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CASE REPORT

Rituximab therapy prevents focal and segmental glomerulosclerosis recurrence after a second renal transplantation

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Summary

Preventive treatment of focal and segmental glomerusclerosis (FSGS) allograft recurrence in high risk recipients having a prior history of graft loss caused by FSGS recurrence is still a challenging question. We retrospectively identified four patients who underwent a second renal transplantation because of recurrent FSGS and who received Rituximab therapy as a prophylactic treatment. Loss of their first allograft was directly related to an early (<3 months) recurrence of FSGS that was either resistant to plasmapheresis therapy in two cases or had escaped to this therapeutic management in the two others. After the second renal transplantation, all patients were free of FSGS recurrence during follow-ups that were between 12 and 54 months long. These preliminary results demonstrate for the first time that Rituximab therapy may constitute an attractive prophylactic option for patients being considered for a second renal transplantation because of recurrent FSGS in their first graft.

Introduction

The major risk after renal transplantation for primary focal and segmental glomerulosclerosis (FSGS) is the recurrence of nephrotic syndrome (NS), which is associated with a significant decrease in graft survival [1–4]. The overall frequency of recurrence in all cases is nearly 30% for the first renal transplant, and increases to more than 80% for a second transplant if the first graft was lost because of FSGS recurrence [5–8]. Consequently, numerous transplant centers are reluctant to consider such patients for a second renal transplantation. The pathogenesis of FSGS recurrence is still unknown but is likely to involve synthesis of a factor, such as soluble urokinase receptor (suPAR) [9–11]. Plasma exchange (PE) seems to be the gold standard treatment for significantly induces complete remission in some patients [6]. Recently, Canaud *et al.* described an attractive therapeutic approach combining intravenous CsA administration and PE sessions for the curative treatment of FSGS recurrence [2].

Preventive treatment of FSGS in patients with a high risk of recurrence remains controversial despite reports that PE therapy decreases the risk of early recurrence in some patients [12]. Rituximab treatment has recently

emerged as a new therapeutic option for treating idiopathic NS before and after renal transplantation [13]. After renal transplantation, Rituximab has been widely used as a curative treatment for recurrent FSGS in cases of incomplete remission or PE treatment dependence [14]. We report for the first time, that Rituximab was an effective prophylactic treatment for recurrent FSGS in four patients who underwent a second renal transplantation because of early recurrent NS in their first graft.

Patients and methods

We performed a national screening by sending a questionnaire to all centers in France involved in renal transplantation ($n = 30$) to identify patients who met the following inclusion criteria: biopsy-proven FSGS leading to End Stage Renal Disease (ESRD); prior kidney graft loss caused directly by recurrent FSGS; and intravenous Rituximab administration on the day of the second transplantation to prevent FSGS recurrence. Four patients who underwent a second renal transplantation between February 2007 and September 2010 were retrospectively identified in two centers (Henri Mondor Hospital in Creteil and Rangueil Hospital in Toulouse). We analyzed usual data with respect to the transplantation characteristics, including: the mean ages of the donor and recipient; the duration of dialysis; the number of human leukocyte antigen (HLA) mismatches; the presence or absence of anti-HLA antibodies; the induction therapy and the maintenance immunosuppressive therapy. All recipients who had positive anti-HLA antibody were considered to be immunized. HLA-DSA detection was based on Luminex single-antigen assays. Follow up data were obtained for all patients up to August 2011.

Results

Four patients (two men and two women) were included in the study.

First transplantation outcome

All patients displayed primary steroid-resistant FSGS that required additional immunosuppressive agents to control the NS and the mean age at FGSG diagnosis was estimated to be 17 years (range of 9–22 years) (Table 1). After diagnosis, the four patients progressed rapidly to ESRD and had a mean interval of 45 months between FSGS diagnosis and dialysis initiation. Recurrence of NS on the first renal allograft occurred in all cases within the first three months after the transplant (mean delay of 31 days). Renal graft biopsies revealed no significant glomerular

Table 1. Demographic, clinical and biological characteristics of patients at the time of and after the first renal transplantation.

Characteristics	P1	P2	P3	P4
Renal transplantation center	Henri Mondor	Henri Mondor	Henri Mondor	Rangueil
Sex	F	M	F	M
Age at FSGS diagnosis (years)	22	22	9	15
Treatment of primary FSGS	Steroids, CsA	Steroids, CsA, chlorambucil	Steroids, cyclophosphamid, CsA	Steroids, chlorambucil CsA
Age at initiation of dialysis therapy (years)	24	28	13	18
Age at first renal transplantation (years)	26	30	19	19
Origin of the graft	Deceased donor	Deceased donor	Deceased donor	Deceased donor
Induction therapy	None	ATG	None	ATG
Maintenance immunosuppressive regimen	CsA, MMF, steroids	CsA azathioprin steroids	CsA MMF steroids	CsA azathioprin steroids
Delay between proteinuria recurrence and renal transplantation (days)	12	85	26	2
Proteinuria level at the time of NS recurrence (g/day)	12	6.5	13.6	12
Renal graft biopsy finding (delay between graft biopsy and renal transplantation)	CsA graft toxicity, no glomerular lesions (60 days)	Minimal change lesions (90 days)	Normal appearing glomeruli (40 days)	FSGS (45 days)
Treatment of FSGS recurrence	Methylprednisolone pulses, increase in CsA blood level, PE	Methylprednisolone pulses, oral steroid therapy, PE	Oral steroid therapy, PE	Oral steroid therapy, PE
Age at the time of graft loss (years)	29	36	24	19

ATG, antithymocyte globulin; CsA, cyclosporin A; FSGS, focal segmental glomerulosclerosis; MMF, mycophenolate mofetil; NS, nephrotic syndrome; PE, plasma exchange.

lesions consistent with recurrent disease in the transplanted kidney in patients P1–P3 whereas a biopsy revealed typical FSGS lesions in patient P4. Multiple renal graft biopsies were subsequently performed that did not demonstrate some other common reason for nephrotic proteinuria occurrence outside FSGS lesions observed finally in all patients including patients P1–P3. In all cases, therapeutic management of FSGS recurrence included plasmapheresis therapy. Finally, graft loss occurred in all patients after a mean post-transplantation period of 45 months (between 12 and 72 months).

Second transplantation outcome

The demographic, clinical and laboratory data of the patients at the time of second transplantation and during the follow-up are summarized in Table 2. Prior to the second transplantation, all patients required induction therapy because of the presence of HLA antibodies. For two patients (P1 and P4), PE therapy was performed in the early post-transplantation period because of the presence of pre-existing donor specific antibodies (DSA). The number of PE sessions for these patients was six for patient P1 and 15 for patient P4. In these two high risk recipients, induction therapy included ATG (antithymocyte globulin, Fresenius) treatment. In both cases ATG treatment (9 mg/kg at day 0, 3 mg/kg at day 1 and day 5) was started before renal transplantation. Immunosuppressive treatment included 14 days of intravenous CsA treatment (2 mg/kg/day) in two patients (P1 and P4) to obtain target blood levels of between 200 and 400 ng/ml. Two patients (P1 and P2) were treated with a single dose of Rituximab (375 mg/m^2) whereas the other two (P3 and P4) received a second injection (375 mg/m^2) at day 7. All patients received Rituximab therapy immediately after surgical procedure. One patient (P2) experienced a biopsy proven acute rejection episode (grade IA) successfully treated by three consecutive days of methylprednisolone

Table 2. Demographic, clinical and biological characteristics of patients at the time of the second renal transplantation and follow-up laboratory data concerning proteinuria evolution after Rituximab infusion.

Characteristics	P1	P2	P3	P4
Recipient age (years)	33	43	28	40
Donor age	33	35	55	49
Number of HLA mismatches (A-B-DR)	3 (2A, 1DR)	2 (1 A, 1DR)	3 (1A, 1B, 1DR)	4 (1A, 2B, 1DR)
Presence of anti- HLA antibodies (%)	48%	10%	15%	80%
Donor specific antibodies	Anti-B7, Anti-B59	No	No	Anti-A24
Origin of the graft	Deceased donor	Deceased donor	Living donor (father)	Deceased donor
Induction treatment	ATG 9 mg/kg at D 0, 3 mg/kg at D1 and D5	IL2R antagonist	IL2R antagonist	ATG 9 mg/kg at D0, 3 mg/kg at D1 and D5
Maintenance immunosuppressive regimen	CsA (i.v., 14 days), MMF, steroids	Tacrolimus,MMF, steroids	Tacrolimus, MMF, steroids	CsA (i.v., 14 days), MMF, steroids
Dose and time points of Rituximab therapy	375 mg/m^2 D0	375 mg/m^2 D0	375 mg/m^2 D0 and D7	375 mg/m^2 D0 and D7
Acute rejection episodes (Yes/No)	No	Yes (grade IA) (two weeks post-transplant)	No	Yes (AMR at M12)
Post-transplant infectious episodes	None	CMV reactivation (M4)	None	None
Circulating CD20$^+$ B cells at M3	0.8% (9/mm^3)	0.4% (6/mm^3)	0.7% (12/mm^3)	0% (0/mm^3)
Creatinine level at M3 (μmol/l)	72	109	98	170
Proteinuria level at M3 (g/day)	0.07	0.18	0.05	0.07
Follow-up (months)	12	54	20	15
ACE-inhibitor or AT1-receptor blocker therapy	No	No	No	Yes (M7)
Creatinine level at the end of the follow-up (μmol/l)	70	118	80	219
Proteinuria level at the end of the follow-up (g/day)	0.04	0.12	0.3	0.08
Circulating CD20$^+$ B cells	0.8% (7/mm^3)	2% (21/mm^3)	1% (13/mm^3)	0.4% (5/mm^3)

ATG, antithymocyte globulin; AMR, antibody-mediated rejection; CsA, cyclosporin A; CMV, cytomegalovirus; D#, number of day post transplantation; HLA, human leukocyte antigen; M#, number of months post-transplantation; MMF, mycophenolate mofetil.

pulses. Antibody-mediated rejection occurred at 12 months in one case (P4) and required PE therapy and Rituximab administration. None of patients experienced proteinuria recurrence after the third month, so none required a second Rituximab infusion to prevent FSGS recurrence. Only one patient (P4) received angiotensin converting enzyme (ACE)-inhibitor started from the seventh post-transplant month for refractory hypertension. At the end of the follow-up period (mean of 25 months, range of 12–54 months), renal function was considered to be optimal in three patients whereas significant renal impairment was present in one patient (P4). The proteinuria levels remained in the normal range during the post-transplantation period with a mean urinary protein excretion of 0.13 g/day (range of 0.04–0.3 g/day) at the end of the follow-up.

Discussion

We report uneventful outcomes for four recipients of second renal transplants who had experienced early recurrence of FSGS in their primary allograft. All these patients received preemptive therapeutic strategies using Rituximab and did not experience FSGS recurrence in the allograft for up to one year after the transplantation.

Since the report of Pescovitz *et al.* in 2006 [15], many transplant teams have used Rituximab in FSGS recipients but mostly as a curative therapeutic approach. The mechanism by which Rituximab could be effective in primary FSGS is still not fully understood. As it depletes CD20-positive B cells, Rituximab has been hypothesized to influence the production of a circulating factor involved in FSGS pathogenesis, either through its direct effects on B cells or through indirect effects on T cells or other cell types that interact with B cells [16]. The recent identification of suPAR as the potential circulating factor involved in FSGS pathogenesis [11] and the ability of Rituximab to prevent FSGS recurrence suggest that this therapeutic management may contribute to the decrease of suPAR production. According to a recent report, Rituximab is also likely to elicit a potential benefit in FSGS by acting directly on podocyte integrity via the preservation of sphingolipid-related enzymes [17]. This study investigated the ability of Rituximab to prevent FSGS recurrence in 27 paediatric transplant recipients. Only 26% of the recipients who received Rituximab developed nephrotic proteinuria within one month whereas 64% of a control group, who did not receive Rituximab treatment, developed nephrotic proteinuria. All these patients were considered to be at risk of recurrence because of their young age (<25 years old) and because they progressed rapidly to ESRD from the time FSGS was diagnosed (<7 years). However, in a group of similar patients receiving a first renal transplant, the incidence of FSGS recurrence was reported to be close to 30–45% [18]. None of these patients received a second transplant after recurrence in the first transplant, as this constitutes the most well-recognized risk factor for recurrence [6,8].

Two of our patients were DSA-positive and received additional PE therapy for immunological indications. This pointed to the potential benefit of using PE therapy to prevent FSGS recurrence. PE may induce complete remission in some cases but it usually fails to achieve sustained remission [6,8,19,20]. In contrast, few studies have investigated the use of PE as a preemptive treatment for high-risk individuals. In 2005, Gohh *et al.* reported the outcomes of ten patients at high-risk for FSGS recurrence, including six who had experienced recurrence on a prior transplant [12]. Three of the six patients with a history of prior recurrence were free of recurrence at follow-up. As recently nicely demonstrated by Wei *et al.* PE therapy may contribute to decrease suPAR level leading to reduce the risk of recurrence.

Our study is the first to strongly suggest that Rituximab provides a potential benefit in preventing FSGS recurrence in very high-risk transplant recipients with a history of early recurrence in their first transplant. If our preliminary results are confirmed by others, the novelty of this preemptive strategy might offer to the waiting list recipients with high risk of FSGS recurrence, the opportunity to be transplanted with a lower risk of recurrence.

Authorship

VA, NK, DS, ICD, SH, PR, JA, MM, LR, PL and PG: participated in research design and in the performance of the research. VA, NK, LR, PL and PG: contributed to data analysis. VA and PG: wrote the manuscript.

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