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Recurrent Primary Focal Segmental Glomerulosclerosis Managed With Intensified Plasma Exchange and Concomitant Monitoring of Soluble Urokinase-Type Plasminogen Activator Receptor–Mediated Podocyte β 3-integrin Activation

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Abstract

Background—Primary focal segmental glomerulosclerosis (FSGS) often causes nephrotic proteinuria and frequently results in end-stage renal disease and recurrence after kidney transplantation. Recent studies describe soluble urokinase-type plasminogen activator receptor (suPAR) as a circulating factor implicated in FSGS.

Methods—This single-center study included 12 adult patients with histologically proven primary FSGS (n = 2) or recurrent FSGS after transplantation (n = 10). The effect of plasma exchange (PE) on clinical outcome, suPAR levels, and in vitro podocyte β 3-integrin activation was investigated over a median of 11 (6–18) sessions of PE.

Results—The course of treatment was monitored in a total of 70 sessions of PE, which partly eliminated suPAR, with a mean reduction of $37 \pm 12\%$ of serum concentration per session. However, a substantial rebound was observed between sessions, with suPAR levels reaching $99 \pm 22\%$ of the pretreatment levels after a median of 4 days. Podocyte β 3-integrin activation dropped significantly after PE but rebounded within 4 days concomitant with a rising suPAR level. In 11 of 12 patients, multimodal treatment (including extensive PE) reduced proteinuria significantly (from 5.3 [2.0–7.8] to 1.0 [0.4–1.6] g/d), indicating clinical efficacy of the therapy. One patient suffered

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allograft loss due to FSGS recurrence. A persisting response was independent of a lasting reduction in the level of total suPAR because there was no sustained significant change in suPAR levels before and after the course of intensified treatment (3814 ± 908 to 3595 ± 521 pg/mL; $P = 0.496$).

Conclusions—We conclude that multimodal therapy including extensive PE was associated with stabilization of recurrent FSGS and a temporary lowering of plasma suPAR as well as podocyte $\beta 3$ -integrin activation. Whether a sustained lowering of total suPAR results in further improved outcomes requires additional study.

Primary focal segmental glomerulosclerosis (FSGS) is the most common primary glomerular disorder causing end-stage renal disease in the United States. Initial therapy with steroids leads to a response rate greater than 50%, but relapses, steroid-resistant disease, and recurrence of FSGS after kidney transplantation are common. Approximately 40% of transplanted patients with primary FSGS develop recurrent disease in the graft and there is a poor graft survival rate in these patients.¹⁻⁴

The pathophysiological cause of primary and recurrent FSGS is still not completely identified, but a circulating factor is suspected to play a major role in the loss of podocyte structural integrity leading to podocyte foot process effacement, disruption of glomerular barrier function, and nephrotic proteinuria.^{5,6} Recent studies describe soluble urokinase-type plasminogen activator receptor (suPAR) as a candidate circulating factor in patients with FSGS. The suPAR is the soluble form of the urokinase type plasminogen activator receptor and can present with different domain forms.⁷ Total suPAR levels in plasma⁸ and urine⁹ are elevated in patients with FSGS, and high serum levels may be associated with recurrence in transplanted kidneys.¹⁰ The suPAR binds to and activates $\beta 3$ integrin on podocytes.⁸ Active $\beta 3$ integrin acts as a downstream effector for increased podocyte motility causing foot process effacement and proteinuria.¹¹ Decreases of serum suPAR and $\beta 3$ -integrin activation after plasma exchange (PE) were associated with reduction in proteinuria in these studies.^{11,12} The cellular source as well as the precise forms of suPAR that induce pathological podocyte integrin signaling are currently under intense investigation. Data also support the notion that suPAR can potentiate its effects in the presence of autoantibodies against CD40.¹³ Thus, specific suPAR removal might be a potential new therapeutic target for FSGS.^{8,10,11}

The treatment of patients with recurrent FSGS is challenging and not well established. Based on the strategy to remove circulating factors relevant to FSGS, PE is an accepted treatment for patients with disease recurrence used in most centers.^{14,15} Clinical observations found PE to be associated with rapid resolution of podocyte foot process effacement^{10,16} and a reduction of urinary protein excretion. However, not all patients achieve complete remission with PE alone and additional immunosuppressive drug therapy seems to further increase remission rates.^{12,17-19} Besides steroids cyclosporine A (CsA), mycophenolate mofetil (MMF), Tacrolimus (Tac), and Rituximab are options for second-line immunosuppressive drug therapy.²⁰⁻²³

The aim of this study is to evaluate the effects and efficacy of suPAR elimination by PE in the largest patient group studied thus far. We also investigated the clinical course as well as

the correlation of serum suPAR levels to podocyte $\beta 3$ integrin activation and to the clinical outcome during recurrent FSGS.

PATIENTS AND METHODS

In this single-center study, 12 adult patients with histologically proven primary FSGS in the native kidney ($n = 2$) or FSGS recurrence in the transplanted kidney ($n = 10$) were included between January 2012 and October 2013. All 12 patients were treated with PE during the course of treatment. The ethics committee of the Charité-Universitätsmedizin Berlin approved the study. The study complied with the Declaration of Helsinki. All patients had renal biopsies available at time of diagnosis of FSGS or FSGS recurrence.

In all 10 patients with recurrence of FSGS after transplantation, the diagnosis was defined by a repeated proteinuria greater than 1 g/d measured by 24-hour urine collection and was confirmed in all cases by histopathologic changes consistent with FSGS on light microscopy. These included focal segmental glomerular capillary sclerosis, activation of visceral podocytes, and adhesion of sclerotic lesions to the Bowman's capsule. Histological features of immunocomplex deposition associated glomerulitis have been excluded by immunofluorescence microscopy. Focal segmental capillary sclerotic lesions secondary to hypertension or calcineurin inhibitor toxicity have been clinically ruled out. In 7 patients, electron microscopy was performed, which in all cases showed typical diffuse or segmental effacement of foot processes.

The delay of the diagnosis of recurrence after transplantation ranged from 0 to 91 months (median, 9 months). At the time of diagnosis, the mean proteinuria was 3.5 ± 2.0 g/d, mean creatinine was 2.1 ± 0.8 mg/dL. The median delay of the beginning of PE treatment after increasing proteinuria was 1.3 (0.4–2.8) months.

Each PE consisted of 2.5 L plasma volume that was pheresed before replacement with 4% human albumin. The corresponding mean ratio of total plasma pheresed in each session was 0.79 ± 0.17 .²⁴ Patients received variable courses of PE according to the response in proteinuria. Treatments were started 3 times weekly in all patients and then tapered according to the clinical response. After reaching remission of FSGS, maintenance of PE treatment continued according to the response in proteinuria and individual course resulting in a median total number of 21 (8–45) PE sessions. Duration of the full treatment course ranged from 14 days to 15 months.

Seven of the patients with FSGS recurrence after kidney transplantation received additional initial treatment according to the “Multiple Target Treatment” described by Canaud et al.²³ These patients received concomitantly high-dose steroids, intravenous CsA for 14 days followed by oral CsA therapy, MMF and a modified intensive and prolonged course of PE. The other transplanted patients received steroids + MMF and calcineurin-inhibitor therapy (CsA or Tac) as regular immunosuppressive drug therapy. Five of the transplanted patients with FSGS recurrence, and 1 patient with primary FSGS received Rituximab earlier during the course of treatment. The other patient with primary FSGS received additional oral therapy with CsA (Table 1).

The mean age was 44 ± 14 years, 8 patients were men (67%). In the 10 transplanted patients, the median time since transplantation was 12 months. The median baseline creatinine before therapy was 2.0 (1.4–3.1) mg/dL, median proteinuria 5.2 (1.6–7.3) g/d before the start of PE. The patients underwent a median of 11 (6–18) sessions of PE until they reached remission.

The effect of each PE session on serum suPAR concentration was analyzed where suPAR samples before and after PE were available until remission was achieved. In addition, the clinical course, proteinuria, C-reactive protein (CRP), and creatinine were prospectively monitored during the course of treatment. The suPAR levels were measured by using the Quantikine Human urokinase type plasminogen activator receptor immunoassay (R&D Systems, Minneapolis, MN). The activation of $\beta 3$ -integrin was measured using the activation epitope-recognizing antibody AP5.²⁵ In brief, fully differentiated cultured human podocytes are treated with 5% patient serum for 24 hours. Thereafter, the cells are fixed with 4% paraformaldehyde and proceeded for immunofluorescence staining for AP5 (Blood Center of Wisconsin) and paxillin (Millipore). After immunostaining, confocal (Leica) images are acquired to quantify the AP5 and paxillin intensity for each treatment. Paxillin signal is used to correct AP5 signal and limit it to focal adhesions. The relative AP5 signal (AP5/paxillin ratio) from each patient's serum is normalized against that of normal blood donors.

Patient cohort characteristics and parameters were calculated as mean (and standard deviation) or, in case of non-parametric distribution of metric variables, as median (and interquartile range). Differences were tested using *t* tests for independent samples in case of normally distributed variables, using Mann-Whitney *U* tests for skewed variables. Significance level was $\alpha = 0.05$. Statistical analysis was performed with SPSS 22 for Windows (SPSS Inc.).

RESULTS

The suPAR levels were consecutively measured in a total of 70 PE sessions before PE, after PE, and again after a median of 4 (2–14) days in patients with FSGS recurrence after transplantation ($n = 10$) or primary FSGS ($n = 2$). Each session of PE therapy effectively lowered the suPAR level from 3373 ± 1035 pg/mL to 2089 ± 686 pg/mL ($P < 0.001$) which corresponds to $37 \pm 12\%$ reduction. A substantial rebound effect was observed later, with suPAR levels reaching a mean of 3300 ± 882 pg/mL ($99 \pm 22\%$ of the pretreatment levels) after a median of 4 days (Figure 1A).

To gain further insights into the pathogenicity of suPAR in these patients, we evaluated the activity of $\beta 3$ -integrin on cultured human podocytes incubated with the patient's sera using an activation epitope-recognizing antibody AP5 (herein referred to as AP5 level).²⁵

The influence of PE on activation of $\beta 3$ -integrin was analyzed in 70 PE sessions. Each session lowered the AP5 level from a mean of 1.36 to 1.14 ($P = 0.027$). The influence of PE on the rebound of $\beta 3$ -integrin activation after treatment was determined in 42 corresponding PE sessions. Each session of PE significantly lowered relative AP5 level to a mean of $84 \pm 22\%$ of the pretreatment levels. After a median of 3 days, however, a rebound reaching a median of 94% (77%–115%) of the pretreatment levels was observed (Figure 1B).

To evaluate the impact of the intensity of PE treatment on the rebound of suPAR, we analyzed suPAR after PE treatment with different intervals. The rebound effect occurred independently of the intensity of PE therapy. Even the most intensive regimen of PE (three sessions per week) was accompanied by a rebound effect of $96.8 \pm 20.1\%$ compared to values before treatment (Table 2). This rebound persisted even after more than 4 weeks of intensive treatment.

There was no significant correlation between proteinuria and suPAR levels at time of diagnosis ($r = -0.467$; $P = 0.174$). In 11/12 patients, suPAR levels could be lowered significantly and FSGS recurrence could be effectively treated as indicated by a significant decrease of proteinuria after a median of 11 (6–18) sessions of PE.

One patient suffered terminal allograft loss due to FSGS recurrence despite intensive treatment (“multiple target treatment”²³ and rituximab). This patient had undergone his fourth kidney transplant. All previous graft losses were due to FSGS recurrence. In this case, the patient was already an-uric before start of treatment, and despite all treatment efforts, he continued regular dialysis 4 months after transplantation. The patient had a total suPAR plasma level of 6667 pg/mL before the start of treatment, at the end of the treatment course, the level was 5706 pg/mL, and it decreased to a level of 3431 pg/mL during the follow-up of 4 months without renal function.

Five patients (42%) achieved complete remission, 6 patients (50%) achieved partial remission during the PE treatments over a median of 3 (1–10) weeks. Given the rebound phenomenon of plasma suPAR levels, the significant decrease of proteinuria in the 11 successfully treated patients (from 5.3 [2.0–7.8] g/d to 1.0 [0.4–1.6] g/d) was accompanied by a temporary but not sustained decrease in suPAR levels after the course of treatment (3814 ± 908 pg/mL to 3595 ± 521 pg/mL, $P = 0.496$) (Figure 2). The decrease in suPAR levels in patients with complete and partial remission after the course of treatment was 3574 ± 894 pg/mL to 3389 ± 232 pg/mL and 4014 ± 951 pg/mL to 3766 ± 650 pg/mL, respectively. Median CRP levels remained low (before treatment 0.6 (0.4–2.3) mg/L after treatment 0.9 (0.3–4.1) mg/L), and baseline-creatinine did not change significantly during the full course of treatment (before treatment, 1.7 [1.4–2.8] mg/dL; after treatment, 1.9 [1.3–2.2] mg/dL, $P = 0.949$) in these 11 patients, suggesting that suPAR levels were not elevated due to a severe decrease in estimated glomerular filtration rate.²⁶

DISCUSSION

In this prospective observational study, we followed up 12 adult patients with FSGS during the treatment course including extensive PE. We found that serum suPAR concentrations which have been linked to FSGS pathology are elevated in FSGS recurrence and can be eliminated effectively by PE. However, the suPAR lowering effect was limited to a 38% reduction of suPAR levels over a single PE session. A significant rebound effect was noted with suPAR concentrations returning to the pretreatment range within days, even during the most intensive PE regimens. Interestingly, lowering of suPAR was associated with a significant reduction in podocyte AP5 levels, suggesting that suPAR drives pathological podocyte $\beta 3$ -integrin activation. Our findings of high suPAR levels during FSGS recurrence

are in line with Alachkar et al¹⁰ and Morath et al²⁷ but in contrast to those by Harita et al.²⁸ Nevertheless, 92% of the patients achieved complete or partial remission using a multimodal therapeutic approach (including extensive PE). Renal function remained stable, and a significant improvement of proteinuria was observed, suggesting that temporary lowering of suPAR-mediated podocyte β 3-integrin activity may have been beneficial in a subset of these patients.

It has been reported that high serum levels of suPAR are predictive of FSGS recurrence in renal grafts and that lowering the levels of suPAR by PE was associated with disease remission.^{8,10} A single patient report also pointed out that preservation of GFR and periodic lowering of proteinuria can be achieved by repetitive PE or immunoadsorption that also lowered suPAR temporarily and in part.²⁷ In support of this previous report, we also did not find the necessity for a treatment response to be associated with sustained lowered suPAR concentrations. Nevertheless, the phenomena of rebound in suPAR levels and β 3-integrin activity might warrant further study in the long-term prognosis of the disease.

Previous studies have shown that suPAR can interact with β 3 integrin. It was shown that high suPAR levels may induce podocyte injury via activating β 3 integrin in cultured human podocytes.^{8,9,27} To better assess if suPAR lowering in our patient cohort was resulting in podocyte health, we performed analyses on podocyte β 3-integrin activation using AP5 antibody. Generally, a lowered suPAR level was associated with a significant temporary reduction in podocyte β 3-integrin activity that was lost on rebound of suPAR levels. A temporary normalization of podocyte structure as a consequence of normalized integrin activity may allow podocytes to promote healing which may underlie the improvements seen in our cohort. Clearly, more work is required to understand how β 3 integrin deactivation and podocyte effacement work in detail. The combination of suPAR level and AP5 reactivity may provide a useful combination approach to monitor treatment response in future analyses. Moreover, AP5 staining in kidney biopsies could provide additional information.⁸

A declining renal function is a confounder for the interpretation of suPAR levels because of an inverse correlation between serum suPAR levels and estimated GFR.^{29,30} In the study by Wei et al,¹¹ suPAR levels were assessed in patients with normal or mildly reduced renal function. In this study, median suPAR levels, before the start of PE and even after the successful treatment of FSGS recurrence, exceeded the threshold value (3000 pg/mL) obtained in FSGS patients with normal or mildly reduced renal function.¹¹ This observation suggests that suPAR level could be used in combination with podocyte integrin activity assays particularly in recurrent FSGS.

Of note, not all individual cleaved suPAR forms as well as alternative transcript variants⁸ are equally recognized by suPAR enzyme linked immunosorbent assay, and not all forms may cause the same degree of renal disease.³¹ It is possible that the suPAR causing a podocytopathy, such as FSGS, is of a different type than the one that is elevated in conditions of inflammation. It is known that total suPAR levels correlate with CRP levels in conditions of inflammation.³² Systemic inflammation and/or change in renal function as potential confounders can be excluded in our study as median CRP levels remained low and baseline-creatinine did not change significantly during the full course of treatment.

CONCLUSIONS

Temporary PE is an effective therapeutic intervention in a majority of patients with recurrent FSGS. Effectiveness is paralleled by a temporary reduction in plasma suPAR and podocyte β 3-integrin activation. A significant rebound of suPAR and podocyte β 3-integrin activation occurs within 4 days even during the most intensive regiment of PE.

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FIGURE 1.

Reduction and rebound of suPAR and relative AP5 levels during plasma exchange. A, suPAR measured before, directly after, and again after a median of 4 days in each of $n = 70$ sessions. B, Relative AP5 levels measured before, directly after, and again after a median of 3 days in each of $n = 42$ sessions.

FIGURE 2. Change of proteinuria (A) and suPAR (B) of successfully treated patients ($n = 11$) before and after the course of treatment until remission after 3 (1–10) weeks.

TABLE 1**Patient characteristics (n = 12)**

Mean age, y (SD)	44 (14)
Male, n	8 (67%)
Primary FSGS in the native kidney, n	2 (17%)
Recurrent FSGS in the allograft, n	10 (83%)
Median no. of transplants (IQR) ^a	1 (1–3)
Median creatinine before PE therapy, mg/dL (IQR)	2.0 (1.4–3.1)
Median proteinuria before PE therapy, g/d (IQR)	5.2 (1.6–7.3)
Median plasma exchange sessions (IQR)	11 (6–18)
Immunosuppressive drug therapy	
Steroids, CsA, MMF, n	7 (58%)
Steroids, Tac, MMF, n	1 (8%)
Steroids, CsA, n	1 (8%)
CsA, MMF, n	2 (17%)
Multiple target treatment, ²³ n	7 (58%)
Rituximab, n	6 (50%)
Mean suPAR level before PE treatment, pg/mL (SD)	4052 (1195)
Median suPAR level after treatment, pg/mL (IQR)	3595 (3305–4204)

^aIn patients who underwent transplantation (n = 10).

IQR, interquartile range; SD, standard deviation.

TABLE 2

Mean rebound of serum suPAR between treatment sessions (SD)

Interval, 1–2 d	Interval, 3–13 d	Interval, 14–35 d	First to Last Treatment of Course
n = 36	n = 22	n = 22	n = 12
96.8% (20.1)	99.0% (17.6)	105.9% (17.1)	97.5% (22.9)