESRD may be able to prevent and/or delay the recurrence. In case of recurrence, our experience [39] and that of others [28] suggest that administration of ACE inhibitors along with protracted PLX treatment can induce or maintain the remission.

Authorship

GM: designed study, analysed data and wrote the article; BG, collected data; SQ: statistical analysis; GB, GM and PM: designed study.

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