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Effects of pretransplant plasmapheresis and rituximab on recurrence of focal segmental glomerulosclerosis in adult renal transplant recipients

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Background/Aims: Recurrent focal segmental glomerulosclerosis (FSGS) following renal transplantation is relatively common. However, the risk factors and optimal pretransplant treatment preventing recurrence of FSGS remain controversial.

Methods: We retrospectively reviewed 27 adult renal transplant recipients with FSGS over a period of 10 years. We first compared possible risk factors for FSGS recurrence between the recurrence and nonrecurrence groups. Then we evaluated the effect of pretransplant plasmapheresis (PP; n = 4) and PP with rituximab (PP + RTX; n = 5) on recurrence of FSGS after transplantation compared to control patients that were not treated with these modalities.

Results: There were seven recurrences in 27 patients (25.9%), but there were no significant differences in possible risk factors for FSGS recurrence between the two groups. Recurrence rates between patients with pretransplant PP or PP + RTX and control patients were not significantly different (22.2% vs. 27.7%, $p > 0.05$). There was also no significant difference in recurrence between the pretransplant PP and PP + RTX groups (25% vs. 20%, $p > 0.05$).

Conclusions: Pretransplant PP or PP + RTX do not significantly decrease the recurrence of FSGS in adult renal transplant candidates.

Keywords: Rituximab; Plasmapheresis; Glomerulosclerosis, focal segmental; Recurrence; Kidney transplantation

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) recurs in 20% to 50% of renal transplant recipients, often within hours of transplantation, manifesting as massive proteinuria. Newer immunosuppressive agents such as cyclosporine, tacrolimus, and mycophenolate have dramatically decreased acute rejection rates compared to azathioprine. However, the incidence of FSGS recurrence has remained unchanged [1].

The risk factors for FSGS recurrence have not been clearly identified, and the efficacy of plasmapheresis (PP) and rituximab (RTX) for treatment or prevention of FSGS recurrence remains controversial. The absence of an effective treatment regimen frequently results in graft failure [2]. We conducted this observational cohort study to investigate the risk factors for FSGS recurrence, and to determine the efficacies of pretransplant PP and RTX against FSGS recurrence in adult renal transplant recipients.

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METHODS

This study was approved by the Institutional Review Board (IRB) of Seoul St. Mary's Hospital (IRB No. KC11RISI0556), which waived the necessity for informed consent. Between January 2000 and December 2010, 665 renal transplants were performed at Seoul St. Mary's Hospital.

Maintenance immunosuppression, consisting of a calcineurin inhibitor (CNI; cyclosporine or tacrolimus), mycophenolate mofetil (MMF), and prednisone, was initiated 7 days before transplantation. The initial dose of cyclosporine (10 mg/kg/day) was orally administered, resulting in target trough levels of 200 to 400 ng/mL in the first 4 weeks and 100 to 200 ng/mL thereafter. The initial dose of tacrolimus (0.1 mg/kg/day) was also orally administered, and increased to 0.16 mg/kg/day after transplantation resulting in target trough levels of 10 to 15 ng/mL in the first 3 months and 5 to 10 ng/mL thereafter. The initial dose of MMF was 1.5 g/day, and reduced in response to adverse effects, such as diarrhea or leukopenia. Methylprednisolone was administered by intravenous infusion (125 mg/day) for 7 days prior to transplantation, and was increased to 1 g/day on transplant day 0 and tapered to 30 mg/day of oral prednisone on posttransplant day 4. For induction therapy, basiliximab (20 mg) was administered intravenously on transplant days 0 and 4.

A renal biopsy was performed in cases of suspected graft dysfunction, as determined by elevated serum creatinine or persistent proteinuria. Based on the biopsy findings, cases of acute cellular rejection were treated with steroid pulse therapy, and steroid-resistant cases were treated with OKT3 or antithymocyte globulin. Antibody-mediated rejection was treated with PP followed by intravenous immunoglobulin (IVGV), in addition to steroid pulse therapy. In a case of CNI toxicity without evidence of rejection, the CNI dose was reduced.

Renal transplant patients at high immunologic risk were defined as those with positive cross match tests by antihuman globulin-enhanced, complement-dependent cytotoxicity, or flow cytometry, those with detectable donor specific antibody as determined by enzyme-linked immunosorbent assay or Luminex methods, or the presence of panel-reactive antibody ≥ 50%. These patients were desensitized with PP and IVGV infusion after each session of PP prior to transplantation, and RTX (375 mg/m^2) was administered within 1 week prior to transplantation. In ABO-incompatible transplants, patients received PP and IVGV infusion to lower the anti-ABO antibody titer, and RTX (375 mg/m^2) was administered at 1 month and 1 week before transplantation.

FSGS recurrence was defined as the occurrence of persistent proteinuria with pathologic confirmation of recurrent FSGS by allograft biopsy, or as rapidly developing persistent heavy proteinuria within several days after transplantation without any evidence of graft dysfunction, such as elevated serum creatinine and oliguria. We discriminated between late (> 3 months) and early (< 3 months) recurrence. To evaluate treatment response, complete remission was defined as proteinuria ≤ 0.3 g/day, and partial remission was defined as a ≥ 50% reduction in proteinuria; other cases were categorized as nonresponders.

We compared the following recipient and donor characteristics between recurrence and nonrecurrence groups: age, gender, body weight (BW), donated kidney weight, BW ratio of recipient to donor, age difference between recipient and donor, total ischemic time in transplantation, human leukocyte antigen mismatch numbers, frequency of related and deceased donors, amount of proteinuria and urine volume before transplantation, time from initial diagnosis to ESRD and duration of renal replacement therapy before transplantation. In the recurrence group, we further evaluated the clinical courses and responses to treatments including PP. We also investigated whether PP with or without RTX administration was performed prior to transplantation. Next, we compared long-term graft survival between the patient group with nonrecurrent FSGS as the primary renal disease (PRD) and the other patient group with non-FSGS as the PRD, as well as between the subgroups with and without FSGS recurrence.

Continuous data were compared using the Mann-Whitney *U* test, categorical data were compared using the chi-square test, and Kaplan-Meier and log-rank tests were used to compare graft survival between groups. Significance was defined as $p < 0.05$. Statistical analysis was performed using SPSS version 15.0 (SPSS Inc.,

Chicago, IL, USA).

RESULTS

Among the 665 renal transplant patients, 27 with FSGS as their PRD were identified and enrolled. Of these, 24 cases were living-donor renal transplants and three were deceased-donor renal transplants. No patient had received a second transplant. The mean follow-up period was 49 months.

The incidence of recurrence was 25.9% (7/27), with four early and three late recurrences. Univariate analysis showed no significant differences between the recurrence and nonrecurrence groups (Table 1). Posttransplant therapeutic PP was performed in six of the seven patients after recurrence; one patient refused PP. Of these six patients, three experienced graft failure despite PP (Table 2).

Pretransplant PP without RTX (n = 4) or with RTX (n = 5) was performed in nine cases for the following reasons: prevention of FSGS recurrence (n = 3), desensitization in high-risk cases (n = 4), and ABO-incompatible transplantation (n = 2) (Table 3). Recurrence rates in patients with PP or PP + RTX and without it were not significantly different (22.2% [2/9] vs. 27.7% [5/18]) and there was also no significant difference in recurrences between pretransplant PP and PP + RTX groups (25% [1/4] vs. 20% [1/5]). Nevertheless, all of the cases with PP + RTX treatment prior to transplantation had successful transplants because the recurrent FSGS with PP + RTX was completely resolved by posttransplant therapeutic PP (Fig. 1).

Long-term graft survival between the patient group with nonrecurrent FSGS as the PRD and the other patient group with non-FSGS as the PRD was not significantly different (p = 0.5). However, among the patients with FSGS, the subgroup with recurrence showed poor long-term graft survival, compared to the subgroup without recurrence (p = 0.01) (Fig. 2).

Table 1. Comparison of characteristics between two groups of focal segmental glomerulosclerosis in adult renal transplantation

Characteristic	Group with recurrence (n = 7)	Group without recurrence (n = 20)	p value
Recipient gender, female	2 (28.6)	9 (45)	0.66
Recipient age, yr	39 ± 14	36 ± 11	0.74
Donor gender, female	6 (85.7)	10 (50)	0.18
Donor age, yr	32 ± 16	42 ± 11	0.15
Donor BW, kg	53.8 ± 21.2	63.0 ± 8.4	0.34
Donated kidney weight, g	172 ± 59.9	197.5 ± 44.7	0.36
BW ratio of recipient to donor	1.6 ± 1.7	1.0 ± 0.2	0.31
Age difference recipient to donor	4 ± 23	−3 ± 20	0.54
Total ischemic time, min	57 ± 42	83 ± 131	0.84
No. of HLA mismatch	3.1 ± 2.5	2.7 ± 1.2	0.63
Related donor	5 (71.4)	12 (60)	0.68
Deceased donor	1 (14.3)	3 (15)	1.00
Proteinuria before KT, g/day	7.0 ± 11.1	4.7 ± 8.3	0.69
Urine volume before KT, mL	1,102.9 ± 1,070.5	813.3 ± 597.9	0.67
Time from initial diagnosis to ESRD, mon	46 ± 44	68 ± 67	0.54
The duration of RRT before KT, mon	50 ± 74	21 ± 29	0.62

Values are presented as number (%) or mean ± SD.
BW, body weight; HLA, human leukocyte antigen; KT, kidney transplanation; ESRD, end stage renal disease; RRT, renal replacement therapy.

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Table 2. The clinical courses and responses to treatments in recurring cases

Case	Recurrence subtype	Recurrence after KT	Total PP sessions	Response to PP	Other treatments	Graft survival, mon	Current status
1	Early	3 day	19	Partial	Rituximab CYP	19	Failure
2	Early	1 day	24	Partial	CYP	22	On-going
3[a]	Early	1 mon	9	Partial	None	18	On-going
4	Early	4 day	5	Partial	None	21	Resolution
5	Late	12 mon	5	No	CYP	89	Failure
6	Late	11 mon	None[b]	UA	None	58	On-going
7	Late	6 mon	5	No	CYP	15	Failure

KT, kidney transplantation; PP, plasmapheresis; CYP, cyclophosphamide; UA, unavailable.
[a]Deceased-donor transplantation; [b]The patient refused plasmapheresis.

Table 3. Characteristics of the cases that received plasmapheresis with or without rituximab prior to transplantation

Case	Reason for plasmapheresis	Rituximab before KT	Recurrence	Follow-up period after KT, mon	Current status
1	Prevention of FSGS	Yes	No	43	Favorable
2	Prevention of FSGS	No	Yes	22	On-going
3	Prevention of FSGS	Yes	No	18	Favorable
4	Desensitization	Yes	No	25	Favorable
5	Desensitization	No	No	111	Favorable
6	Desensitization	No	No	124	Favorable
7	Desensitization	No	No	138	Favorable
8	ABO-incompatible	Yes	Yes	21	Resolution
9	ABO-incompatible	Yes	No	19	Favorable

KT, kidney transplantation; FSGS, focal segmental glomerulosclerosis.

DISCUSSION

Risk factors for FSGS recurrence include prior history of allograft loss due to FSGS recurrence, which is the most important, as well as rapidly progressive disease in native kidney and pediatric renal transplantation. Advanced age, related donor, and Caucasian descent have also been reported to be risk factors for FSGS recurrence, although these factors remain controversial [3]. Other reports have suggested that longer dialysis duration prior to transplantation and deceased-donor transplantation are beneficial, but this has not been adequately established [4,5].

In the present study, no significant risk factor for recurrence was found in the adult renal transplant groups, although the pediatric transplantation cases, in which recurrence is relatively common, were excluded from the analysis and there were no cases of a second transplant following failure of the initial graft caused by FSGS recurrence. The time from initial diagnosis to ESRD before transplantation tended to be longer in the nonrecurrence group, although this difference was not statistically significant.

Treatments for FSGS recurrence include PP, cyclophosphamide, high-dose cyclosporine, and RTX [5-7]. PP has typically been performed in cases of FSGS recurrence since studies reporting its efficacy were first published between the late 1980s and early 1990s [8-10]. However, its efficacy in FSGS recurrence is quite variable, with some patients responding favorably and others experiencing graft failure despite PP. The average response rate of PP is 50% to 60%. Interestingly, in

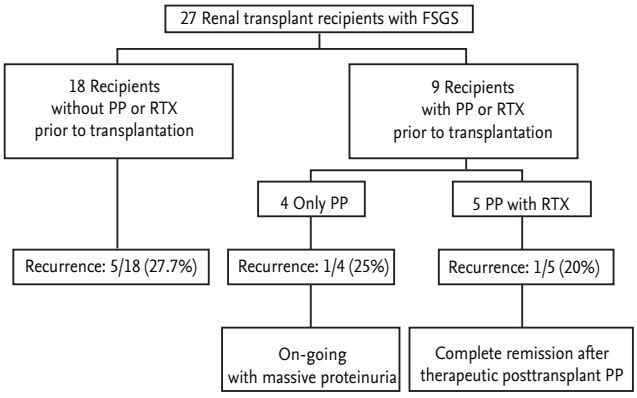

Figure 1. Flow chart showing the treatments and outcomes of adult renal transplant recipients with focal segmental glomerulosclerosis (FSGS). PP, plasmapheresis; RTX, rituximab.

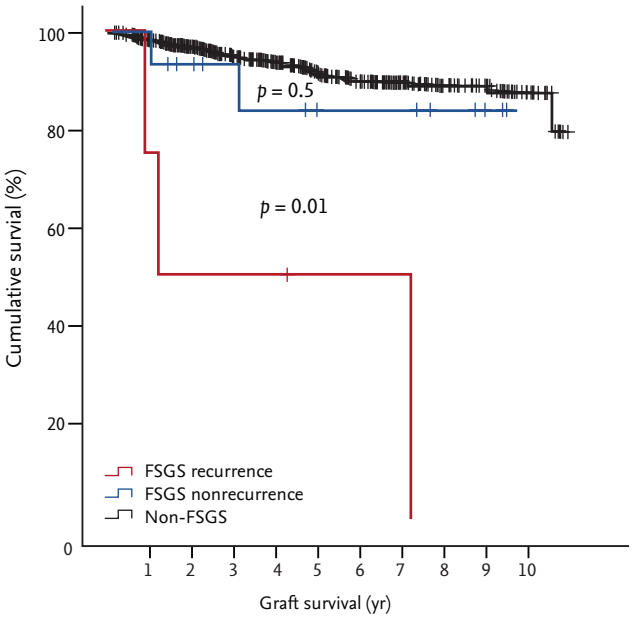

Figure 2. Long-term graft survival based on primary renal disease and recurrence rate in a case with focal segmental glomerulosclerosis (FSGS).

pediatric FSGS cases, favorable responses to PP and high-dose cyclosporine after recurrence have been reported [6,7]. In addition, some studies have reported improvement in the response rate by maintaining PP for prolonged periods, with tapering after recurrence in some trials, or prior to transplantation in others, although the clear benefit of intensive or pre-emptive PP has not yet been demonstrated [11-13].

Because RTX has produced favorable responses in cases with nephrotic syndrome refractory to current treatments and in cases of both recurrent FSGS after transplantation and posttransplant lymphoproliferative disease in some anecdotal reports, it has been used to treat recurrent FSGS after transplantation with or without PP. RTX has shown good efficacy in certain cases [2,14-16]. However, its efficacy after FSGS recurrence in renal transplantation has not yet been established [17], and it has even been reported to be ineffective in certain cases [18].

Two recent studies reported on the effectiveness of RTX for the prevention of recurrent FSGS. Audard et al. [19] reported that RTX might prevent FSGS recurrence in transplant recipients with a history of recurrence in their previous grafts. Fornoni et al. [20] also reported that RTX might prevent recurrent FSGS in patients at high risk because of their young age (< 25 years old) and history of rapidly progressive disease in native kidneys. They further demonstrated that RTX, along with CD20 on B lymphocytes, binds sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) protein and regulates acid sphingomyelinase activity, suggesting that RTX may prevent recurrent FSGS in an SMPDL-3b-dependent manner.

In conclusion, the usefulness of PP for treatment after relapse or prevention in transplant recipients with FSGS remains unclear, although pediatric cases have appeared to have better responses to PP than adults in clinical trials. There is also no definite benefit for RTX treatment of recurrent FSGS after transplantation; however, administration in the early stages of relapse is crucial for an improved response, and a few studies have reported that pre-emptive administration might prevent FSGS recurrence after transplantation.

Living-donor renal transplantation has better long-term graft survival compared to deceased-donor transplants and should be considered renal replacement therapy in patients suffering from ESRD [21]. However, the high incidence of FSGS recurrence, usually followed by graft failure, after transplantation is a burden for living donations in clinical practice [22,23]. Despite numerous studies, the only established risk factors for FSGS recurrence are a prior history of allograft loss due to FSGS recurrence, rapidly progressive disease in the native kidney and pediatric trans-

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plantation. In addition, the efficacies of current PP and RTX treatment strategies against the recurrence of FSGS are not satisfactory. In the present study, risk factors for recurrence of FSGS after renal transplantation were not identified and the response rate of therapeutic PP after recurrence was 50% (3/6), the same as reported in previous studies. In addition, pretransplant PP or PP with RTX did not significantly decrease the recurrence of FSGS. Further studies should focus on pre-emptive administration of RTX with or without PP in the transplant candidates with FSGS at high risk after risk assessment of recurrences before transplantation, close monitoring of recurrence after transplantation, and therapeutic RTX with or without PP as soon as recurrence is detected to improve graft survival in FSGS.

KEY MESSAGE

1. Pretransplant plasmapheresis (PP) or PP with rituximab does not significantly decrease the recurrence of focal segmental glomerulosclerosis in adult renal transplant candidates.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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