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Long-term Apheresis in the Management of Patients With Recurrent Focal Segmental Glomerulosclerosis After Kidney Transplantation

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INTRODUCTION

Primary focal segmental glomerulosclerosis (FSGS) recurs in 30% to 60% of allografts after kidney transplantation.[1] A circulating factor has been thought to cause podocyte damage in native and recurrent FSGS, but this factor has not yet been identified.[2]

Although the exact pathogenesis of FSGS is unknown, empirical therapies such as plasmapheresis and immunoadsorption have been shown to be effective in a large subset of patients with post-transplant FSGS.[3] Some patients who are treated with apheresis cannot be weaned off, as proteinuria recurs shortly after cessation of treatment and, in most transplant centers, apheresis is therefore discontinued after weeks to months. However, some case reports have described chronic treatment, ranging from months to several years. The aim of the current study was to establish a larger series of patients who have been treated with long-term apheresis, to provide an overview of how these treatments are constructed, how effective they are in achieving remission of post-transplant FSGS, and what the main complications and outcomes are.

We analyzed a multicenter, international, retrospective case series to determine the clinical course of adult patients with recurrent FSGS treated with long-term apheresis (>6 months). Further details can be found in the Supplementary Methods.

RESULTS

Cohort Demographics

A total of 27 transplants were included in 11 international transplant centers (Supplementary Figure S1). Patient characteristics are shown in Table 1 and detailed in the Supplementary Results.

Post-transplant FSGS and Treatment

Median time to FSGS recurrence was 5 (interquartile range [IQR], 1–11) days post-transplant, and treatment

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Table 1. Patient characteristics and transplant details

Variables	(*N* = 27)
Follow-up, yr	4.1 [3.0–6.3]
Age at transplantation, yr	37 [27–49]
Male gender	15 (56)
Race/ethnicity	
White	15 (56)
African American	1 (4)
Asian	1 (4)
Mixed	1 (4)
Unknown	9 (33)
BMI at transplantation	22.3 [18.9–24.7]
Year of transplantation	
2005–2010	2 (7)
2010–2015	9 (33)
2015–2019	16 (59)
Time from diagnosis to KF, mo	60 [36–96]
Time on dialysis, mo	22 [8–36]
Type of dialysis	
Hemodialysis	19 (70)
Peritoneal dialysis	2 (7)
Both	4 (15)
Pre-emptive transplant	2 (7)
Number of prior transplants	
None	14 (52)
1	9 (33)
2–3	4 (15)
DSA at time of transplant	5 (19)
Deceased donor	12 (44)
Extended criteria donor	4 (33)
Cold ischemia time, h	17 [14–21]
Donor age, yr	47 [42–52]
HLA-A/-B/DR mismatch	3 [1–4]
Delayed graft function	7 (26)
Induction therapy	
None	1 (4)
Antithymocyte globulin	16 (59)
Basiliximab	10 (37)
Initial immunosuppressive regimen	
Tac + MMF + St	22 (81)
CsA + MMF + St	2 (7)
Tac + AZA + St	1 (4)
CsA + AZA + St	1 (4)
Tac + EVR + St	1 (4)
Early steroid withdrawal	3 (11)
Prophylactic plasmapheresis	6 (22)
Prophylactic rituximab	1 (4)

AZA, azathioprine; BMI, body mass index; CsA, cyclosporine; DR, donor–recipient; DSA, donor-specific antibody; EVR, everolimus; HLA, human leukocyte antigen; KF, kidney failure; MMF, mycophenolate mofetil; St, steroid; Tac, tacrolimus.
Values represent frequency (percentage) or median [interquartile range].

was started after a median of 4 days (IQR, 1–15) (Supplementary Table S1). Apheresis was performed using plasmapheresis, immunoadsorption, or both modalities in 20 (74%), 3 (11%), and 4 (15%) patients, respectively. Median time on apheresis was 23 (IQR, 12–48) months, and rituximab was administered in 78% of the cases (21 patients). Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were used in 23 patients (85%).

Treatment Outcomes

Of 27 patients who received long-term apheresis, 23 patients (85%) had achieved partial or complete remission at one point after treatment. At maximum follow-up, 9 of these patients (39%) were still on active treatment (plasmapheresis, $n = 6$; immunoadsorption, $n = 3$), with a median time on apheresis of 47 (IQR, 36–54) months. A median apheresis frequency of twice a month resulted in proteinuria levels between 0.1 and 1.1 g/g in all patients. In the 14 other patients who achieved remission, chronic apheresis was stopped for various reasons (Supplementary Table S1): 10 patients (43%) were successfully weaned off apheresis after a median time of 11 (IQR, 9–23) months (Supplementary Figure S2). Three patients (13%) experienced increasing levels of proteinuria, and 1 patient experienced COVID-19, after which treatment was stopped (Supplementary Figure S3A and B, respectively).

There were 4 patients (15%) who did not achieve any form of remission despite chronic treatment (median time on apheresis 20 [IQR, 15–25] months; Supplementary Figure S4).

There were 5 patients (19%) who experienced graft failure because of recurrent FSGS ($n = 4$) and chronic antibody-mediated rejection ($n = 1$), with a median time-to-graft failure of 7.3 (IQR, 4.8–7.7) years. Death-censored graft survival was 87% at 5 years post-transplant (Supplementary Figure S5). Furthermore, 1 patient died because of COVID-19 1.8 years after transplantation.

Treatment Regimen

Starting frequency of apheresis was 3 sessions a week in 20 patients (74%). Other patients started at 2 ($n = 2$), 4 ($n = 1$), or 5 ($n = 3$) times a week. For patient 3, initial treatment frequency could not be retrieved. Although apheresis was slowly tapered in the majority of patients, regimens differed greatly in how and at what pace this was executed. A restart or increased frequency of apheresis was successful in achieving another remission in all patients with an initial response to apheresis, but there was increased proteinuria after stopping or tapering apheresis (patients 1–6, 10, 12–14, 16, 17, 20, and 21; Figure 1 and Supplementary Figures S2–S3).

Safety

Bacterial and/or viral infections were observed in 24 patients (89%). Regarding viral infections, cytomegalovirus (CMV) was observed in 8 patients (30%), BK viremia occurred in 3 patients (11%), and 4 patients (15%) had varicella zoster infection. No trends were observed between viral infections and total duration of apheresis, treatment modality, and/or rituximab use,

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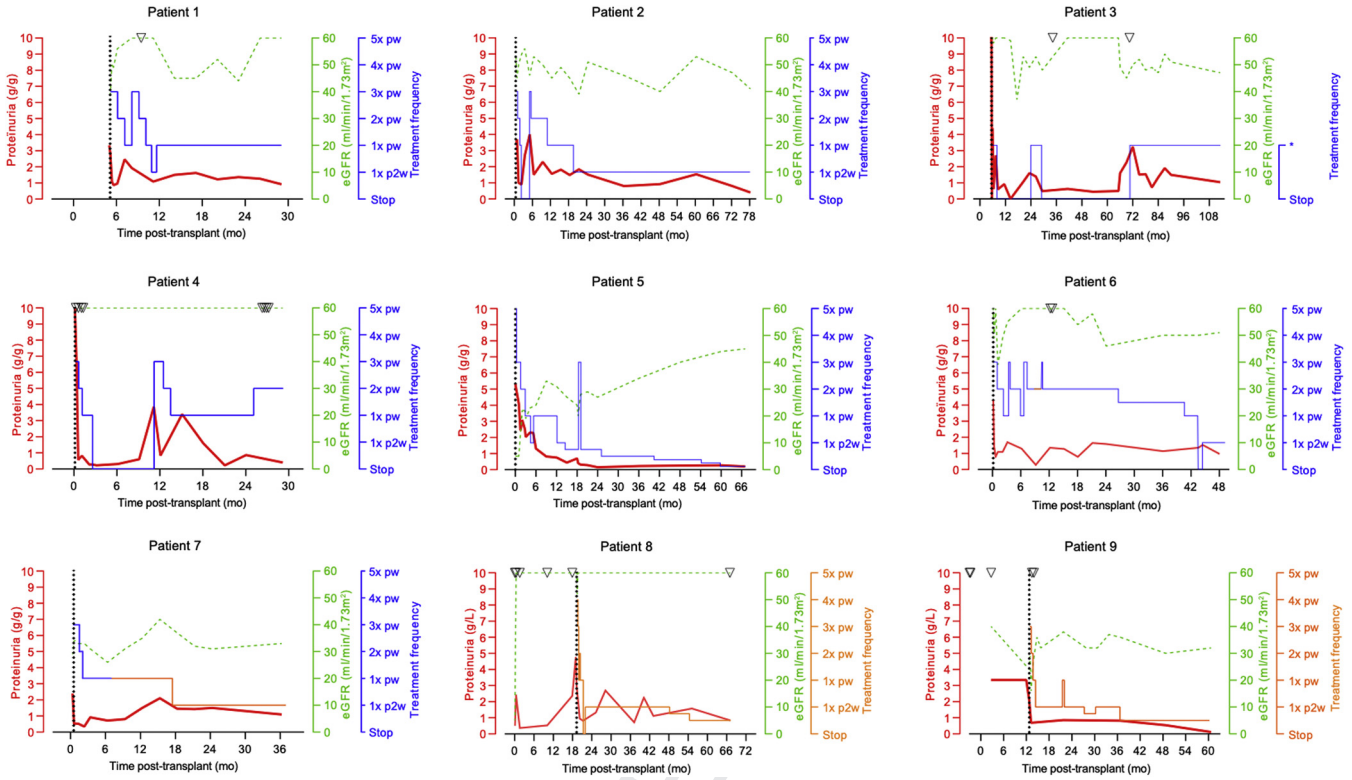

Figure 1. Clinical course of patients with post-transplant FSGS actively treated with long-term apheresis. Proteinuria, eGFR, and treatment regimen in patients on long-term apheresis. Each graph represents 1 patient. Blue and orange lines represent plasmapheresis and immunoadsorption, respectively. The dashed vertical line indicates start of apheresis. Triangles represent 1 dose of rituximab. Patient 5 received prophylactic plasmapheresis pre-transplant. * In patient 3, frequency of treatment could not be retrieved; at maximum follow-up, treatment frequency was once per week. eGFR, estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease Study; FSGS, focal segmental glomerulosclerosis; Pw, per week; p2w, per 2 weeks.

including cumulative dose. However, in patients who received antithymocyte globulin induction therapy, the incidence of any viral infection (CMV, BK viremia, and/or varicella zoster) was 63% (10 of 16), compared with 27% (3 of 11) of patients receiving basiliximab or no induction therapy.

DISCUSSION

In this international, multicenter study, we provided a detailed analysis of 27 patients with recurrent FSGS who were treated with long-term apheresis. Of the patients who achieved initial remission, 39% remained on active treatment and 43% could be successfully weaned, whereas 13% experienced therapy failure.

The number of patients being treated with long-term apheresis for post-transplant FSGS is low. In the largest study of FSGS recurrence so far, only 7% of patients who received apheresis were treated chronically.[1] As reflected in our cohort, apheresis is usually performed with plasmapheresis, but it has been partially replaced by immunoadsorption, with the reported advantage that it removes circulating antibodies more selectively without removal of coagulation factors.[9] Our data show that both modalities can be used to achieve continued remission and both methods are tolerated for multiple years.

The higher rate of rituximab use in our cohort (78%) compared with that in literature on recurrent FSGS (~60%)[1] could be due to selection bias: patients achieving quick remission without need for additional treatment were not included in our study. The timing and cumulative dose of rituximab differed greatly across patients, and therefore, its contribution to achieving (partial) remission could not be determined.

Long-term apheresis and rituximab in immunocompromised patients may lead to increased susceptibility to infections, yet it is difficult to assess the specific role of additional versus baseline transplant immunosuppression. The rate of viral infections such as CMV was higher compared with transplant recipients with primary FSGS from the same TANGO transplant centers (CMV: 30% vs. 11%).[1] The increased rate of CMV could be explained by the high use of antithymocyte globulin in our cohort because antithymocyte globulin has been linked to increased risk of CMV after organ transplantation.[5–7] Overall, there might be a rationale for increased surveillance for viral infections in patients who are treated with long-term apheresis for

recurrent FSGS, particularly in patients who received antithymocyte globulin.

Although case series cannot be used to draw robust conclusions, there are some important notes that can be taken from our data. In patients who had an initial response to treatment, increases in proteinuria when apheresis was weaned were successfully countered by reinitiation or increased frequency of apheresis. After a failed attempt to reduce frequency of apheresis, a second, slower tapering schedule was in some cases successful. Slower tapering schedules seemed to be more efficient in maintaining disease remission compared with a quick taper. In patients without initial response to apheresis, remission was never achieved, which would imply that long-term treatment in these patients would not be justified. Finally, 5 of 9 patients who are stable on long-term apheresis had lost 1 or 2 prior transplants because of recurrent FSGS, which could be informative in the discussion whether to retransplant patients with graft loss because of FSGS. However, it should be emphasized that our cohort is selected and patients with graft loss early after transplant were not included. Another limitation of our study is its retrospective design and the large variety in type, timing, and intensity of treatment for FSGS. Nonetheless, the clinical course of the patients who were included might provide information and guidance for clinicians who are dealing with patients with recurrent FSGS with an apheresis-dependent response to treatment.

In conclusion, we show that in a subset of patients with post-transplant FSGS, long-term apheresis can be an effective, well-tolerated treatment strategy to maintain remission. The high rate of viral infections provides a rationale for increased surveillance in these patients.

DISCLOSURE

DAH has received lecture and consulting fees from Astellas Pharma, Chiesi Pharma, and Novartis Pharma, as well as grant support (paid to his institution) from Astellas Pharma, Bristol-Myers Squibb, and Chiesi Pharma. All the other authors declared no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

AU and SPB designed the study, using the TANGO network of transplant centers constructed by LVR, PC, and AU. FH, DAH, JBM, PM, APJV, HS, RCM, PN, AXW, RRS, and LSR included patients and were responsible for data acquisition at their own institution. AU coordinated the inclusion of data and analyzed the final cohort. AU wrote the manuscript with support of SPB, PC, and LVR. All authors read, revised, and approved the final manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary Results.

Figure S1. Flowchart of the study population.

Figure S2. Clinical course of patients with continued (partial) remission after cessation of long-term apheresis for post-transplant FSGS.

Figure S3. Clinical course of patients with termination of long-term apheresis because of refractory FSGS or infection.

Figure S4. Clinical course of patients without response to long-term apheresis for post-transplant FSGS.

Figure S5. Graft survival in patients with long-term apheresis.

Table S1. Treatment and outcomes of long-term apheresis for recurrent FSGS.

Supplementary References.

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