An Important Problem: Posttransplant Focal Segmental Glomerulosclerosis Recurrence and Plasmapheresis

Önemli Bir Problem: Transplantasyon Sonrası Fokal Segmental Glomeruloskleroz Nüksü ve Plazmaferez

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ABSTRACT

OBJECTIVE: Focal segmental glomerulosclerosis (FSGS) as a primary glomerular disease are refractory to therapy and progress to End stage renal disease. (ESRD). After transplantation, the major problems are recurrence of the disease and its treatment. In this study, We investigated FSGS recurrence.

MATERIAL and METHODS: The graft and patient's survivals, complications, recurrence rates, and therapeutic approach were documented. Twenty patients with FSGS and 20 patients as controls were included in the study.

RESULTS: The recurrence rate was significantly higher in FSGS group than controls (55 % vs 0 %, p<0.0001). We found that living and cadaveric donor transplantation have similar survival rate in FSGS. One of the most effecting factors on graft survival was genetic similarities between recipient and donor. Pre transplant plasmapheresis was found as effective treatment way for the prevention of FSGS recurrence. While proteinuria recurrence was 38% in the preemptive plasmapheresis group, it was 85% in the other patients with FSGS (p<0.05).

CONCLUSION: The importance of genetic similarities, similar results for graft survival in both living and cadaveric donor transplantation, and plasmapheresis as an effective approach for recurrent disease were the most important findings in this study. It also seems that the most effective therapeutic approach for the prevention of recurrence is pretransplant preemptive plasmapheresis.

KEY WORDS: Focal segmental glomerulosclerosis, FSGS recurrence, Recurrent disease, Plasmapheresis, Transplantation

ÖZ

AMAÇ: Fokal segmental glomeruloskleroz (FSGS), primer glomerül hastalığı olarak tedaviye dirençlidir ve son dönem böbrek yetersizliğine (SDBY) ilerler. Transplantasyondan sonra majör problem hastalığın nüks etmesi ve onun tedavisidir. Bu çalışmada FSGS nüksünü araştırdık.

GEREÇ ve YÖNTEMLER: Greft ve hasta sürvileri, komplikasyonlar, nüks oranları ve tedavi yaklaşımları dökümente edildi. FSGS li 20 hasta ve kontrol olarak da FSGS dışı glomerülonefritli 20 hasta çalışmaya dahil edildi.

BULGULAR: Nüks oranı, FSGS li grupta, FSGS dışı gruba göre anlamlı olarak yüksek bulundu. (%55'e karşın %0, p= 0,0001). FSGS li hastalarda canlı ve kadavra nakillerinde, sürvi oranlarını birbirine benzer bulduk. Greft sürvisini en çok etkileyen faktörlerden birinin, alıcı ve verici arasındaki genetik benzerlik olduğunu saptadık. Transplantasyon öncesi plasmaferez tedavisinin, FSGS nüksünü önlemek açısından etkin bir tedavi olduğunu tesbit ettik. Transplantasyon öncesi plasmaferez uygulanan grupta proteinüri oranı % 38 olarak saptanırken, plasmaferez uygulanmayan grupta bu oran %85 olarak bulundu. (p= 0,05).

SONUÇ: Sonuç olarak bizim bu çalışmadaki en önemli çıkarımlarımız; genetik yakınlığın önemli olması, canlı ve kadavra nakillerinde greft sürvilerinin benzer bulunması, nüks hastalığının tedavisinde plasmaferezin etkin bir tedavi yöntemi olarak saptanmış olmasıdır. Ayrıca, daha da önemlisi, nüks hastalığının önlenmesinde, pre emptif plasmaferezi, en etkin tedavi yaklaşımı olarak saptadık.

ANAHTAR SÖZCÜKLER: Fokal segmental glomeruloskleroz, FSGS nüksü, Nüks hastalık, Plazmaferez, Transplantasyon

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INTRODUCTION

Today should we still be discussing obtaining allografts from living donors for focal segmental glomerulosclerosis (FSGS) patients? There is no discussion about FSGS being the most frequently seen glomerulopathy in the allograft that can lead to graft loss. Nearly, the next allograft will always be lost but there is a dilemma in some issues about living or cadaver donation. On the other hand, new therapies have been investigated to prolong graft survival.

Focal segmental glomerulosclerosis is an important cause of end stage renal disease (ESRD) in children; its incidence appears to gradually increase in adult patients, as well. The incidence of FSGS is not exactly known. It is supposed that the exact numbers of FSGS are likely to be higher than recorded data since many patients with ESRD have no histological proof of their original disease.

Primary or idiopathic FSGS presents with massive proteinuria, early progression to ESRD, and the highest rate of recurrence in renal allograft (1,2).

Secondary FSGS can be seen in a number of underlying conditions including obesity (3), heroin use, HIV and parvovirus B19 infection, lithium treatment, pamidronate therapy (4), plasma cell proliferative disorders (5), urinary reflux, interferon alpha (6) use and conditions leading to nephron loss.

Although renal transplantation is the treatment of choice in patients with FSGS, a high risk of recurrence after transplantation is a major drawback. (7). Hoyer et al. were the first authors to point out to this problem in 1972 (8). Afterwards the recurrence rate was reported to be about 30% for transplanted FSGS patients (9,10). Reported recurrence rate has a wide ratio between 20 to 80% of patients. (11-17). Recurrence rate increases in the subsequent grafts, and even reaches 80-90% of the patients. (16,18,19). Generally, recurrence occurs in the first few weeks after transplantation, however it can occur as late as a few years after transplantation (20).

Since recurrence may result in graft failure, many studies have demonstrated that the patients with FSGS as a primary diagnosis have decreased graft survival compared to other primary kidney diseases in both living and cadaveric donor transplantation (7).

In this study, our aim was to determine outcome of patients with FSGS after renal transplantation and to demonstrate the factors responsible for the incidence and timing of recurrence, as well as the success of treatment of FSGS recurrence and graft and patient survivals.

MATERIALS and METHODS

A total of 820 patients who underwent kidney transplantation between 1983 and 2007 were evaluated retrospectively (Figure 1). Twenty patients with biopsy proven primary FSGS constituted the study group. Patients with secondary FSGS (seven patients including VUR nephropathy and other reasons) were excluded from this study.

Twenty patients with other primary glomerulopathies formed the control group. The patients were matched according to age, gender, date of transplantation and donor type.

The patients were then classified into two subgroups for the recurrence of proteinuria. Proteinuria recurrence was defined by the reappearance of proteinuria (> 1 gr / 24 h) in the absence of acute rejection, chronic allograft nephropathy or urinary tract infection.

Proteinuria over than 1 g/day and graft dysfunction that could not be otherwise explained was considered as indication for transplant biopsy. Proteinuria per se was not considered as the recurrence of FSGS unless to be proven by biopsy.

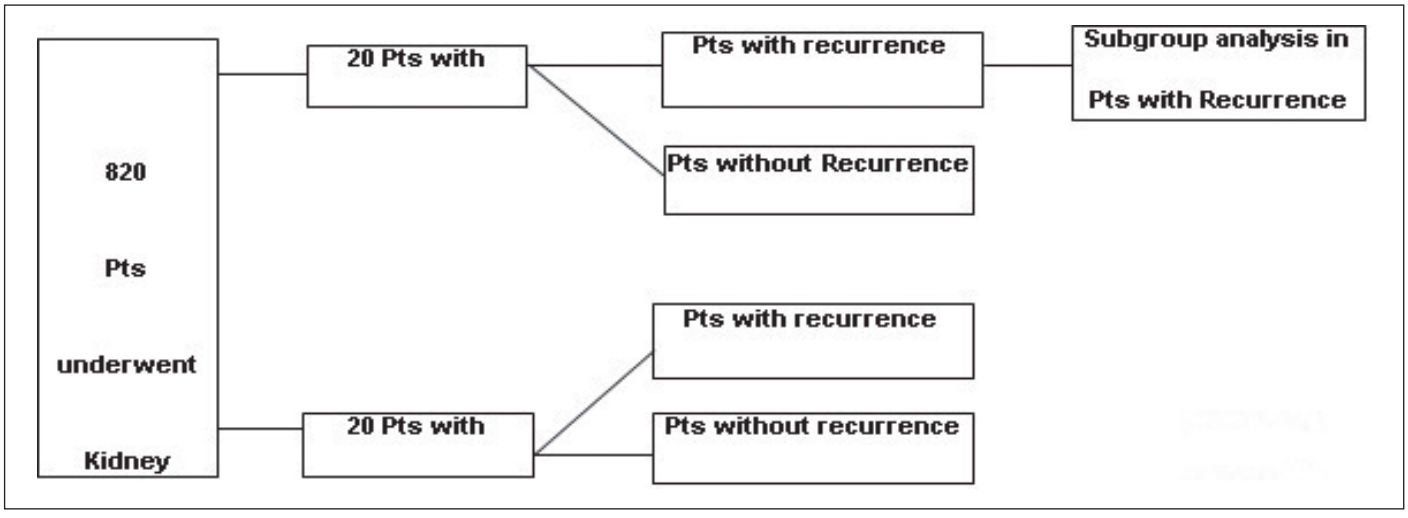

Figure 1: *Evaluation of 820 patients underwent kidney transplantation between 1983 and 2007, retrospectively.*

ATG was used as an induction therapy in only deceased donor transplantation but not in living donor transplantation. Maintenance treatment was the same for both. Maintenance regimen consisted of a triple therapy: prednisone, azathioprine or mycophenolate mofetil and cyclosporine A or tacrolimus. Acute rejections were treated with intravenous 500 mg methylprednisolone pulses on 3 subsequent days and anti thymocyte globulins (ATG) in cases of steroid resistant rejections.

Renin angiotensin system receptor blockers were given for the treatment of hypertension and proteinuria to all of the patients in both the study and the control group. Plasmapheresis treatment was performed either preemptively before operation or therapeutically after operation.

Since FSGS patients have a high risk for recurrence, plasmapheresis was used before live donor transplantation as a method to prevent recurrence. However, in the case of the recurrent disease, plasmapheresis was used again. Three weeks before transplantation, 3 times a week an average of 5-10 sessions of plasmapheresis were performed in 13 FSGS patients with heavy proteinuria (>3 gr/day) in the study group. As long as proteinuria remained, plasmapheresis was continued and transplantation was performed as soon as proteinuria disappeared. Plasmapheresis could not be carried out prior to cadaveric donor transplantations due to time limitations.

After transplantation, plasmapheresis was administered in 5 of 11 patients with FSGS recurrence. Therapeutic plasmapheresis was administered in the case of biopsy proven FSGS and having proteinuria greater than 3 gr/24 h. As long as proteinuria continued, plasmapheresis has been performed 3 times a week until lowering proteinuria below 0.3 g r /24 h.

After plasmapheresis session, we also used intravenous immunoglobulin (IVIG) to the patients for the treatment of FSGS recurrence. The total dose of 0.5 g r/kg IVIG was administered in 3 or 5 different days.

We had used rituximab with plasmapheresis together in only 2 patients with recurrent disease among the patients fulfilling the criteria of therapeutic plasmapheresis.

Several risk factors for recurrence were analyzed, including duration of dialysis, former modality of dialysis, HLA matching, donor type, kindred for donor, occurrence or presence of acute rejection, graft loss.

STATISTICS

Study analysis was performed using standard statistical methods. The description and comparison of graft and patients survival were estimated by the Kaplan – Meier analysis and log-rank tests. Values were expressed as mean ± SD or median with interquartile range (IQR) and P <0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of study and control patients are shown in Table I.

Median duration of disease from diagnosis to renal replacement therapy was 40.5 months (range: 1 - 135 months) and 6 months (range: 1 -194 months) in FSGS group and control group, respectively.

Table I: The demographical and clinical characteristics of the patients.

	FSGS Group	**Control Group**	**Significance (p)**
Age (years)	32 ±8	33 ±8	NS
Gender	14 males 6 females	14 males 6 females	NS
Donor type (Live or Cd)	14 Live 6 Cd	15 Live 5 Cd	NS
Duration of RRT (Month)	32 ±7 :	28 ±7	NS
Modality of RRT	HD: 16 PD: 3 Preemptive: 1	HD: 14 PD: 5 Preemptive: 1	NS
Kindred between R&D	Positive: 13 Neg: 7	Positive: 13 Neg: 7	NS
Full-matched graft	13	13	NS
Haplotype graft	7	7	NS
Gender of donor	11 males 9 females	9 males 11 females	NS
Acute rejection	2	1	NS
Return to dialysis (graft loss)	4	1	NS
Patients with recurrent disease	**11**	**0**	**P<0,0001**

Cd: cadaveric, **Tx:** Transplantation, **RRT:** Renal replacement therapy, **R:** Recipient, **D:** donor, **HD:** Hemodialysis, **PD:** Peritoneal dialysis.

No differences were observed between groups concerning age at transplantation, HLA matching, gender, gender of donor, donor type, duration of renal replacement therapy before operation and former modalities of renal replacement therapy.

Median follow up in FSGS group was 39 months (25th percentile: 11.75 and 75th percentile: 55.0 months). It was 39.5 months of median follow up in the control group (25th percentile 17.5 and 75th percentile 68.75 months).

While recurrent disease was seen in 11 of 20 patients (55%) in study group, there was no recurrent disease in control group ($p<0.0001$).

Besides the acute rejection attacks, there was no recurrence of proteinuria in control group.

The recurrence occurred in the study group at posttransplant 11 weeks (Range (IQR) 1 to 159 weeks, median: 11 weeks).

Postoperatively mean creatinine was 1.11± 0.24 mg / dl versus 1.21± 0.20 mg/dl in FSGS group and control group, respectively (p=NS). Mean creatinine in the last visit was 2.18± 1.98 mg/dl versus 1.56±1.08 mg/dl in FSGS group and control group, respectively (p=NS).

In subgroup analysis, 5 of 11 FSGS patients with recurrent disease were kindred to donors, but 6 of 11 were not. On the other hand 8 of 9 FSGS patients without recurrent disease were kindred to donors (p=0.043).

It was observed to have been kindred to donor and histocompatibility played an important role in graft survival (Figures 2,3).

We found similar results for recurrence in LD and CD patients with FSGS (LD: 6 vs.CD: 5 p=NS). We also found that the difference between living and cadaver donor in patients with FSGS for the graft survival were not significant statistically (p=0.446) (Figure 4). Two vs. one patient underwent acute rejection in study and control group, respectively (p=NS).

Any patient neither in FSGS group nor control group had died with functioning graft. Four patients in FSGS group versus one patient in control group lost their grafts because of chronic allograft nephropathy (CAN).

There was no patient who lost the allograft due to acute rejection in the control or study groups. There was no meaningful difference between the creatinine values of the non recurrent FSGS group and the control group in spite of the different follow up periods. Basal creatinine values were 1.11 ± 022 versus 1.21 ± 0.20 in non recurrent FSGS group and control group, respectively. Last visit creatinine values were 1.22 ± 0.23 versus 1.56 ± 1.08 in non recurrent FSGS group and control group, respectively. (P=NS)

Preoperative, preemptive plasmapheresis was performed in 13 patients (65%) with FSGS. In this group, proteinuria recurrence was seen in 5 patients. However, 6 of 7 patients presented with recurrent proteinuria without preemptive plasmapheresis. Preoperative, preemptive plasmapheresis was found effective and statistically significant ($p<0.043$) therapeutic approach.

In order to treat recurrent disease, IVIG was administered intermittently in 5 patients for 1 year after transplantation.

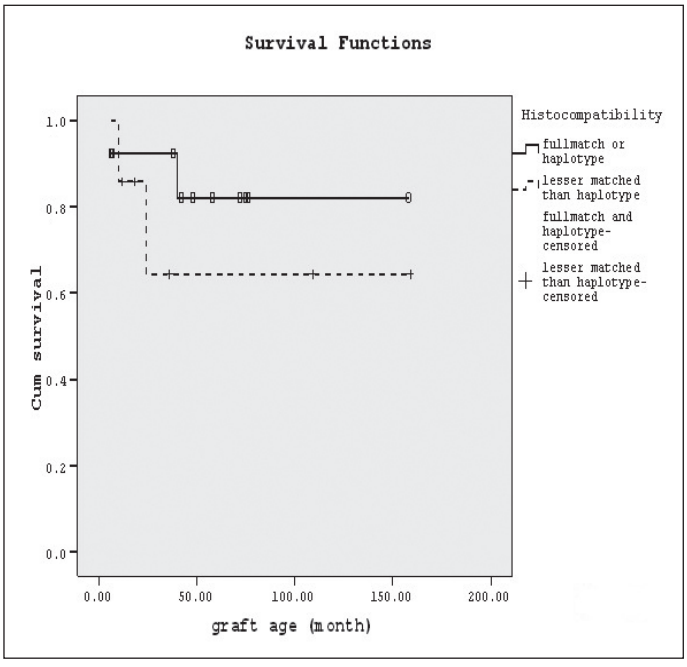

Figure 2*: Histocompatibility and graft survival in FSGS patients (graft age as months).*

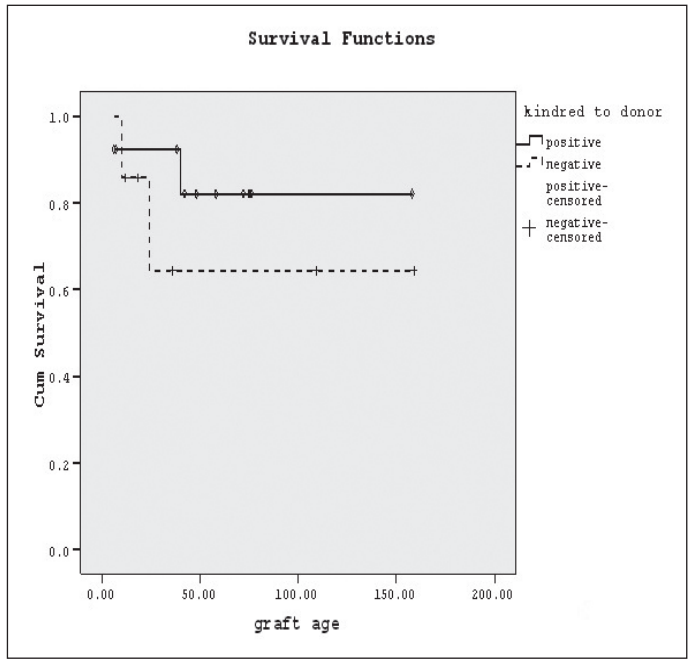

Figure 3: *Kindred to donor and graft survival in FSGS patients (graft age as months).*

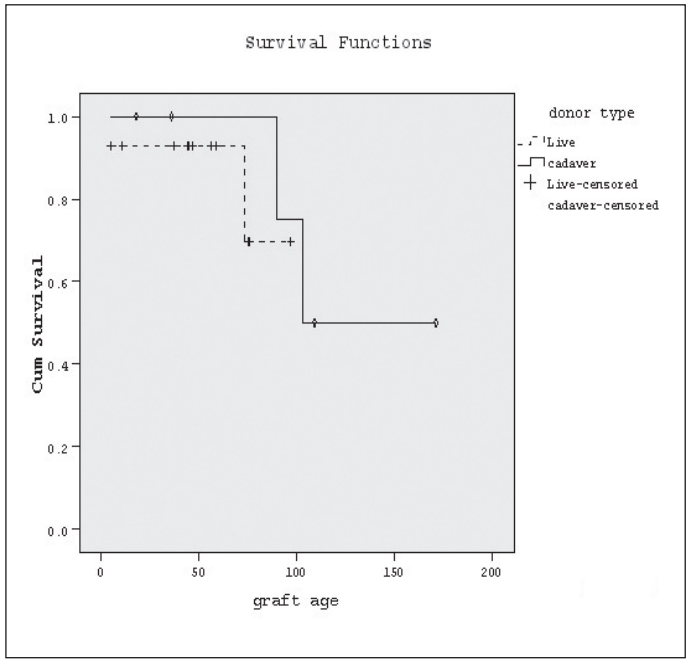

Figure 4: *Donor type and graft survival in FSGS patients (graft age as months). (Kaplan Meier analysis P=0.446)*

Besides plasmapheresis, we also used intravenous IVIG three times a week (in 0,5 gram /kg/ w) to these patients. But rituximab was used in only two patients two times totally monthly interval (0,375 mg/m^2). As long as the treatment continued, recovery of proteinuria was maintained. However; one of them returned to dialysis.

We observed double recurrence in a single patient who had the first graft from a cadaver and the second one from his mother. His graft is still functioning and he is treated with plasmapheresis intermittently.

DISCUSSION

We demonstrated that the rate of FSGS recurrence in allograft is 55%. In previous reports, the recurrence rate was found to be 20 to 80% (11-17). The large range may be attributed to different etiologies of patients with FSGS and may be differing for ethnicity.

We found no differences between groups for recurrence regarding the pre transplant dialysis modalities. Different trials suggest that no differences were found among former modalities of renal replacement therapy and post-transplant recurrence (21).

In our study, we found no increase in acute rejection rates in patients with FSGS compared to patients without FSGS (Study group: 2, control group: 1 p=NS).

In several reports, recurrent FSGS has also been associated with an increased number of acute rejection episodes (22-24). Surprisingly, a higher number of acute rejections in the non-recurrent group were found when compared with the recurrent group. This could be related to the use of plasma exchange in the recurrent group or, unlikely, to an increase in the immunosuppressive therapy in patients with acute rejection. Therefore, most of the results suggest that there is no relationship between recurrence and the risk of rejection (25). Moreover there was no difference in acute rejection rate between the FSGS and no FSGS groups (7).

We found similar results for recurrence in LD and CD patients with FSGS (LD: 6 vs.CD: 5 p=NS).

Baum et al. showed that recurrent primary disease accounted for 15.2% of all graft failures in adolescents transplanted for FSGS with no difference between LD (17%) or CD (13.8%) grafts (7). In our study, we found that the more matching and kindred were the lesser recurrence of FSGS in allograft.

Some of the previous reports suggest that the recurrence of FSGS after renal transplantation is more common in recipients who have received an HLA-identical living-related (LD) transplant. To address these questions, FSGS patients from the United States Renal Data System database (USRDS) between the years 1988–97 were analyzed by Diane at al. (25). It was found 19259 adult primary renal transplant recipients, of which 2414 patients had FSGS as their primary diagnosis as compared to 16845 patients who had other types of glomerulonephritis (GN). Focal segmental glomerulosclerosis patients receiving a zero mismatch LD kidney transplant had the lowest rate of graft loss. Zero mismatch LD kidney transplants are not a risk factor for graft loss in FSGS patients as compared to CD 6-antigen match or mismatched donations.

In FSGS patients, no difference was found for recurrence between LD and CD but histocompatibility has a markedly importance. This result was similar to literature (7).

We also observed that plasmapheresis is effective and has beneficial effects on preserving the allograft when performed before or after transplantation. The plasmapheresis protocols vary from one institution to another. Several studies have shown marked reduction in protein excretion and complete remission in some cases (26-30).

Moroni et al. (31) obtained good results with plasmapheresis treatment in their study on FSGS patients. They found that the prophylactic treatment of plasmapheresis prior to transplantation decreased the incidence of recurrence to 26% versus 54% in controls.

They also found that the use of plasmapheresis and ACE inhibitors led to a complete or partial remission and improved graft survival in 80% of patients (31).

In one study, patients with recurrent FSGS were treated with protein A immune absorption columns with significant reduction in protein excretion in the patients (32). Pre-operative plasmapheresis was shown to reduce the risk of recurrence of FSGS after transplantation; however, relapse after

discontinuation is common (16, 33-35). After transplantation, plasmapheresis or immunadsorption can significantly reduce protein excretion or induce complete remission in patients with recurrent FSGS (36-39).

All available reports were uncontrolled, small-sized and with short-term follow-up evaluation. The long-term prognosis of patients with complete remission after plasmapheresis or immunoadsorption is not clear (40).

Most recently, rituximab, a genetically engineered, chimeric, immunoglobulin G1 monoclonal antibody directed against CD20, was shown to be effective in reducing proteinuria in two pediatric patients with recurrence of FSGS and post-transplant lymphoproliferative disease (PTLD) (9, 41-43).

Plasmapheresis and subsequent rituximab therapy was able to induce remission of proteinuria in one patient, but was ineffective in the other. Another patient responded only to rituximab, but not to plasmapheresis (40). We had used rituximab with plasmapheresis together in 2 patients with recurrent disease. One of them lost his graft and returned to dialysis. The other patient still remains at the treatment of plasmapheresis without rituximab, intermittently. Two more patients with recurrent FSGS have been treated with plasmapheresis.

We often used IVIG in our patients. However, its mode of action was not completely understood, the most important effect seems to be a reduction of alloantibodies via inhibition of antibody production and increased catabolism of circulating antibodies (44). IVIG include potential mechanism for inhibition of complement-mediated injury, inhibition of cytokine generation, and neutralization of circulating antibodies by anti-idiotypes (44).

Limitation of this trial is mainly the limited number of patients included. So some findings that were yielded by Kaplan Meier method could not be confirmed by Cox regression analysis in multivariate statistics.(P=NS) Moreover; this retrospective trial could not provide information about the podosine gene mutation or plasma permeability factor. Complete descriptions of biopsies were not available for us to use the recent classification of D' Agati and colleagues that would improve our findings (45).

CONCLUSION

We found that living donors is not a contraindication for FSGS patient and living donor transplantation has similar survival rate to cadaveric donor transplantation. The most important factor effecting the graft survival is the genetic similarities between recipient and donor.

The most effective approach either to prevent the recurrence of FSGS or treatment of recurrence currently seems to be plasmapheresis. However, its criteria have not yet been defined and vary in different institutions. Further investigations with large patient groups are needed to clarify the plasmapheresis use for FSGS.

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