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Plasma exchange improves graft survival in patients with recurrent focal glomerulosclerosis after renal transplantation

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Abstract Recurrence of primary focal glomerulosclerosis (FGS) after renal transplantation is associated with poor graft survival. Plasma exchange (PE) can reduce proteinuria and even induce complete remission of proteinuria. It is, however, unknown whether the use of PE therapy improves long-term graft survival. In our center, PE has been used to treat recurrent FGS after renal transplantation since 1994. Thus far, 13 patients have been treated with PE for recurrent FGS and followed for up to 77 months after the onset of the recurrence. We reviewed the transplantation data in these patients, and, for comparison, ten patients who underwent transplantation between 1973 and 1991 and were not treated with PE served as historical controls. Recurrence of FGS occurred within 4 weeks of transplantation in 74% of the patients. PE was started within 14 days of the onset of proteinuria in 85% of the patients. Two patients lost their graft within the first month of transplantation due to untreatable rejection; the remaining 11 patients (85%) achieved complete ($n=7$) or partial ($n=4$) remission. Seven patients remained in remission after a short period of treatment with PE (≤ 18 sessions in 2 months), whereas four patients needed prolonged treatment (median of 58 sessions). The need for prolonged PE was associated with a late (>30 days after transplantation) recurrence of FGS ($P=0.02$). A comparison with the historical control group revealed not only a significant reduction in proteinuria, but also significantly better long-term graft survival in the treated group, 85% and 30%, respectively, at 5 years ($P=0.02$). In conclusion, PE is an effective form of treatment for recurrent FGS, especially if initiated early. Failure to maintain stable remission after the initial period of PE does not necessarily imply a poor outcome, and sustained remissions can be achieved after prolonged treatment.

Keywords Focal glomerulosclerosis · Plasmapheresis dependence · Plasma exchange · Recurrent renal disease · Renal transplantation

Introduction

The reported recurrence rate of focal glomerulosclerosis (FGS) after renal transplantation averages 30% [1, 2, 3]. The risk of recurrence is even higher (50%) in patients younger than 20 years of age, in patients with a rapid clinical course of their original disease and also in patients with evidence of mesangial proliferation in their native kidney biopsy [3, 4, 5]. Recurrent FGS typically becomes manifest within 3 months of transplantation

[6, 7]. Alterations in baseline immunosuppressive regimens have not influenced recurrence rate [8, 9, 10, 11]. Prognosis is poor in patients with a recurrence, and approximately half the patients will loose their graft within 5 years [4].

Recent studies have suggested that recurrent FGS is mediated by a circulating protein factor that alters the permeability of glomeruli [3, 12]. This finding has led to the use of plasma exchange for the treatment of recurrent FGS. We and others have reported that plasma exchange treatment effectively reduces proteinuria, especially when plasma exchange is started shortly after onset of proteinuria [2, 3, 13, 14, 15, 16, 17]. Long-term results of plasma exchange are less well known.

Earlier, we published the short-term effect of plasma exchange treatment in seven patients with recurrent FGS [13]. In this paper we describe the extended follow-up of these patients, who have now been followed for up to 77 months after the onset of the recurrence. In addition, the results of plasma exchange in six more patients are reported. For comparison, we have used a group of historical controls, consisting of patients with recurrent FGS not treated with plasma exchange.

Patients and methods

In the period between 1973 and 2002 a diagnosis of recurrent FGS was made in 23 adult patients (≥17 years) who received a renal graft at our center. In 19 patients the original disease was biopsy proven FGS, but in four patients a biopsy was not available pre-transplantation. In these patients recurrent FGS was considered the most likely diagnosis because heavy proteinuria developed almost immediately after transplantation and the transplant biopsies did not disclose evidence of other glomerular diseases. A clinical diagnosis of recurrent FGS was made in the case of a rapid onset or firm increase in proteinuria of >3 g/day. The renal transplant biopsy of patients with recurrent proteinuria either disclosed glomeruli with evidence of focal and segmental glomerulosclerosis on light microscopy (LM) or normal glomeruli on LM, but evidence of effacement of the epithelial foot processes on electron microscopy [13]. In three patients with recurrent proteinuria no renal biopsy was done; however, the clinical course was compatible with a recurrence of FGS, and there was a rapid improvement of proteinuria after the start of plasma exchange.

During the study period we used different regimens of immunosuppressive therapy. From 1973 to 1983, basic immunosuppressive therapy consisted of prednisone (25 mg/day for 1 month tapered to 10 mg/day after 4 months) and azathioprine (3 mg/kg per day). From 1983 to 1985, patients were treated in a randomized study with either cyclosporin A (CyA; starting with 17.5 mg/kg per day and tapering to 5 mg/kg per day at 3 months) and prednisone for the first 3 months, followed by conversion to azathioprine and prednisone thereafter, or azathioprine and prednisone for the whole period [18]. From 1985 to 1989, all patients received CyA and prednisone during the first 3 months and azathioprine and prednisone thereafter. In the period from 1989 to 1992, patients were treated with CyA (starting with 12 mg/kg per day and tapering to 4 mg/kg per day at 3 months) and prednisone for the first 3 months and thereafter randomized for continued treatment with either azathioprine and prednisone or CyA monotherapy [19]. From 1992 to 1997, patients were treated with a combination of CyA and prednisone, and since 1997, patients have been treated in a randomized study with mycophenolate mofetil (MMF; 1 g b.i.d.), prednisone and high-dose (10 mg/kg per day) or low-dose (6 mg/kg per day) CyA [20]. Since 2000, patients have been treated with tacrolimus and MMF in combination with either prednisone or daclizumab. Patients who received an HLA-identical living, related-donor kidney were treated with different immunosuppressive regimens. Until 1985 these patients received azathioprine and prednisone. Thereafter, they were treated with CyA (starting with 12 mg/kg per day and tapering to 4 mg/kg per day at 3 months) and prednisone for the first 3 months, followed by conversion to azathioprine and prednisone.

During their hospital stay, patients' serum creatinine level and urine protein levels were measured daily. After discharge, all patients were followed weekly for the first 4 months, every 2–4 weeks thereafter, and at least every 3 months from 1 year on. At each visit, serum creatinine level and urinary protein concentration were recorded. For the purpose of this study the medical records of the 23 patients with recurrent FGS were analyzed. The following data were documented for each patient: gender, age at diagnosis of the original disease, biopsy result, time from diagnosis to end-stage renal failure, time on dialysis, age at transplantation, donor source, immunosuppressive therapy post-transplantation, time from transplantation to recurrence, proteinuria, serum creatinine, and time from recurrence to the start of plasma exchange therapy. Before 1998, the time of onset of recurrent FGS was defined as proteinuria exceeding 3.5 g/day. At that time we became aware that plasma exchange should be started as quickly as possible after onset of proteinuria. Therefore, since then, even lower values of proteinuria were considered compatible with recurrent FGS.

Since 1994, all patients with recurrent FGS have been treated with plasma exchange. Plasma exchange was performed with the CS-3000 Plus Cell Separator (Baxter, Deerfield, Ill., USA). A total of 1.5 plasma volumes were replaced per session with either fresh frozen plasma or 5% albumin. The treatment protocol consisted of daily plasma exchanges for up to 3 days. Thereafter, intensity of plasma exchange treatment was decreased, depending on the clinical response. The initial cycle of plasma exchange treatment consisted of a maximum of ten treatment sessions. In cases of relapse, plasma exchange was re-instituted and the frequency of treatment sessions was slowly reduced, based on the effect on protein excretion.

Two patients, recipients of a kidney from a living donor, received pre-emptive treatment with plasma exchange. The pre-emptive treatment regimen consisted of one plasma exchange session on the day before transplantation.

Complete remission was defined as proteinuria of less than 0.2 g/day and stable serum creatinine; a partial remission was defined as a decrease in proteinuria of more than 50% to less than 2 g/day.

Statistical analysis

The values are given as means ± SD or median (range) when appropriate. Survival probabilities were calculated with the Kaplan–Meier method. Log-rank test was used for comparison of survival curves. For comparison between groups, an unpaired t-test or Mann–Whitney U-test were used. Categorical variables were assessed with use of the χ^2-test or Fisher's exact test, as appropriate. A P value of 0.05 was considered as the level of statistical significance.

Results

A diagnosis of recurrent FGS was made in 23 patients. Ten patients, who received transplants before February

1991, were not treated with plasma exchange and served as historical controls. In Table 1 the demographic characteristics of the 13 patients with recurrent FGS who were treated with plasma exchange are compared with those of the controls. It should be noted that recurrence could not be prevented by any of the immunosuppressive protocols that were used. Four patients in the plasma-exchange group received a graft from a living donor, and three patients had already lost one or more previous renal grafts due to recurrent FGS.

In the control group, renal biopsy showed characteristic changes of FGS on LM in eight patients. In addition, there was evidence of acute interstitial rejection in two, and of a chronic vascular rejection in one of these patients. In two patients, LM showed no evidence of FGS, only changes compatible with acute interstitial rejection or cyclosporine toxicity. In both patients there was evidence of foot process effacement on electron microscopy. No patient in the control group achieved remission of proteinuria. Heavy proteinuria persisted, both in patients treated with azathioprine and in those treated with CyA. The median time between the diagnosis of recurrence and graft failure was 44 months (range 0.3–97 months). Graft failure occurred in all ten control patients.

Recurrent FGS was the sole cause of graft failure in five patients. Graft failure was due to recurrent FGS in combination with acute interstitial rejection in four patients and recurrent FGS in combination with chronic vascular rejection in one patient. Graft survival at 3 and 5 years was 70% and 30%, respectively (Fig. 1). Graft survival of the cohort of patients without FGS, aged 15–55 years, who received a first cadaveric renal graft in the same period (1973–February 1991; $n = 672$) was 65% and 59% at 3 and 5 years, respectively (Fig. 1). Thus, in the period that plasma exchange was not regularly used, graft survival was significantly lower in the patients with recurrent FGS ($P < 0.01$).

Individual data for the patients treated with plasma exchange are given in Tables 2 and 3. FGS recurred early (within 30 days of transplantation) in ten patients and late (more than 30 days after transplantation) in three patients. A renal-graft biopsy was performed in ten patients. No glomerular abnormalities were found by LM in eight patients (nos. 1, 3, 5, 7, 9–12); however, by electron microscopy, effacement of the epithelial foot processes was seen in all of them. There was also evidence of acute interstitial rejection in two of these patients (nos. 1 and 5) and acute vascular rejection in another patient (no. 10). In patient no. 2, whose biopsy showed signs of acute tubular necrosis and rejection, an adhesion was found in one glomerulus, suggestive of FGS. Patient no. 6, who was biopsied 14 days after onset of the proteinuria, had evidence of focal segmental sclerosis on LM. A renal biopsy was not performed in two patients (nos. 8 and 13) because renal function and proteinuria improved within several days of initiation of plasma exchange.

Finally, in one patient the diagnosis of recurrence was made late after transplantation (no. 4). This patient was treated with cyclosporine monotherapy. She developed mild proteinuria and a decrease in renal function. A renal biopsy revealed vascular changes compatible with cyclosporine toxicity and/or chronic vascular rejection.

Table 1 Characteristics of patients with recurrent FGS treated or not treated with plasma exchange (*PE*). Values are given as mean ± SD or as median (range) for non-parametric data. *ESRD*end-stage renal disease, *Pred* prednisone, *Aza* azathioprine, *Tacro* tacrolimus

Characteristic	Treated with PE ($n = 13$)	Not treated with PE ($n = 10$)
Gender (M/F)	8/5	6/4
Age at diagnosis (years)	27 ± 13	24 ± 12
Time to ESRD (years)	8.4 ± 8.8	7.1 ± 4.9
Age at transplantation (years)	40 ± 16	33 ± 13
1st/2nd/3rd/4th transplantation	10/1/1/1	10/0/0/0
Donor source		
Cadaver	9	10
Living related	2	0
Living unrelated	2	0
Immunosuppressive medication		
Pred/Aza	1	3
Pred/CyA	4	7
Pred/CyA/Aza	1	0
Pred/MMF/Tacro	4	0
Pred/MMF/CyA	3	0
Acute rejection (number of patients)	7	5
Onset of recurrence (days)	4 (0–2100)	9 (0–137)
Proteinuria at onset (g/day)	5.7 ± 3.9	5.8 ± 4.8
Interval recurrence to biopsy (days)	7 (2–93)	28 (0–217)
Follow-up (years)	3.4 ± 2.4	3.6 ± 2.6
Allograft loss (*n*)	2	10*
Due to recurrence	0	5*

*$P < 0.001$

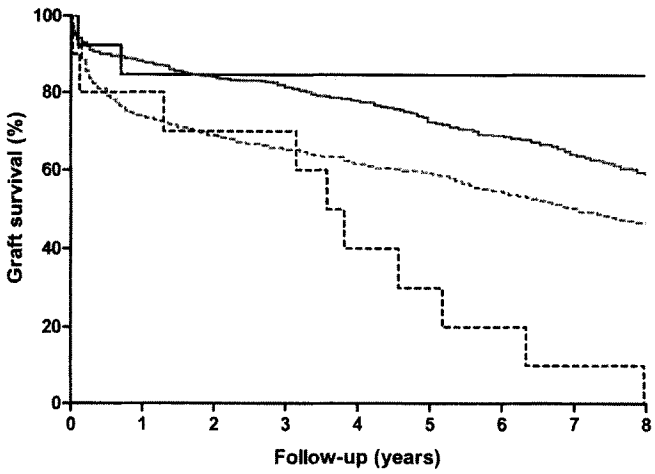

Fig. 1 Kaplan–Meier probability of graft survival in patients with recurrence of FGS who either underwent transplantation after 1991 and were treated with plasma exchange (*solid line*) or underwent transplantation before 1991 (*broken line*). For comparison, graft survival curves are depicted *in gray* for the contemporary patient cohort, who received transplants before (*broken line*) and after (*solid line*) 1991

In the glomeruli there was mesangial matrix and cell proliferation with mild influx of mononuclear leukocytes. There was mild swelling of the epithelial cells. Electron microscopy (EM) showed a focal fusion of the foot processes. Cyclosporine was replaced by azathioprine and prednisone. Shortly thereafter, a tremendous increase in proteinuria occurred, without evidence of renal function deterioration. A clinical diagnosis of recurrent FGS was made, but a renal biopsy was not done in view of the known abnormalities in the previous biopsy.

Patients with evidence of rejection in the biopsy received anti-rejection treatment consisting of oral prednisone (no. 4), intravenous (i.v.) methylprednisolone (no. 5), i.v. methylprednisolone followed by anti-thymocyte immunoglobulin (no. 1), i.v. methylprednisolone followed by oral prednisone (no. 2) or i.v. methylprednisolone followed by monoclonal anti T-cell antibody therapy (no. 10).

Plasma exchange was initiated within 14 days of recurrence of FGS in 85% of patients ($n=11$) and in the two other patients at 19 and 50 days after the onset of a recurrence. Two patients (nos. 2 and 5) lost their graft after 0.7 and 1.0 month because of concomitant biopsy-proven untreatable rejection. In all the remaining patients treatment with plasma exchange resulted in a decrease in proteinuria. Seven patients achieved sustained remission of proteinuria, either complete ($n=5$) or partial ($n=2$). Four patients suffered a relapse and needed prolonged treatment. However, after a median of 58 sessions (range 43–63 sessions) these four patients also achieved complete ($n=2$) or partial ($n=2$) remission.

Subgroup analysis of the 11 patients without graft failure showed that those with a late recurrence (> 30 days after transplantation) were more likely to need prolonged therapy ($P=0.02$). These patients also tended to be younger ($P=0.08$). During follow-up, serum creatinine has remained stable in all 11 patients. For patients treated with plasma exchange, graft survival after recurrence of FGS was as high as 85% at 5 years (Fig. 1). Graft survival was significantly better for patients who underwent plasma exchange than for historical controls ($P=0.02$). Graft survival of the cohort of patients without FGS, aged 16–69 years, who received either a renal graft from a living donor or a cadaveric renal graft in the same period (after May 1991; $n=1{,}032$) was not significantly different, with 72% at 5 years.

Discussion

Our study clearly demonstrates that patients with recurrent FGS after transplantation benefit from treat-

Table 2 Characteristics of patients treated with plasma exchange for recurrent FGS after transplantation (*ATN* acute tubular necrosis, *Tx* transplantation, *ESRD* end-stage renal disease, *CAD* cadaveric, *LRD* living related donor, *LURD* living unrelated donor, *P* prednisone, *Tac* tacrolimus)

Patient no.	Age at transplantation (years)	Gender	Time to ESRD (years)	Time on dialysis (months)	Donor source	Immunosuppressive medication	ATN	Number of Tx
1	46	Male	6.6	11	CAD	P-CyA	No	1st
2	54	Male	0	48	CAD	P-Aza	Yes	1st
3	59	Male	19.3	28	CAD	P-CyA	No	1st
4	27	Female	5.7	57	CAD	CyA	No	1st
5	37	Male	2.7	61	LRD	P-CyA-Aza	No	3rd
6	17	Male	5.2	28	CAD	P-CyA	No	1st
7	32	Female	6.0	57	CAD	P-CyA	No	1st
8	50	Female	18.4	23	LURD	P-Tac-MMF	No	1st
9	68	Male	30.2	49	CAD	P-Tac-MMF	Yes	1st
10	43	Male	1.4	242	LURD	P-Tac-MMF	No	4th
11	20	Male	7.0	29	LRD	P-CyA-MMF	No	1st
12	49	Female	4.7	29	CAD	P-CyA-MMF	No	1st
13	20	Female	2.4	90	CAD	P-Tac-MMF	Yes	2nd

Table 3 Results of treatment with plasma exchange (*PE*) (*rec* recurrence, *ESRD* end-stage renal disease)

Patient no.	Time to recurrence (days)	Proteinuria before PE (g/day)	Creatinine before PE (mg/dl)	Interval rec-PE (days)	Proteinuria after PE (g/day)	Creatinine after PE (mg/dl)	Number of PE sessions	Duration of plasma exchange (months)	Follow-up after recurrence (months)	Outcome
1	4	6.8	3.1	1	0	2.0	2	1	73	Complete remission
2	9	7.4	4.5	9	ESRD	8.5	11	1	1	ESRD
3	21	3.5	1.6	14	0.2	1.5	10	1	74	Complete remission
4	2100	13.2	2.2	50	1.3	2.3	63	45	71	Partial remission after prolonged PE
5	1	16.1	6.8	0	ESRD	6.4	13	1	1	ESRD
6	66	5.9	1.4	19	0.1	1.4	43	51	59	Complete remission after prolonged PE
7	3	6.9	2.6	6	0.5	1.7	10	1	77	Partial remission
8	1	5.7	5.3	0	0	2.1	9	1	21	Complete remission
9	26	8.3	1.9	8	0	1.6	9	1	29	Complete remission
10	0	12.7[a]	4.9	−1	1.9	2.9	14	1	29	Partial remission
11	0	4.6[a]	5.7	−1	1.6	1.3	52	37	50	Partial remission after prolonged PE
12	44	3.0	1.4	14	0.2	1.5	63	14	43	Complete remission after prolonged PE
13	5	6.5	1.4	6	0.2	0.9	18	2	9	Complete remission

[a]Proteinuria measured before second PE session

ment with plasma exchange. We have extended our previous observations that plasma exchange therapy rapidly decreases proteinuria in the majority of patients [13]. Most importantly, the beneficial effects of plasma exchange are well maintained during longer follow-up, thus improving graft survival rates in our cohort of treated patients when compared with untreated, historical controls. Admittedly, the use of historical controls introduces a bias, since, in recent years, supportive therapy and immunosuppressive treatment have changed. However, most authors would agree that outcome is poor in patients with recurrent FGS who are not treated with plasma exchange. Reported rates of graft failure in untreated patients vary from 58% to 68% in adults and from 50% to 80% in children, values comparable to the 70% graft failure rate at 5 years in our historical controls [2, 4, 9, 21, 22].

Moreover, we have compared graft survival rates of our patients with recurrent FGS with graft survival rates of patients who received transplants in the same periods. It is evident that graft survival of patients with recurrent FGS was significantly less in the period before 1991. This survival disadvantage was completely lost with the introduction of plasma exchange after 1991. This indicates that plasma exchange, and not a different immunosuppressive regimen, caused the difference in graft survival between patients treated with plasma exchange and the historical controls.

Could our results have been biased otherwise? We have included three patients in whom a diagnosis of recurrent FGS was made on clinical grounds, i.e., the rapid occurrence and incremental rise of proteinuria after transplantation. Some authors have required histological evidence of FGS in the allograft before starting plasma exchange [17, 23]. However, in early biopsies, glomerular lesions are mostly absent under LM [13, 24]. Moreover, we feel that the clinical course in patients with recurrent FGS is quite specific. Recently, Kaplan-Pavlovcic et al. [25] have also provided evidence that the development of nephrotic range proteinuria early after transplantation is sufficient to allow a diagnosis of recurrent FGS.

We have included two patients who were pre-emptively treated with plasma exchange therapy. One might argue that the inclusion of these patients may have favored the outcome data. This is unlikely, however, since these patients still developed massive proteinuria after transplantation, which necessitated further plasma exchange therapy. Also, exclusion of these patients did not alter the results. From the patients' characteristics, one might even have suspected a worse prognosis in our treated patients, since we have included patients who received a second, third and fourth transplant after having lost a previous graft due to recurrent FGS. Also, we have allowed living-donor transplantation. This demonstrates the change in our recent policy, being less restrictive in accepting patients with FGS for transplantation, in view of the potential benefits of plasma exchange therapy.

Overall, 11 patients (85%) achieved sustained remission of proteinuria (54% complete, 31% partial). Admittedly, in four of these patients repeated courses of plasma exchange therapy were needed. Young age and development of a recurrence somewhat later after renal transplantation characterized these patients. Still, it is evident that prolonged treatment is justified in view of the good ultimate outcome. The overall rate of sustained remissions in our study is quite high when compared

Table 4 Results of plasmapheresis for recurrent FGS after renal transplantation in adults and children (*NA* not available)

Author	Number of patients (*n*)	Interval recurrence to plasmapheresis (days)	Sustained remissions (%)	Prednisone part of maintenance immunosuppressive therapy?
Adults				
Artero et al. [26]	9	19 (9–91)	67	Yes
Dantal et al. [3]	9	28 (21–120)	0	No
Dantal et al. [28]	8	63 (11–292)	13	No
Matalon et al. [17]	13	60 (0–1520)	8	NA
Present study	13	6 (−1–50)	85	Yes
Children				
Cheong et al. [31]	6	NA	33[a]	Yes
Cochat et al. [29]	3	10 (7–18)	100	Yes
Dall'Amico et al. [15]	13	NA	62	Yes
Greenstein et al. [14]	6	2 (1–441)	83	Yes
Laufer et al. [16]	2	124 (86–180)	100	Yes

[a]Two children also had acute rejection, and plasmapheresis treatment was delayed for 2 months in another child

with the reported remission rates in adult patients, which range from 15% to 67%. A likely explanation for the difference in remission rates is the early initiation of plasma exchange therapy in our patient group, with treatment being started within 14 days in 85% of patients. Larger series also suggest an association between rapid initiation of plasma exchange and remission rates, since all remissions in these studies occurred in patients who were started on plasma exchange early after the onset of recurrent disease [3, 14, 17, 26]. In addition, although the onset of a recurrence cannot be prevented by any of the immunosuppressive regimens used, relapse after plasma exchange might be prevented by an immunosuppressive maintenance regimen containing prednisone.

We have recently described a patient (no. 12) who was initially managed on steroid-free immunosuppression [27]. Proteinuria recurred whenever plasma exchange therapy was reduced. Only after re-introduction of prednisone was sustained remission achieved. A review of the literature data on recurrent FGS supports the notion that prednisone must be part of the immunosuppressive therapy to achieve a sustained remission of proteinuria after plasma exchange treatment (Table 4). In addition to our study, sustained responses in adult patients have also been reported by Artero et al. [2]. In contrast, in the studies of Dantal et al. most patients suffered a relapse of proteinuria after discontinuation of plasma exchange [3, 28]. Differences in baseline characteristics and timing of initiation of plasmapheresis treatment cannot explain these differences. However, the maintenance immunosuppressive regimen was clearly different, prednisone being stopped within 60 days of transplantation by Dantal. Matalon et al. also reported a low rate of sustained remissions. In this study, however, plasmapheresis was initiated more than 30 days after recurrence in over half the patients [17]. This probably contributed to the lower rate of remission. Furthermore, the latter authors do not report the duration or dose of prednisone therapy.

Plasmapheresis treatment has been more effective in children, with over 60% achieving sustained, plasmapheresis-independent, remission of proteinuria (Table 4) [14, 15, 16, 29]. Notably, in children, plasmapheresis treatment has been accompanied by more intensive immunosuppression, either pulse solumedrol, cyclophosphamide or high-dose CyA. Furthermore, in all studies in children, prednisone has been part of maintenance immunosuppression.

In children, there is also limited evidence that recurrent FGS can be successfully treated with high-dose intravenous CyA, without the need for plasma exchange. A recently published uncontrolled study by Salomon et al. demonstrated that high-dose intravenous CyA could induce persistent remission of proteinuria in 65% of children with recurrent FGS [30]. The role of high-dose intravenous CyA in adults is unknown. Of note, we observed recurrences of FGS in 15 patients who were treated with i.v. CyA for 3 days, followed by high-dose oral CyA therapy.

In conclusion, plasma exchange therapy improves outcome in patients with recurrent FGS. For a high success rate to be obtained, plasma exchange therapy must be instituted shortly after onset of the recurrence. If a relapse of proteinuria occurs after the first course of plasma exchange, prolonged treatment is warranted. In view of the improved outcome with plasma exchange, we have adopted a less-restricted policy for transplantation in patients with primary FGS.

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