Yonsei Medical Journal
Vol. 42, No. 2, pp. 209 - 214, 2001

Long-term Outcome of Kidney Transplantation in Adult Recipients with Focal Segmental Glomerulosclerosis

Kyu Hun Choi[1], Soon Il Kim[2], Soo Young Yoon[1], Jae Hun Kim[1], Shin Wook Kang[1], Sung Kyu Ha[1], Ho Yung Lee[1], Dae Suk Han[1], Yu Seun Kim[2], Kiil Park[2], Hyeon Joo Jeong[3], and Dong Kee Kim[4]

Departments of [1]Internal Medicine, [2]Surgery, [3]Pathology and [4]Biostatistics Institute of Kidney Disease, Yonsei University College of Medicine, Seoul, Korea.

Focal segmental glomerulosclerosis (FSGS) is an important cause of nephrotic syndrome and end-stage renal disease. FSGS recurrence after renal transplantation has a potentially detrimental course leading to the loss of renal function. In order to establish FSGS recurrence rates and evaluate the course of the disease on living-related-donor renal transplantation in ethnic Korean adults ($\geq$18 years), we reviewed our experiences of 27 kidney transplantations with FSGS over the last 15 years. Of the 27 renal allografts, 13 were found to have recurrent FSGS by graft biopsy. In comparison with background data upon patients with and without recurrence of FSGS, the donor age of patients with recurrent FSGS was significantly higher than that of those without recurrence (median, 39 years vs 26, $p<0.05$). In terms of, age at transplantation, length of dialysis period, and mode of dialysis no differences were found between recurrent and nonrecurrent cases. The graft survival rate of recipients from a kidney donor of age less than 40 years was significantly higher than that of recipients from a kidney donor of age more than 40 years, at 5 and 10 years, respectively (87% vs 33%, 41% vs 0%, $p<0.05$). The association between clinical variables and recurrence was assessed by multiple logistic regression analysis, and donor age was found to be a risk factor of FSGS recurrence ($p<0.05$). Variables such as HLA-mismatch numbers and immunosuppression were not found to be associated.

In conclusion, the recurrence rate of FSGS in adult recipients with FSGS was 48% and patients that received kidney from an older donor appear to be at higher risk of developing recurrence. The use of a renal graft from a younger donor is considered advisable for adult recipients with FSGS.

Key Words: Focal segmental glomerulosclerosis, renal transplantation, recurrence

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is an important cause of end-stage renal disease (ESRD), occurring in about 20% of adults with nephrotic syndrome and recent studies have demonstrated an increasing incidence of FSGS in adults.[1,2] Kidney transplantation is indicated in ESRD caused by FSGS, but graft loss is well reported to be common due to high incidence of recurrence, and various authors have reported recurrence rates of 15% to 100%.[3-5] The introduction of cyclosporine into the immunosuppressive regimen has modified the course of recurrent disease, but has not reduced its incidence.[6]

Attempts to identify risk factors, with a view towards predicting the likelihood of FSGS recurrence in transplants, have yielded conflicting results. Factors studied include: age at FSGS onset, interval between diagnosis to chronic end-stage renal failure, duration of dialysis, immunosuppressive therapy, and evidence of mesangial proliferation in the native kidney. Graft survival rate in the affected population appears to vary considerably, for example, while Ismali-Allouch et al.[7] recorded a rate of 50% in FSGS patients, which was lower than that recorded for unaffected transplant patients, Holgado et al.[3] report a 5-year graft survival of 77.4%. In addition, the majority of studies were performed in recipient populations that included pediatric patients, and heavy proteinuria or nephrotic syndrome was considered to be recurrence.[3-7] Meanwhile, in adult recipients, the rate of recurrence and outcome of biopsy-proven recurrent FSGS are not well defined.

Therefore, to establish the biopsy-proven FSGS recurrence rates and evaluate the course of the

Received November 8, 2000
Accepted December 18, 2000

disease in the case of living-related-donor renal transplantation in adults, we reviewed our experiences of kidney transplantation with FSGS among the Korean population over the last 15 years.

MATERIALS AND METHODS

Patient population

Between January 1984 and June 1999, 27 patients with biopsy-proven primary FSGS underwent renal transplantation at our center. Grafts were from 23 living-related, two living-unrelated, and two cadaveric donors. One patient underwent secondary transplantation after losing the primary kidney graft due to recurrence of the original disease. The following parameters were recorded; age at the time of FSGS diagnosis, interval from FSGS diagnosis to ESRD, duration of dialysis, immunosuppressive therapy employed and HLA compatibility. The average number of HLA-AB, and DR mismatches were 1.3 and 0.8, respectively.

Immunosuppression: A cyclosporine-based regimen which included steroids was used in all patients. Azathioprine was added when there was an increased risk of rejection or in patients requiring a reduction in cyclosporine because of drug toxicity (Table 1). Acute rejection was treated with pulsed intravenous methylprednisolone.

Definition of FSGS recurrence: In all cases graft biopsies were performed and recurrence of FSGS was defined as the development of proteinuria (> 50 mg/m^2/day), in the absence of clinical or histological evidence of acute rejection, and pathologic findings of segmental collapse with or without adhesion to Bowman's capsule in the graft kidney.

Table 1. Patient Characteristics

	Non-recurrence (N=14)	Recurrence (N=13)
Follow-up period, months	77 (13-129)	70 (11-114)
Recipient age, years	28 (18-55)	27 (18-56)
Recipient M/F ratio	1.2	1.3
Donor age, years	26 (20-38)	39 (25-57)*
Donor M/F ratio	1.2	1.5
Disease duration, months	54 (8-190)	44 (12-170)
Time on dialysis, months	15 (2-117)	5 (1-21)
Immunosuppression, n(%)		
Cyclosporine+Steroid	10 (71)	8 (61)
Triple	4 (28)	5 (38)

*$p<0.05$, by Mann Whitney test.

Statistical analysis

Group mean values were compared using either the Mann Whitney test or the Student's t-test. Stepwise multivariable logistic regression was used in order to identify variables predictive of recurrence. Graft survival rate was calculated using the Kaplan-Meier method using the Wilcoxon test. Results are expressed as median (range) or mean ± S.D. Statistical significance was defined as a p value of <0.05.

RESULTS

Patient characteristics

Of the 27 renal allograft recipients with FSGS, 13 proved to have recurrent FSGS (48%). All patients with recurrent FSGS showed nephrotic proteinuria, which presented 2 to 24 months post-transplantation. Patients were divided by recurrence, and Table 1 summarizes the demographic characteristics of the two groups. The median follow up period was 70 months for patients with recurrence and 77 months for those without. The median age at transplantation was not significantly different in those with recurrent FSGS and those without (27 years vs 28), and the median interval between the histologic diagnosis of FSGS to ESRD tended to be longer in those without recurrence. The length of dialysis therapy before transplantation was longer in nonrecurrent group but this was not statistically significant. Immunosuppression after transplantation was also not significantly different between 2 groups. However, the median age of the kidney donor was significantly higher for patients with recurrence that for those without (39 years vs 26, $p<0.05$).

Graft function

During the 1st post-transplant year, the mean

serum creatinine values were comparable in both groups ($p > 0.05$, Table 2). The transplant recipients of both groups also showed the similar frequency of acute rejection episodes (Table 2). Graft survival rates in recipients of kidneys from donors of less than 40 years of age were 87% at 5 years and 41% at 10 years, and these figures were significantly higher than the 33% at 5 years and the 0% at 10 years in those with kidneys from donors older than 40 years ($p < 0.05$, Fig. 1). Graft loss was defined as graft failure with a return to dialysis or death for whatever reason.

Predictors of recurrence

The association between clinical variables and recurrence was assessed by multiple logistic regression analysis, and donor age was determined to be a risk factor of FSGS recurrence ($p < 0.05$, Table 3). Variables including length of dialysis, disease duration, and immunosuppression were not significantly associated.

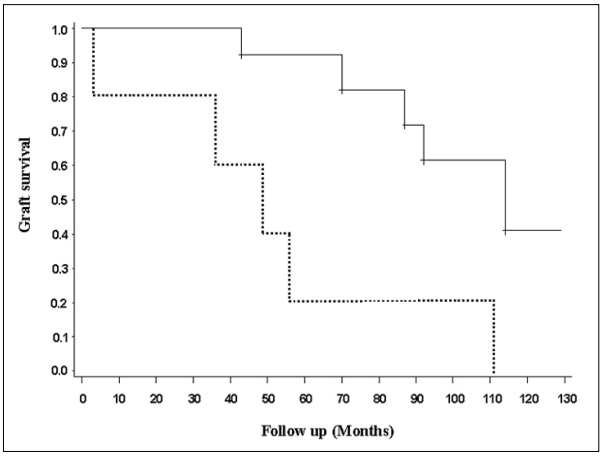

Fig. 1. Graft survival in renal allograft recipients with focal segmental glomerulosclerosis from the kidney donor with age less than 40 years (—) and with age more than 40 years (···). ($p < 0.05$)

DISCUSSION

FSGS is considered among the primary glomerulopathies with the highest recurrence rates in renal transplants. The recurrence rate recorded in the present study was 48%, which is similar to the rate reported by Dall'Amico et al in children as 52%,[8] and higher than the 37.8% reported by Otsubo et al.[4] In addition, broad differences in recurrence have been reported at various institutions.[3,4,8] This variation in quoted extents of recurrence may due to the different criteria used for FSGS recurrence. While many studies have regarded heavy proteinuria followed by nephrotic syndrome as recurrence,[4,8] our study was based on the pathological finding of FSGS in adults over age 17 years. On the basis of this data, it is apparent that relatively high recurrence rates can be expected in adult recipients due to FSGS.

Ingulli and Tejani[9] reported upon a correlation between the increased incidence of recurrence and a lower patient age at the onset of nephrotic syndrome. In contrast, Muller et al.[10] found no significant difference between recurrence and nonrecurrence groups with respect to age at FSGS diagnosis. In our study, age at transplantation was similar in the groups. However, the mean age of

Table 2. Graft Function

	Non-recurrence (N=14)	Recurrence (N=13)
Mean serum creatinine level, mg/dl	11.4 ± 3.4	12.0 ± 3.4
Pre-transplantation	1.1 ± 0.4	1.8 ± 1.6
Post-transplantation, 1 month	1.0 ± 0.4	1.7 ± 1.7
3 months	1.1 ± 0.4	1.3 ± 0.3
12 months		
Frequency of acute rejection episodes, n (%)		
No rejection	10 (71)	4 (30)
Single	3 (21)	8 (61)
Two or more episodes	1 (7)	1 (7)

All comparisons are not statistically significant.

Table 3. Multiple Logistic Regression Analysis of Clinical and Biochemical Variables to Identify Predictors of FSGS Recurrence

	β	p value	Odds ratio
Donor age	0.15	0.013*	1.287
Recipient age	0.04	0.145	1.04
Recipient M/F ratio	-1.018	0.877	0.897
Donor M/F ratio	-1.232	0.118	0.292
Disease duration	0.001	0.866	1.001
Dialysis duration	-0.031	0.318	0.97
Mode of dialysis			
Hemodialysis	-0.629	0.474	0.533
Peritoneal dialysis	1.163	0.2	3.2
HLA compatibility	0.012	0.628	1.012
Immunosuppression			
Cyclosporine+Steroid	-0.31	0.678	0.733

*$p<0.05$.

kidney donors for those with recurrence was significantly higher than for those without, which surprisingly seems not to have been evaluated in previous reports on the subject.[3,9,10]

The progression of FSGS into end-stage renal failure was also identified as another strong risk factor recurrent FSGS.[10,11] However, the mean interval between the histologic diagnosis of FSGS and ESRD was no longer in nonrecurrent patients than that in recurrent patients in our study. Muller et al.[10] also failed to find statistically significant differences between recurrent and nonrecurrent cases. The duration of dialysis is another factor often taken into consideration. In several studies,[3,10] the duration of dialysis therapy before transplantation was longer in the nonrecurrent group than in the recurrent group but this was without significance. In the present study, those with recurrence also underwent dialysis prior to surgery for a shorter period, i.e. 7.2 years versus 22.3 years, but again this was not significant, and there was no difference in mode of dialysis between two groups.

It has been postulated that patients with inherited or spontaneous mutations may be predisposed to nephrotic syndrome, which may manifest itself as primary FSGS,[12] and that the recurrence of primary FSGS following transplantation may be more likely to occur in recipients of kidneys from related donors, rather than those that received cadaveric kidneys.[13] In this study all patients, with the exception of four, received living-related kidney transplantation, and therefore, the difference in recurrence of living related and cadaveric transplantation could not be evaluated. However, the differences in HLA compatibility was not observed between the recurrent and nonrecurrent groups. Again immunosuppression after transplantation was also not significantly related to recurrence, and neither was the frequency of acute rejection episodes. Cyclosporine therapy used for the prevention or control of FSGS-induced proteinuria after renal transplantation has yielded conflicting results in the past.[14,15] Cattran et al.[16] reported that cyclosporine is an effective therapeutic agent for the treatment of steroid-resistant cases of primary FSGS, but Vincenti et al.[6] reported that cyclosporine did not prevent the recurrence or the clinical manifestations of FSGS after kidney transplantation. The use of cyclosporine as an immunosuppressive therapy after renal transplantation did not show any significant influence on the recurrence of FSGS or the course of recurrent FSGS in the present study.

All patients with recurrent FSGS lost their graft. The causes of graft loss were recurrent FSGS in all 12 cases and death caused by infection in one patient. In the present study, we found that donor age significantly affected graft survival. In recipients from kidney donor with age under 40 years, graft survival rate at 5 and 10 years post-transplantation was significantly higher than those from donors over 40 years of age. This finding indicates that patients receiving a kidney from a younger donor can expect longer graft

survival.

In the present study, all patients with recurrent FSGS showed nephrotic proteinuria, which presented at 2 to 24 months post-transplantation, and therefore, in adults with recurrent FSGS, the onset of proteinuria seems to be delayed, compared to children, who showed a median recurrence of only 14 days after transplantation.[17] None of the therapeutic schedules employed in the treatment of recurrent FSGS has proved wholly effective. Savin et al.[18] observed a decrease in proteinuria in patients with recurrent FSGS following several plasmapheresis sessions. In other studies, however, this treatment proved ineffective.[19,20] In the present study, two patients with recurrent FSGS underwent plasmapheresis treatment immediately after the recurrence of proteinuria, but failed to respond to treatment. Other patients were treated with antiproteinuric drugs, such as angiotensin-converting enzyme inhibitors, but no case showed improvement. One patient underwent secondary transplantation after losing the primary kidney graft due to recurrence of the original disease and displayed satisfactory renal function, without recurrence, after a 1.5-year follow-up.

The association between clinical variables and recurrence was assessed by multiple logistic regression analysis. In the present study, donor age was found to be the only risk factor of FSGS recurrence, however, the mechanism of the association between FSGS recurrence and donor age is not clear. On considering the theory that primary FSGS may be due to a possible circulating humoral factor,[12,18] a kidney from an older donor may be more susceptible to pathogenetic factors, such as permeability factor. Additional studies in more patients are needed to further confirm the significance of donor age as a risk factor of recurrence. Variables including the period of dialysis, disease duration, and immunosuppression were found not to be significantly associated with recurrence, in the present study. Based on these findings, patients who receive a kidney from older donor seem to be at a higher risk of recurrence.

Summarizing, this work indicates that the recurrence rate of FSGS in adults is approximately 48%, and that recipients of kidneys from older donors are more likely to suffer recurrence. The use of renal graft from younger donors in adults with FSGS is advised.

Kyu Hun Choi, M.D.
Department of Internal Medicine,
Yonsei University College of Medicine,
C.P.O. Box 8044, Seoul 120-752, Korea.
Tel: 82-2-361-5437, Fax: 82-2-393-6884,
E-mail: khchoi6@yumc.yonsei.ac.kr

REFERENCES

1. DAgati V. The many masks of focal segmental glomerulosclerosis. Kidney Int 1994;46:1223-41.
2. Haas M, Spargo BH, Coventry S. Increasing incidence of focal-segmental glomerulosclerosis among adult nephropathies: A 20-year renal biopsy study. Am J Kidney Dis 1995;26:740-50.
3. Holgado R, Castillo DD, Mazuecos A, Garcia T, Soriano S, Perez R, et al. Long-term outcome of focal segmental glomerulosclerosis after renal transplantation. Transplant Proc 1999;31:2304-5.
4. Otsubo S, Tanabe K, Tokumoto T, Ishikawa N, Shinmura H, Oshima T, et al. Long-term Outcome in renal transplant recipients with focal and segmental glomerulosclerosis. Transplant Proc 1999;31:2860-2.
5. Refaie A, Sobh M, Moustafa F, Bakr MA, El-Mekresh M, Farahat S, et al. Living-related-donor kidney transplantation outcome in recipients with primary focal-segmental glomerulosclerosis. Am J Nephrol 1999; 19:55-9.
6. Vincenti F, Biava C, Tomlanovitch S, Amend WJC, Garovoy M, Melzer J, et al. Inability of cyclosporine to completely prevent the recurrence of focal glomerulosclerosis after kidney transplantation. Transplantation 1989;47:595-8.
7. Ismail-Allouch M, Burke G, Nery BJ, Roth D, Esquenazi V, Ruiz P, et al. Rapidly progressive focal segmental glomerulosclerosis occurring in a living related kidney transplant donor: case report and review of 21 cases of kidney transplants for primary FSGS. Transplant Proc 1993;25:2176-7.
8. Dall'Amico R, Ghiggeri G, Carraro M, Artero M, Ghio L, Zamorani E, et al. Prediction and treatment of recurrent focal segmental glomerulosclerosis after renal transplantation in children. Am J Kidney Dis 1999;34: 1048-55.
9. Ingulli E, Tejani A. Incidence, treatment, and outcome of recurrent focal segmental glomerulosclerosis post-ransplantation in 42 allografts in children-a single-center experience. Transplantation 1991;51:401-5.
10. Muller T, Sikora P, Offner G, Hoyer PF, Brodehl J. Recurrence of renal disease after kidney transplantation

in children: 24 years of experience in a single center. Clin Nephrol 1998;49:82-90.
11. Habib R, Antignac C, Hinglais N, Gagnadoux MF, Broyer M. Glomerular lesions in the transplanted kidney in children. Am J Kidney Dis 1987;10:198-207.
12. Schachter AD, Strom TB. Postransplant recurrent FSGS: molecular insights and future directions. Nephron 1999; 82:300-5.
13. First MR. Living-related donor transplants should be performed with caution in patients with focal segmental glomerulosclerosis. Pediatr Nephrol 1995;9 Suppl:40-2.
14. Artero M, Biava C, Amend W, Tomlanovich S, Vincenti F. Recurrent focal glomerulosclerosis: Natural history and response to therapy. Am J Med 1992;92:375-83.
15. Pirson Y, Squifflet JP, Marbaix E, Alexandre GPJ, Strihou CY. Recurrence of focal glomerulosclerosis despite cyclosporine treatment after renal transplantation. Br Med J 1986;292:1336.
16. Cattran DC, Appel GB, Hebert LA, Hunsicker LG, Pohl MA, Hoy WE, et al. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. Kidney Int 1999;56:2220-6.
17. Tejani A, Stablein DH. Recurrence of focal segmental glomerulosclerosis posttransplantation: A special report of the North American Pediatric Renal Transplant Cooperative Study. J Am Soc Nephrol 2 Suppl 3:258-63.
18. Savin VJ, Sharma R, Sharma M, McCarthy ET, Swan SK, Ellis E, et al. Circulating factor associated with increased glomerular permeability to albumin in recurrent focal segmental glomerulosclerosis. N Engl J Med 1996;334:878-83.
19. Morzycka M, Croker BP, Seigler HF, Tisher CC. Evaluation of recurrent glomerulonephritis in kidney allografts. Am J Med 1982;72:588-98.
20. Munoz J, Sanchez M, Perez-Garcia R, Anaya F, Valderrabano F. Recurrent focal glomerulosclerosis in renal transplants proteinuria relapsing following plasma exchange. Clin Nephrol 1985;24:213-4.