Single Center Contribution to the Recurrence Rate and Treatment Options of Post-transplant Focal Segmental Glomerulosclerosis

Articoli originali

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ABSTRACT

Background. Post-transplant Focal Segmental Glomerulosclerosis (FSGS) recurrence, the third cause of graft failure in the first year, and its treatment still remains an open challenge. Available evidence reports different approaches both to primary FSGS and post-transplant recurrence but optimal therapeutic management has not been established. This retrospective study aimed to analyze in a monocentric cohort of kidney transplanted patients those with primary FSGS to establish the post-transplant recurrence rate of FSGS and its treatment.

Patients and Methods. 2816 kidney transplanted patients at Padova University Hospital from 1995 to 2023 were retrospectively evaluated to identify those with pretransplant primary FSGS, establish the recurrence rate of post-transplant FSGS and the adopted treatment.

Results. 20 patients out of 2816 had pretransplant primary FSGS and in 5 of them post-transplant recurrences of FSGS were observed (25%). In these patients, immunosuppression regimens with tacrolimus/mycophenolate mofetil/corticosteroids were the most used (75%). Plasmapheresis was used in 4 recurrences and one patient was also treated with rituximab.

Conclusions. Optimal management of FSGS recurrence after transplantation is not yet established while evidence regarding the positive effect of current treatment strategies is very little and limited by a very low number of well-designed randomized trials. Although with limitations, our study might be considered as a further contribution to the limited number of available studies on the still open challenge of identifying the most effective management to reduce/prevent post-transplant FSGS recurrence and provide its best treatment.

KEYWORDS: FSGS, Posttransplant FSGS recurrence, Posttransplant FSGS treatment, Kidney transplant

Introduction

Focal Segmental Glomerulosclerosis (FSGS) is a histopathological picture of nephropathy defined podocytopathy. FSGS has a range of causes including genetic, virus-associated, drug induced and a primary form. This latter is characterized by a sudden onset of nephrotic syndrome induced by a severe foot processes and podocytes damage (effacement and injury), leading to sclerosis [1]. FSGS accounts for 40% of cases of nephrotic syndrome in adults, with an incidence of 7 cases/million/year [2].

The risk of FSGS recurrence after kidney transplant is approximately 32% [3] and goes up to 80% in subsequent transplants, with more than half of these recurrences resulting in a graft loss [4].

Although there have been sensible advances in the pathophysiology, pathology, diagnosis, and management of other types of podocytopathies, primary FSGS remains the most elusive. The cause of primary FSGS is, in fact, still unknown, but also the recurrence of FSGS in transplant patients contributes to the assumption of the existence of a circulatory permeability factor that could play a pathogenetic role in mediating the podocyte injury [3]. The partial or complete remission of post-transplant FSGS recurrence with plasma exchange (PE) and the positive effect of B cell depleting therapy, support the potential for an autoimmunity and autoantibody mediated form, opening the way to the use of rituximab in primary FSGS and in post-transplant FSGS recurrence [5].

There are different histological variants of FSGS, which have a diverse prognostic significance in primary form of FSGS, that however have not been associated with the risk of recurrence after transplantation. The genotype has also been shown not to correlate with post-transplant FSGS recurrence, although screening for genetic mutations has become a routine part of pretransplant evaluation in patients with primary FSGS [6–8].

The main risk factors for the prediction of post-transplant FSGS recurrence seem to be the younger age at the onset of nephrotic syndrome, rapid progression to ESKD within 3 years from diagnosis, heavy proteinuria before transplantation, mesangial hypercellularity or minimal change histology on native biopsy, initial steroid responsiveness that evolves to secondary steroid resistance [9–11].

The TANGO study reported that the median time of post-transplant recurrence of FSGS was 1.5 months [2], therefore, the screening for FSGS recurrence is recommended in transplanted patients with pretransplant FSGS, via monitoring of proteinuria, although the recurrence of FSGS in these patients may be confirmed only by biopsy [12].

Although available evidence reports different treatment options for primary FSGS and recurrence of post-transplant FSGS [13], including the use of rituximab [5] and those still under study with the dual endothelin A and angiotensin II type 1 antagonist spasentan, [14, 15] the SGLT-2 inhibitor dapaglifozin [16] and TNF inhibitor adalimumab [17, NCT04009668], the search of the best treatment of post-transplant FSGS recurrence still remains an open challenge.

Our retrospective study aimed to analyze, in our cohort of patients who underwent kidney transplantation and in follow-up at the Nephrology, Dialysis and Transplantation Unit, University of Padova, those patients with primary pretransplant FSGS to establish the FSGS post-transplant recurrence rate and consider the treatment adopted.

Patients and Methods

All 2816 adults who received a kidney transplant in the Kidney and Pancreas Transplant Unit at the University of Padova between January 1995 and April 2023 were evaluated. Twenty of these patients

were identified having a diagnosis of pretransplant primary FSGS confirmed at the kidney biopsy.

All the 20 patients in the study with a primary FSGS with a worsening of the kidney function and/or proteinuria after transplantation underwent renal biopsy.

The patients with FSGS after transplantation were considered as patients who achieved a complete remission, defined as proteinuria values below 250 mg/day, or partial remission if the daily proteinuria ranged between 300 and 2000 mg/day or reduction below nephrotic range proteinuria.

Data of all patients included in the study were extracted from their medical records: age, sex, type of transplant (deceased donor [DD], living donor [LD] or not genetically-related living donor [NGD]), type of induction and maintenance therapy, mean value of creatinine (µmol/L) and proteinuria (g/24h) after the treatment of FSGS recurrence.

Patients with a diagnosis of genetic form of FSGS as main nephropathy leading to transplantation were excluded. Patient characteristics, as well as the cases of post-transplant FSGS recurrence, are shown in Table 1. Ethical review and approval were waived for this study as required for a retrospective clinical investigation. Patients were not exposed to any risk by the irreversible anonymization of data. The anonymization process prevented any possible transmission of sensible data, saving subject's privacy.

CHARACTERISTICS	VALUE
Men (%)	12 (60%)
Women (%)	8 (40%)
Age at diagnosis (years)	25 years (3-48)
Age at the time of transplant (years)	36 years (7-59)
Previous hemodialysis (%)	16 (80%)
Previous peritoneal dialysis (%)	4 (20%)
Deceased donor kidney transplant (%)	16 (90%)
Living donor kidney transplant (%)	4 (10%)
Re-transplant (%)	5 (25%)
Hypertension after transplantation(%)	11 (55%)
DM after transplantation(%)	3 (15%)
Dyslipidemia	7 (28%)
Post-transplant nephropathy (%)	3 (15%)
Loss of graft (%)	8 (40%)
Mean time to graft loss (years)	5 years
Mean time from tranplantation to diagnosis of FSGS recurrence	6 years
Post-transplant induction therapy (%): ATG + corticosteroids basiliximab + corticosteroids eculizumab	 15 (75%) 4 (20%) 1 (5%)
Post transplant maintenance therapy (%): tacrolimus+mycophenolate+corticosteroids tacrolimus+everolimus+corticosteroids sirolimus+mycophenolate+corticosteroids cyclosporine+mycophenolate+corticosteroids	 15 (75%) 3 (15%) 1 (5%) 1 (5%)

Table 1. Baseline and clinical characteristics of the study patients.

Statistical Analysis

Data were evaluated on a Mac mini (Apple Computer, Cupertino, CA, USA) using the SPSS software 22.0 version (Chicago, SPSS, Inc., Chicago, Illinois, USA). Data are shown as frequencies (percentages) for categorical variables and as mean ± standard deviation for continuous variables.

Results

The mean age of the 20 kidney transplanted patients out of 2816 identified with pretransplant FSGS at the time of histological diagnosis was 25 years. All patients before the transplantation were under renal replacement therapy, 4 with peritoneal dialysis, 16 with hemodialysis and the mean age at transplantation was 36 years. The mean time between the histological diagnosis of FSGS and ESKD was not considered.
The induction and maintenance therapy after kidney transplant were similar for all patients with a triple therapy based on cyclosporine or tacrolimus, antimetabolite or mTORis and low dose of steroids. Of the 20 patients with primary FSGS, 16 (90%) received a deceased donor kidney transplant, while 4 (10%) received a living donor kidney transplant.

About comorbidities, 55% of the patients included in the study were hypertensive, while 15% were affected from diabetes. Three of the 20 patients with primary FSGS before transplantation (15%) underwent to post-transplant nephropathy while 8 patients (40%) lost the graft for causes not related to FSGS recurrences (6 infections and 2 tumors). In the period of the study, 5 recurrences of post-transplant FSGS (25%) were observed in the 20 patients with pre-transplant primary FSGS (Table 2). The diagnosis was confirmed through a biopsy and the mean time between transplantation and recurrence was around 6 years.

Four of these patients received anti-thymocyte globulins (ATG) plus corticosteroids as induction therapy, while 1 patient received basiliximab plus corticosteroids as induction therapy and tacrolimus, mycophenolate, and corticosteroids as maintenance therapy. Two patients with transplants from LD received PE as pre-transplant prophylaxis.

The 5 patients with post-transplant recurrence of FSGS, were treated with PE and one patient, in addition to 6 cycles of PE, was treated with rituximab (375 mg/m^2 once a week for two weeks). After treatment, the remission of the patients was partial with a mean of creatinine of 209.8 mmol/L vs 120.13 mmol/L in the patients without a recurrence and with a maximum of proteinuria of 3 g/dL after treatment. None of the 5 patients with recurrence lost the graft during the mean time of follow-up of 14.78 years. Mean values of proteinuria during the study observation time of the 20 patients with primary FSGS before transplantation are shown in Figure 1. The figure also includes proteinuria values of the 5 patients with FSGS post-transplant recurrence with their mean values after 3 months of treatment (red bars).

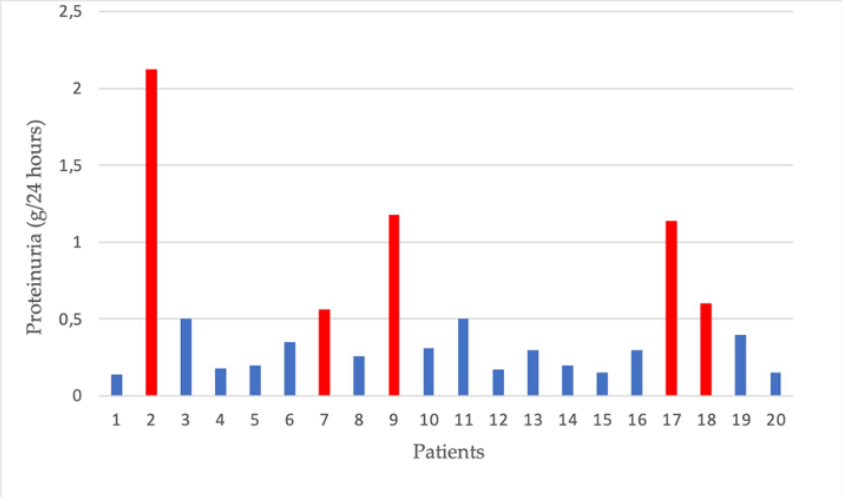

Figure 1. Mean values of proteinuria during the observation period in the 20 patients with primary FSGS before kidney transplant including the 5 patients with FSGS post-transplant recurrence (red bars).

POST-TREATMENT VALUE	
FSGS recurrence (%)	5 (25%)
Mean creatinine (umol/L)	209.8
Mean proteinuria (g/24 h)	1.12

Table 2. Post treatment values of FSGS recurrence (after a mean period of 3 months)

Discussion

The retrospective analysis of post-transplant recurrence of primary FSGS in our cohort of 20 kidney transplant patients with primary FSGS before transplantation showed that the incidence rate of the recurrences was 25% (5 patients).

The therapeutic immunosuppression regimen with tacrolimus, mycophenolate and corticosteroids was the most used (75 %) and 4 cases of recurrence were treated with PE and in one case with the combination of PE and rituximab.

The rationale for the use of PE in these patients is based on the hypothesis of the pathogenetic role of still unidentified circulatory permeability factors whose existence has also been supported by the increased incidence of post-transplant FSGS recurrences when nephrectomies were performed before kidney transplant. This may imply that native kidneys could absorb every potentially harmful circulatory factor, which might damage the graft, indirectly confirming the existence of circulatory permeability factors [18]. Thus, the use of extracorporeal systems (such as PE, immunoadsorption, LDL-A therapy) aimed at removing circulatory factor/s have been supported. The outcome of PE, for example, seems to be linked to the number of sessions performed, typically ranging from 5 to 13 PE treatments, and as reported in literature also the time to remission is highly variable, ranging from 5 to 27 days [19].

The addition of rituximab to PE is now common. It was found in fact that this monoclonal antibody acts directly on podocyte as well as restores regulatory T lymphocytes likely leading to decreased production of possible circulatory permeability factors. Nowadays, however, the optimal timing of rituximab administration and the required number of doses remain not clearly established and different protocols are suggested [5, 20].

It has been recently reported positive results on patients with FSGS managed with combination therapy including rituximab [21] and, although the reduced sample size of the study might limit these results, they contribute to support the hypothesis that depletion of B cells and multitargeted treatment may be effective in the management of primary FSGS including post-transplant recurrence of FSGS [21]. However, Morris and coworkers in their very recent editorial have explored all the available evidence of rituximab use in the management of primary FSGS, which suggest how and in whom the use of this drug might play a positive role [5], including in those patients with post-transplant FSGS recurrence.

Rituximab has also been used in 27 patients at high risk of FSGS recurrence at the time of transplantation [22]. In addition to immune modulating effect, rituximab acted also through the modulation of podocyte function and via prevention of podocytes apoptosis and disruption. This, according with the authors, has determined a lower incidence of post-transplant proteinuria and renal impairment. This study, however, showed only a trend to higher graft survival in rituximab treated patients.

Newer anti-CD 20 therapies, such as ofatumumab, have also been utilized for FSGS recurrence. Ofatumumab is a second generation anti-CD20 monoclonal antibody fully humanized, which is chimeric with murine Fab fragment. In a small cohort of pediatric patients with recurrent and

multidrug resistant FSGS post kidney transplant, ofatumumab was shown to lead to partial remission in 3 out of 6 patients. Ofatumumab has also been shown to induce remission in a patient who did not respond to plasmapheresis, rituximab, or LDLA [23].

Although the pathogenesis of FSGS recurrence in allografts is not fully understood, evidence suggests that anti-CD40 autoantibody may play a role in its development, with blockade of the CD40–CD40 ligand interaction implicated in protection against in vivo induction of FSGS. In vitro and in vivo studies demonstrate altered immunogenicity of the extracellular CD40 domain in FSGS recurrences, with a potential mechanism involving synergism between the anti-CD40 autoantibody and soluble urokinase-type plasminogen activator receptor (suPAR), resulting in podocyte injury and proteinuria. Bleselumab (ASKP1240) is a novel, fully human immunoglobulin G4 anti-CD40 antagonistic monoclonal antibody that displayed a dose-dependent, prolonged occupancy of B-cell CD40 receptors in a phase 1b study in de novo kidney transplant recipients.

A multicenter randomized study of Phase IIA demonstrated that treatment incorporating the fully human immunoglobulin G4 anti-CD40 antagonistic monoclonal antibody, bleselumab, reduced the occurrence of proteinuria in kidney transplant recipients at risk of posttransplant recurrence of FSGS, but this difference was not statistically significant from the standard of care (PE and Rituximab) [24].

Optimal management of FSGS recurrence after transplantation is not well established yet, due to the few evidence regarding available strategies of treatment, partly limited also by the small number of patients, the retrospective nature of the studies and the very low number of well-designed randomized trials.

Conclusions

In conclusion, currently, there is no clear evidence to support a single therapy in the treatment of post-transplant FSGS recurrence. The combination therapy of PE and rituximab to achieve remission or reduce proteinuria and serum creatinine levels is however the most used in these patients. In addition, a very recent French study of Uro-Coste et al. [25] suggested that prophylactic treatment for avoiding FSGS recurrence should not be routinely used in the population of patients with a history of FSGS recurrence on a previous graft based on the lack of difference in the recurrences in the two groups of population (pretreatment VS not pretreatment).

Our study, also due to the small number of patients, does not allow to reach any conclusive evidence about different therapeutic protocols performed for FSGS recurrences after kidney transplant. It, however, adds to the limited number of available studies on the still open challenge of identifying the most effective management to reduce/prevent post-transplant FSGS recurrence and provide its best treatment.

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