Clinical and Experimental Nephrology (2019) 23:700–709
https://doi.org/10.1007/s10157-019-01690-0

ORIGINAL ARTICLE

Successful management of post-transplant focal segmental glomerulosclerosis with therapeutic plasma exchange and rituximab

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Received: 20 December 2017 / Accepted: 2 January 2019 / Published online: 14 January 2019

Abstract

Background Post-transplant focal segmental glomerulosclerosis (FSGS) is associated with renal allograft loss. Currently, optimal treatment remains controversial.

Methods The aim of our study was to examine the efficacy and safety of therapeutic plasma exchange (TPE), and rituximab (RTX), in the management of post-transplant FSGS. The treatment protocol consisted of RTX and monthly cycles of 5 plasma exchanges for 6 months. We treated 10 transplant recipients with biopsy-proven post-transplant FSGS. Lastly, we compared the studied group to a historic control group of nine patients with post-transplant FSGS.

Results 9 out of 10 patients achieved remission after the conclusion of treatment (4 complete and 5 partial), while 1 patient did not respond to treatment. During the follow-up period, there was one graft loss and one patient died while in remission from unrelated complications. There was a significant reduction in mean uPCR between diagnosis (517.4 ± 524.2 mg/mmol) and last follow-up (87 ± 121.6 mg/mmol) in the patients with sustained remission ($p = 0.026$). There was no significant decline in eGFR in the eight relapse-free responders at the end of follow-up. (54.4 ± 16.7 from 49.8 ± 20.4 ml/min) ($p = 0.6$) An increased response rate to the combined TPE and RTX treatment was demonstrated, when compared to a historic control group of nine patients with post-transplant FSGS, as only five out of nine patients achieved remission (two complete and three partial) in that group.

Conclusions In this study, treatment with TPE and RTX appears to be safe, well tolerated and effective in the management of patients with post-transplant FSGS.

Keywords Rituximab · Transplantation · Focal segmental glomerulosclerosis · Therapeutic plasma exchange

Abbreviations

FSGS	Focal segmental glomerulosclerosis
uPCR	Urine protein creatinine ratio
eGFR	Estimated glomerular filtration rate
EM	Electron microscopy
FPE	Foot process effacement
MMF	Mycophenolate mofetil
TPE	Therapeutic plasma exchange
ESRD	End-stage renal disease
RTX	Rituximab
HAS	Human albumin solution

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Introduction

Focal segmental glomerulosclerosis (FSGS) is defined by focal segmental sclerotic glomerular lesions on histology and proteinuria [1]. FSGS has an estimated incidence of 8 cases/million/year [2, 3]. In primary FSGS, 40–60% of patients develop ESRD within 10–20 years from diagnosis.

Following transplantation, approximately 30% (range 15–50%) of patients [4–6] will have recurrence of FSGS. Outcomes of recurrent FSGS typically range from chronic proteinuria to allograft dysfunction and loss [7]. Patients with post-transplant FSGS have 52% 5-year graft survival compared to 83% in the patients without recurrence [8] and when compared to patients with recurrence of other

types of glomerulonephritis, they have double the risk of losing their graft over 10 years [9]. Currently, optimal post-transplant FSGS treatment remains controversial. Successful use of therapeutic plasma exchange (TPE) and rituximab (RTX) for the treatment of recurrent FSGS has been described only in case reports and small case series [10–14].

In the literature, 63% of adults and 70% of children will have some response to TPE [15]. TPE is thought to remove a putative plasma-permeability increasing factor, leading to reduction of proteinuria [16]. Other therapies, including high doses of calcineurin inhibitors [17], cyclophosphamide, as well as immune adsorption, have been tried with variable results [10]. Despite the absence of controlled trials, and the scarcity of prospective data [18, 19], TPE is widely employed to treat FSGS in kidney transplant recipients [20].

RTX, an anti CD-20 monoclonal antibody, is another therapeutic option for post-transplant FSGS, based on reports of successful treatment of FSGS with RTX. It has been proposed that B cells may be involved in the pathogenesis of FSGS through an abnormal cross-talk with T cells or by directly releasing a permeability factor [21–23]. A systematic review of 39 reported cases of recurrent FSGS treated with RTX showed that remission occurred in 64% of patients [24]. Recent evidence has shown that RTX can directly target podocytes in recurrent FSGS [25]. According to case series, combined treatment of post-transplant FSGS with TPE and RTX may potentiate the efficacy of both treatments [14].

In order to investigate the potential benefit of combination treatment with TPE and RTX for post-transplant FSGS, we reviewed retrospectively the outcomes of the management protocol that is currently in use in our institution.

Materials and methods

This was a study aiming to examine the efficacy and safety of TPE and RTX in the treatment of post-transplant FSGS. This was a retrospective review meeting the criteria for a service evaluation study and hence did not require approval from a Research Ethics Committee. This study was approved by the Departmental Transplant Research Group. All patients gave their consent for treatment and received standard care according to our accepted unit protocol. This therapeutic protocol for the management of post-transplant FSGS was introduced in our institution in 2011 and became the standard treatment for this clinical condition as approved by the Transplant Clinical and Research Group in our Centre. Our retrospective study is in compliance with the Helsinki Declaration.

Patients

We reviewed the outcomes of 10 adult ESRD patients who received a live or deceased donor transplant between 2010 and 2015 in our center. All the patients received a steroid-sparing immunosuppressive regimen (7-day course of steroids) with alemtuzumab induction and tacrolimus monotherapy.

Post-transplant FSGS diagnosis

Transplant recipients presenting with an increase in urine protein/creatinine ratio (uPCR) of over 100 mg/mmol, were subjected to an indication allograft biopsy. Post-transplant FSGS was diagnosed by renal histopathology, in the presence of new onset of proteinuria.

For the purpose of this study, we utilised the term post-transplant FSGS to include both patients with biopsy-proven FSGS as their primary disease as well as transplant recipients with unknown or non-biopsy proven primary diagnosis that presented with histologically proven FSGS post-transplantation which was classified as non-secondary. Non-secondary refers to the fact that cases with an identifiable potential cause for secondary FSGS were excluded, specifically, those with evidence of past or current glomerulonephritis or with past or current alloimmune transplant glomerulopathy, as well as cases with moderate or severe tubulointerstitial scarring. Foot process effacement was qualitatively described as minor (< 10% capillary loops involved), segmental (10–70%), fairly extensive (70–90%) or extensive (> 90%).

Treatment protocol

The post-transplant FSGS treatment protocol consisted of RTX (total of 2 g over 2 infusions, 2 weeks apart) and monthly cycles of 5 TPE (against 3 l of 5% human albumin) over 7 days for 6 months. During and post-treatment the patients were followed up using uPCR, renal function and lymphocyte subsets. Partial remission was defined as 50% reduction of proteinuria, and complete remission as proteinuria < 0.3 g/day or uPCR < 30. Remission was defined as sustained when continued for more than 1 year. Cameron's classification was applied to define time of recurrence: immediate (< 48 h), early (< 3 months) and late recurrence (> 3 months) [26]. A post-treatment allograft biopsy including EM was performed. Following the end of treatment, patients in complete remission with stable allograft function were actively monitored without further TPE or RTX. The management protocol is illustrated in Table 1.

Table 1 The diagnostic and management protocol

Diagnosis of post-transplant FSGS	Daily urine PCR for the first week post-transplant for all recipients and at every clinic visit for 3 months, and then monthly until month 12 If urine PCR increases ≥ 100 mg/mmol and safe to biopsy then proceed with allograft biopsy including EM If unsafe to biopsy or < 1 week post-transplant then treat empirically
Treatment of post-transplant FSGS	Total of 5 TPE over 5–7 days, monthly for 6 months 3-L plasma exchange vs 5% HAS, unless fibrinogen < 1.0 mmol/L or biopsy within 1 week (1-L FFP in this case) Rituximab 2 × 1 g 2 weeks apart. 1st dose pre-TPE and 2nd dose 14 days later
Reassessment and biopsy	Allograft biopsy after 6 months of treatment If complete remission and allograft function stable—continue to monitor If no response or partial remission consider repeating treatment for 3–6 months—cases to be discussed individually

uPCR urine protein creatinine ratio, *HAS* human albumin solution, *FFP* fresh frozen plasma, *EM* electron microscope

Statistics

Continuous variables are presented as mean ± standard deviation. For nominal or non-parametric variables, Chi square test was performed. Confidence interval was set to 95% and p was considered significant at < 0.05. Analysis was performed using SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).

Results

Patients

Ten transplant recipients (8 male) with a mean age of 51 years (range 23–67) with biopsy-proven post-transplant FSGS were treated. Demographics are shown in Table 2. Four of ten patients had biopsy-proven FSGS as their primary disease. Two of ten had unknown primary diagnosis, while the remaining four had either presumed diabetic

Table 2 Patients characteristics

Treatment	Patient	Demographics			Transplantation	
		Gender	Age at transplant	Ethnicity	Primary disease	Graft number
Combined treatment RTX–TPE	P1	f	55	Afro-Caribbean	FSGS	1
	P2	m	58	Other	DM	1
	P3	m	67	Caucasian	HTN	2
	P4	m	66	Caucasian	DM	1
	P5	m	41	Other	FSGS	1
	P6	m	57	Asian	DM	1
	P7	m	57	Asian	FSGS	1
	P8	m	49	Asian	FSGS	1
	P9	m	42	Caucasian	Unknown	1
	P10	f	23	Caucasian	Unknown	1
Historic control group	P11	m	37	Asian	DM	1
	P12	F	56	Afro-Caribbean	Unknown	1
	P13	f	71	Caucasian	FSGS	1
	P14	m	39	Afro-Caribbean	DM	1
	P15	m	64	Asian	DM	1
	P16	m	53	Caucasian	FSGS	1
	P17	f	34	Other	FSGS	1
	P18	m	59	Asian	DM	1
	P19	m	70	Afro-Caribbean	Unknown	1

DM diabetes mellitus, *HTN* hypertension, *FSGS* focal segmental glomerulosclerosis

nephropathy or hypertension as the primary diagnosis. It should be noted that P3 lost his first transplant due to post-transplant FSGS.

4/10 had early (< 3 months) and 6/10 patients had late (> 3 months) diagnosis of post-transplant FSGS. The mean time to diagnosis was 6.8 (0.1–34.6) months. 5/10 patients presented with nephrotic range proteinuria. Mean uPCR on diagnosis was 509 ± 482 mg/mmol, mean albumin 33.9 ± 4.9 mg/dl and mean eGFR 49.1 ± 19.4 ml/min.

Histopathology

All patients underwent indication kidney biopsies (mean glomeruli per biopsy sampled = 20.4 ± 11) that included tissue processed for EM (Table 3). On histology, there was no glomerulitis, peritubularcapillaritis, transplant glomerulopathy, thrombotic microangiopathy, tubulitis, vasculitis or C4d deposition. Tubular atrophy was mild (mean 8.5% of cortex, range 0–15%). The histology diagnoses included three tip lesion, one collapsing and three NOS variants of FSGS. P1, P8 and P10 were diagnosed as podocytopathies, as extensive foot podocyte effacement (FPE) was found on EM, without segmental sclerosis on light microscopy. Histopathology is summarised in Table 3. A repeat biopsy after the completion of treatment was performed in 9/10 patients (mean glomeruli sampled = 12.1 ± 6.1). In the repeat biopsies, P1, P3, P7 and P8 showed no segmental sclerosis on light microscopy (Table 3). EM was performed in 8/9 patients with a post-treatment biopsy and revealed improvement in FPE in P1, P2, P5, P7 and P9 (Fig. 1).

Treatment and outcome

All patients received treatment with at least 2 g of RTX in total and remained B-cell deplete for 6.4 ± 3.5 months. Mean time from diagnosis to initiation of treatment was 39.4 (range 2–131) days. Eight patients completed six cycles of 5TPE as intended. P4 had only one cycle of TPE, as he did not tolerate further treatment and received 4 g of RTX in total. P10 had five cycles of TPE, after which complete remission was achieved and further treatment was stopped after she developed acute obstruction due to ureteric stricture and urosepsis. P9 had an episode of line sepsis, which was treated with 2 weeks of IV antibiotics and the infected line was replaced.

Mean follow-up after FSGS diagnosis was 20 ± 9.3 months. Nine out of ten patients achieved remission after the conclusion of treatment; four patients achieved complete remission (P1, P7, P8, P10) and five partial (P2, P3, P4, P6, P9), while one patient did not respond to treatment (P5). During the follow-up period, P3 relapsed, and required dialysis, despite further TPE, at 11 months post-diagnosis. It should be noted that this was the second transplant for P3 and the second allograft lost to FSGS. P6 died from unrelated complications (cardiac cause) while still in remission, at 16 months post-diagnosis. Overall, 9/10 patients responded to treatment with 8 of them achieving sustained remission of over a year (5 partial and 3 complete) (Table 4).

There was no significant decline in eGFR in the eight relapse-free responders at the end of follow-up (54.4 ± 16.7 from 49.8 ± 20.4 ml/min) ($p = 0.6$). For the full responders there was an improvement in mean eGFR from 39 (± 24.6) to 59 (± 12.5) ml/min, although it did not reach statistical significance ($p = 0.35$) (Fig. 2). There was a significant reduction in mean uPCR between diagnosis (517.4 ± 524.2 mg/mmol) and last follow-up (87 ± 121.6 mg/mmol) in patients with sustained remission ($p = 0.026$) (Fig. 3). On review of potential predictive factors for response, the eight relapse-free responders had post-transplant FSGS diagnosed and treated earlier, at a mean of 25.7 ± 19.6 vs 79.5 ± 72.8 days ($p < 0.001$) and 3.8 ± 3.05 vs 18.9 ± 22.1 months ($p = 0.001$), respectively.

Lastly, we compared the study group to a historic control group of nine KTRs with post-transplant FSGS (Table 2). The mean time to diagnosis was longer at 13.5 (1.5–40.3) months for the historic control group. There was no difference in uPCR at diagnosis between the two groups (509.5 ± 482.4 mg/mmol vs 518.9 ± 599.9 mg/mmol, $p = 0.48$), while the control group had lower mean eGFR at diagnosis (49.1 ± 19.34 ml/min vs 31.2 ± 8.534 ml/min, $p = 0.02$). The historic group of patients received a variety of treatments; IVIG + TPE ($n = 4$), TPE ($n = 4$) or no treatment ($n = 1$). 9 out of 10 patients treated with TPE and RTX achieved remission after the conclusion of treatment (4 complete and 5 partial), while in the historic group only 5 out of 9 patients achieved remission (2 complete and 3 partial). 1 patient from each group relapsed, and ended up requiring dialysis at 11 and 24 months post-diagnosis, respectively. At 1 year post-diagnosis 8/10 patients (80%) treated with TPE and RTX were in remission (5 partial and 3 complete), while 5/9 patients (56%) from the historic group were in partial remission. In relapse-free responders there was a significant reduction in mean uPCR between diagnosis (645 ± 667 mg/mmol) and 1 year (126 ± 130 mg/mmol) in the group treated with TPE and RTX ($p = 0.026$), but not in the historic control group (777 ± 867 mg/mmol vs 152 ± 158 mg/mmol, $p = 0.17$) (Fig. 4).

Discussion

Our results suggest that first-line combined TPE and RTX treatment is safe and achieves an increased rate of remission in post-transplant FSGS. Our treatment protocol resulted in the majority of treated patients achieving sustained

Table 3 Histopathology findings in pre- and post-treatment biopsies

Patient	Histopathology									
	Pre-treatment biopsy					Post-treatment biopsy				
	Glomeruli	Segmentally sclerosed	TA (%)	Extent of FPE	Diagnosis	Glomeruli	Segmentally sclerosed	TA (%)	Extent of FPE	Diagnosis
P1	6	0	< 5	3	Podocytopathy	8	0	10	0	No evidence of podocytopathy or segmental scars
P2	10	4	< 5	1	FSGS NOS	7	1	< 5	0	FSGS NOS
P3	9	1	10	1	Collapsing FSGS	4	0	20	No EM	No evidence of segmental scars
P4	28	4	15	2	FSGS NOS	19	4	20	2	FSGS NOS
P5	18	4	15	3	FSGS NOS/recurrent	15	3	30	1	FSGS NOS/recurrent
P6	24	4	0	No EM	FSGS tip	12	1	40	3	FSGS tip
P7	41	4	15	1	FSGS NOS/recurrent	20	0	10	0	No evidence of podocytopathy or segmental scars
P8	23	0	0	2	Podocytopathy	6	1	10	2	FSGS NOS/recurrent
P9	14	2	10	1	FSGS tip	18	4	0	0	FSGS tip
P10	31	0	10	3	Podocytopathy	N/A				

Extent of foot process effacement as per a semi-quantification score of 0, 1, 2, 3 for minor (0, < 10%), segmental (1, 10–70%), fairly extensive (2, 70–90%) and extensive (3, > 90%)

EM electron microscope, *FSGS* focal segmental glomerulosclerosis, *TA* tubular atrophy, *FPE* foot process effacement

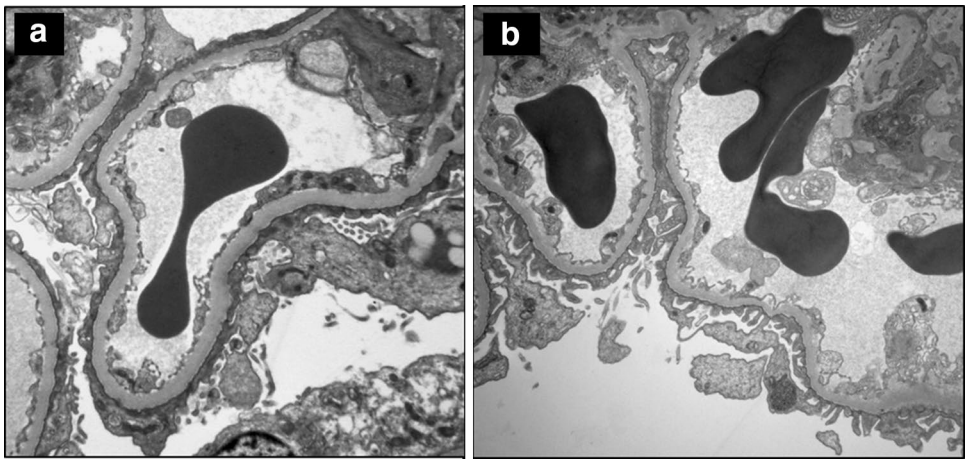

Fig. 1 EM pre- and post-treatment. Extensive foot process effacement on diagnosis in P1 (**a**), and well-preserved foot processes in P1 post-treatment (**b**)

remission without ongoing TPE treatment or augmentation of maintenance immunosuppression, strategies which has been described as successful in the literature, but can increase adverse effects. To our knowledge, none of the reported treatment protocols in the literature have achieved remission rates in excess of 60–70% [17, 27]. In our cohort remission was achieved 90% of patients and sustained remission at 1 year in 80%. Overall, our results suggest an increased response rate compared to that previously reported in the literature, with remission rates of adults receiving either RTX at 58% [24] or TPE at 63% [15].

Comparison to a historic control group of patients from our institution treated with TPE and/or IVIG showed an improved rate of remission with the combined first-line treatment of TPE and RTX. TPE and RTX as first-line treatment also resulted in a significant and sustained reduction in proteinuria, as well as preserved renal function. In a recent meta-analysis of 77 case reports and case series on treatment of post-transplant FSGS with TPE, the overall remission rate in 423 patients with outcome data was 71%. In that analysis, concurrent treatment with RTX was not statistically associated with remission, but RTX was administered in just 4.3% of cases reviewed [28]. The added effect of RTX has been recently reported in a multicenter retrospective study of 19 patients with post-transplant FSGS that received RTX in addition to TPE. Garrouste et al. showed that RTX may be beneficial for cases that have failed initial treatment or are TPE dependent [27].

In our study, combined TPE and RTX treatment proved to be safe with just 2 adverse events; P10 suffered from an episode of urosepsis on a background of complicated ureteric anatomy and P9 had blood stream infection due to line sepsis. One of the patients (P5) did not respond to treatment. P5 had 4/18 segmentally sclerosed glomeruli with extensive foot process effacement on EM. Post-transplant FSGS was diagnosed late (34.6 months) in this patient and initiation of treatment was delayed significantly due to patient's non-adherence. P3 achieved partial remission, but relapsed and eventually lost his allograft. Recurrence on a previous graft is known to be one of the most powerful predictors of relapse, and this patient lost his previous graft due to collapsing FSGS.

In our study, the diagnosis of FSGS was based on clinical presentation together with histopathology findings. Evidence of segmental or focal glomerulosclerosis on light microscopy and/or diffuse effacement of podocyte foot processes on EM were considered diagnostic for FSGS in patients with proteinuria. Patients who showed evidence of an underlying process (CNI toxicity, rejection, glomerulonephritis, extensive tubular atrophy) suggesting secondary FSGS were excluded after careful consideration at a multi-disciplinary meeting. The absence of a fully constituted FSGS lesion in P1, P8 and P10 may be due to the short natural course between the onset of proteinuria and the diagnosis. It should be also noted that foot process effacement alone was the main finding in 3/4 patients that achieved full remission. Previously published data have suggested that TPE appears to be more effective in cases where the treatment is started early, when the only finding on biopsy is foot process effacement. Our findings are consistent with this notion that TPE is more efficacious prior to the development of glomerular sclerosis on LM [29].

The rationale of our choice of treatment protocol was based on targeting two distinct pathophysiological mechanisms: the elusive permeability factor thought to cause recurrent FSGS and the stabilisation of the podocyte cytoskeleton. The exact mechanism causing post-transplant FSGS is unknown. Post-transplant FSGS is thought more likely to be caused by a circulating glomerular permeability factor (or factors) that induce podocyte injury. Supportive of this theory is that application of FSGS patient plasma to human podocytes in vitro results in rapid derangement of the cellular cytoskeleton [30]. It has been argued that the podocyte dysfunction in post-transplant FSGS could be also

Table 4 Clinical response, allograft function and proteinuria (mean ± SD or range)

Treatment	Patient	Post-transplant FSGS diagnosis (months)	uPCR at diagnosis (mg/mmol)	eGFR at diagnosis (ml/min)	Response to treatment	Relapse	UPCR at 12 months	eGFR at 12 months	Follow-up (months)	uPCR at end of follow-up (mg/mmol)	eGFR at end of follow-up (ml/min)
Combined treatment RTX–TPE	P1	1.3	235	32	CR	No	0	43	33.1	0	50
	P2	3.3	489	69	PR	No	36	78	12.9	36	78
	P3	3.3	768	31	PR	Yes	N/A	9	11.5	N/A	N/A
	P4	9.6	1700	64	PR	No	334	48	33.4	368	29
	P5	34.6	188	61	NR	No	136	41	29.1	207	9
	P6	3	370	51	PR	No	139	37	16.2	121	40
	P7	3.5	145	35	PR	No	72	40	22.5	65	48
	P8	6.8	202	74	CR	No	41	75	19	15	75
	P9	2.5	236	58	PR	No	111	70	16.2	91	53
	P10	0.1	797	16	CR	No	0	76	12	0	62
Historic control group	P11	40.3	88	26	NR	No	90	24	52.6	54	13
	P12	32.3	396	34	NR	No	319	18	13.7	291	19
	P13	6.8	521	35	NR	No	276	36	72.9	203	41
	P14	16.1	305	34	PR	No	82	21	24	82	9
	P15	13.5	425	36	CR	Yes	33	47	23.6	308	9
	P16	1.6	2070	14	PR	No	170	36	15.1	388	8
	P17	2.1	133	40	NR	No	154	37	40.1	217	4
	P18	6.2	473	39	PR	No	138	33	56.2	83	17
	P19	2.8	259	23	CR	No	29	35	61.5	54	20
Mean ± STD or range	Combined treatment RTX–TPE	6.8 (0.1–34.6)	513 ± 482.4	49.1 ± 19.4*	Responders 9/10	Relapsed 1/10	96.6 ± 103.6	51.7 ± 22.5*	20.6 ± 8.5*	100.4 ± 12.6	49.4 ± 21.7
	Historic control group	13.5 (1.6–40.3)	518.9 ± 599.9	31.2 ± 8.5*	Responders 5/9	Relapsed 1/9	150.2 ± 100.8	32.9 ± 9.2*	38.4 ± 21.9*	203.3 ± 124.6	15.8 ± 10.9

uPCR urine protein creatinine ratio (mg/mmol), *eGFR* estimated glomerular filtration rate (ml/min per 1.73 m^2), *CR* complete remission, *PR* partial remission, *NR* no response

*$p < 0.05$, **$p < 0.001$

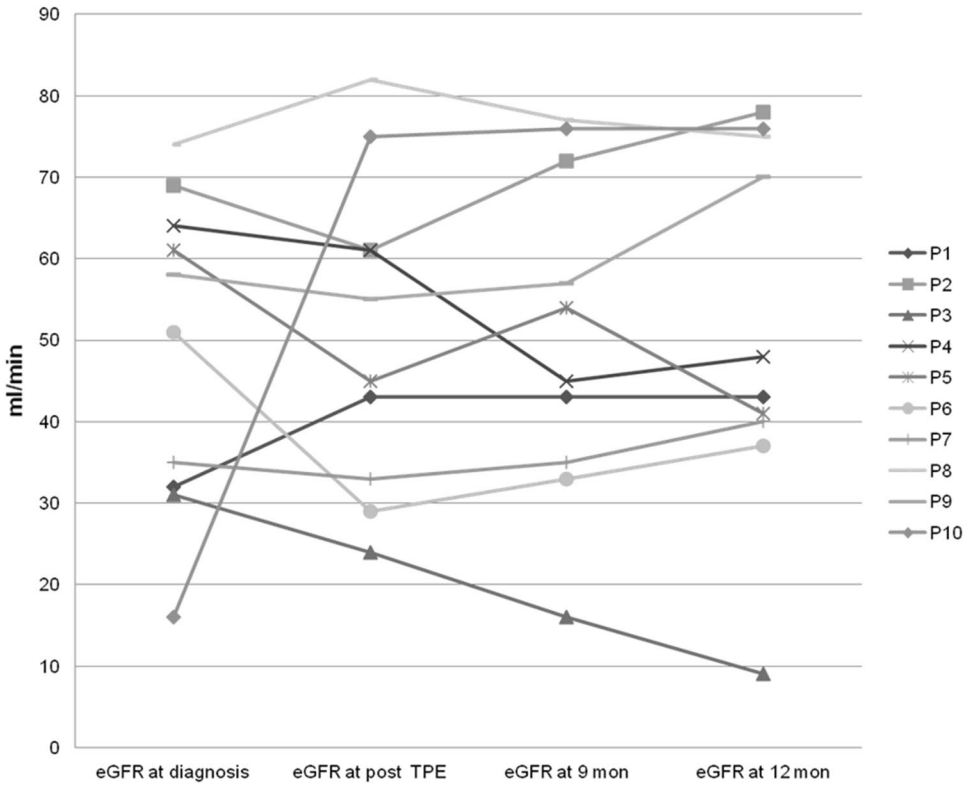

Fig. 2 eGFR (ml/min per 1.73 m^2) for the 1st year of follow-up, over time: P3 relapsed, and required dialysis despite further TPE at 11 months post-diagnosis. P5 did not respond to treatment

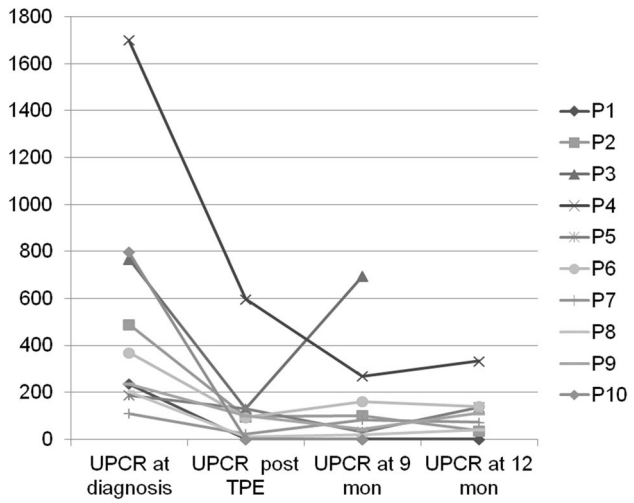

Fig. 3 uPCR (mg/mmol) for the 1st year of follow-up, over time: P1, P7, P8, P10: full remission. P2, P3, P4, P6, P9: partial remission (P3 relapsed, and required dialysis despite further TPE). P5 did not respond to treatment

due to the lack of a normal circulating factor, since replacement of FSGS plasma with normal plasma allows podocyte cytoskeleton recovery in vitro [31]. However, post-transplant FSGS is also responsive to TPE with albumin as the replacement fluid, which is supportive of the existence of a toxic circulating factor, as shown also in our study [17]. A number of potential candidates have been suggested as the toxic circulating factor, including permeability factors [32–34] and autoantibodies [35–37]. Initially, it was assumed that this factor was a T-cell derived cytokine. This proposed mechanism was based on case studies of relapsing nephrotic syndrome and T-cell malignancy that resolved following successful chemotherapy of the malignancy [38]. In support of this idea, animal studies have also indicated a possible link between this elusive circulating factor and T cells [39, 40]. More recently, serum soluble urokinase receptor (suPAR) has been implicated in the pathogenesis of FSGS and has even been proposed as a clinical marker to treatment response [32, 41, 42]. suPAR is elevated in two-thirds of subjects with primary FSGS, and patients with recurrent FSGS had higher levels of suPAR pre-transplantation and during the course of FSGS recurrence post-transplant [41, 42]. However, suPAR is elevated in all patients with chronic kidney disease and not just patients with FSGS. Recent evidence has shown that RTX can directly target podocytes in recurrent FSGS. Fornoni et al. have demonstrated that RTX can bind to molecules expressed in human podocytes, such as SMPDL-3b, a protein that is down-regulated upon in vitro exposure of podocytes to sera of FSGS patients. This effect on SMPDL-3b (a protein implicated in actin remodeling) can be reversed by RTX [25].

Our study has limitations. Firstly, this is a retrospective study. In addition, because of the small number of patients, we were not able to comment on predictors of response to treatment.

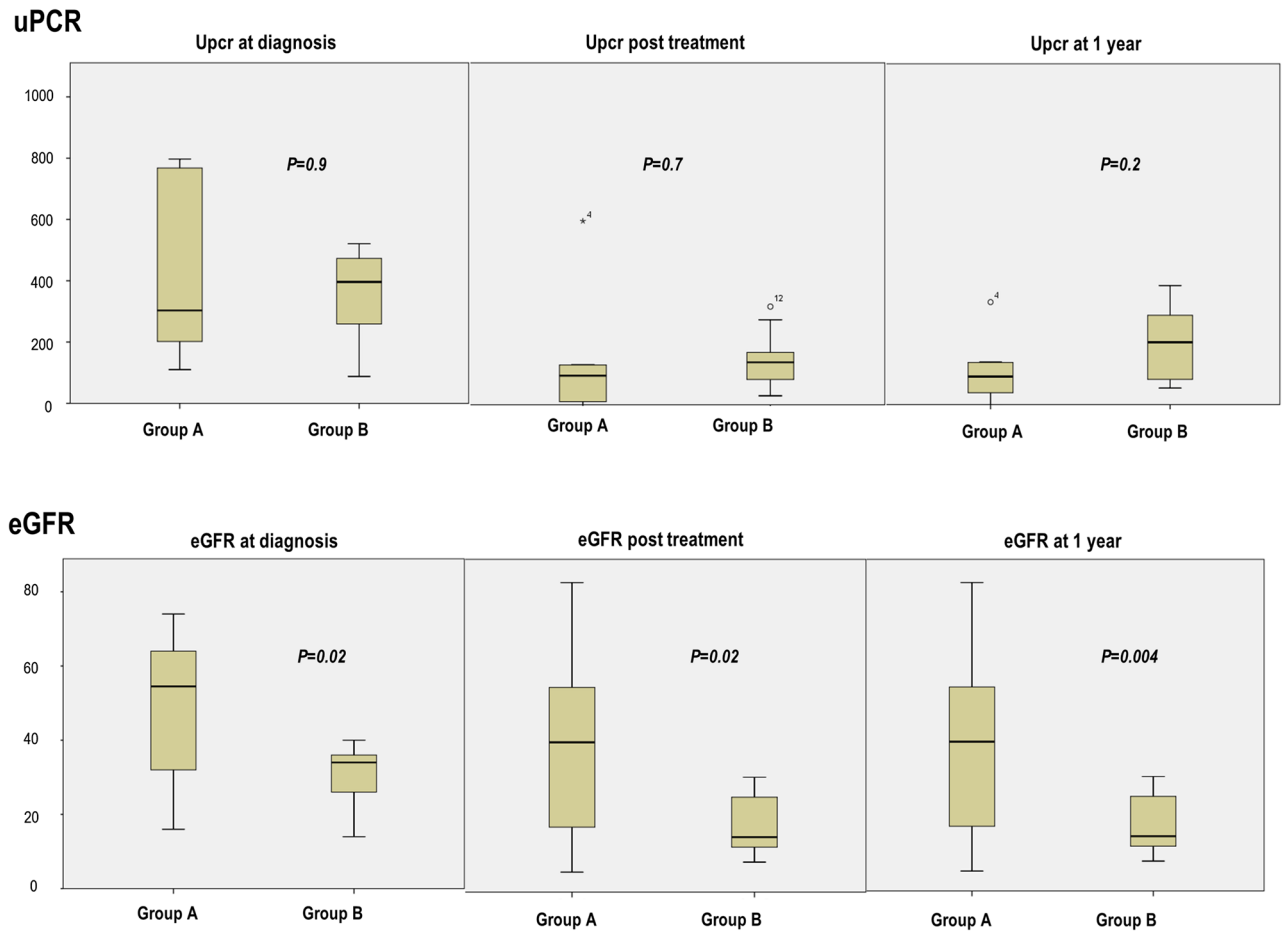

Fig. 4 Box plots for uPCR (mg/mmol) and eGFR (ml/min per 1.73 m^2) at diagnosis, post-treatment and at 1 year post-diagnosis. Group A: KTRs treated with TPE and RTX, group B: historic control group

In conclusion, this study shows that combined first-line treatment with RTX and TPE can have a beneficial effect on post-transplant FSGS in adult kidney transplant recipients. These promising preliminary results will have to be confirmed in a larger population and over a longer follow-up but may provide a basis for effective treatment for this challenging condition.

Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

Research involving Human Participants and/or Animals This article does not contain any studies with human participants or animals performed by any of the authors. This was a retrospective review meeting the criteria for a service evaluation study and hence did not require approval from a Research Ethics Committee. This study was approved by the Departmental Transplant Research Group. This therapeutic protocol for the management of post-transplant FSGS was introduced in our institution in 2011 and became the standard treatment for this clinical condition as approved by the Transplant Clinical and Research Group in our Centre. Our retrospective study is in compliance with the Helsinki Declaration.

Informed consent All patients gave their consent for treatment and received standard care according to our accepted unit protocol.

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