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Rituximab in post-transplant pediatric recurrent focal segmental glomerulosclerosis

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Abstract

Background—Focal segmental glomerulosclerosis (FSGS) recurs in 20–40 % of allografts. Plasmapheresis (TPE) has been one of the mainstays of treatment with variable results. Rituximab (RTX), a monoclonal antibody to the protein CD20, is being used for treatment of recurrent FSGS (recFSGS) but pediatric experience is limited.

Methods—We conducted a retrospective review of eight patients with recFSGS, treated with RTX (1–4 doses) after having minimal response to TPE. Complete response was defined as a decrease in urine protein creatinine ratio (Up/c) to less than 0.2 and partial response was a decrease in Up/c ratio by 50 % of baseline and in the sub-nephrotic range (U p/c <2).

Results—Complete response was seen in two of eight patients, and partial response was seen in four of eight patients. Two patients had no response. At last follow-up, all the partial responders had sub-nephrotic range proteinuria (Up/c ratios ranging from 0.29 to 1.6). Delayed response, up to 9 months post-RTX, was also seen in some of the patients. Significant complications such as rituximab-associated lung injury (RALI), acute tubular necrosis, and central nervous system (CNS) malignancy were also observed in our case series.

Conclusions—Rituximab can be used with caution as a treatment for recFSGS. Efficacy is variable from none to complete response. Even partial reduction in proteinuria is of benefit in

prolonging the life of the allograft. Long-term, multicenter studies are needed to prove its sustained efficacy in those who respond and to monitor for serious adverse effects.

Keywords

Focal segmental glomerulosclerosis; Recurrent disease; Transplant; Proteinuria; Plasmapheresis

Introduction

Focal segmental glomerulosclerosis (FSGS) is a major cause of steroid-resistant nephrotic syndrome in the pediatric age group and accounts for about 11 % of end-stage renal disease (ESRD) cases. This number has increased significantly since the 1980s when it accounted for only about 1 % of incident ESRD cases [1]. The recurrence rate of postrenal transplantation FSGS is as high as 20-40 % [2, 3]. This is one of the most deleterious complications, resulting in allograft loss. The etiology of recurrent focal segmental glomerulosclerosis (recFSGS) is not completely understood but a circulating permeability factor has been implicated. For this reason, plasmapheresis (TPE) has been one of the mainstays of therapy. Response rates to TPE, measured by remission of proteinuria have been variable.

There has been some suggestion in the literature that B cells may be involved in the pathogenesis of focal segmental glomerulosclerosis (FSGS) by releasing a permeability factor or by abnormal cross talk with T cells [4, 5]. The paucity of treatment options and the serendipitous finding of resolution of proteinuria while treating other conditions like idiopathic thrombocytopenic purpura (ITP) [6] and post-transplant lymphoproliferative disorder (PTLD) [7, 8] has led to the use of rituximab (RTX) for recFSGS and there are few case reports suggesting its utility [9-14]. There have been reports of adverse effects such as neutropenia and anaphylaxis with the use of RTX for recFSGS in the transplanted kidney [10, 11]. Since FSGS frequently recurs immediately post-transplant, these patients are already heavily immunosuppressed and may be at higher risk of complications with added immunosuppression.

We report our experience of treating recFSGS that failed TPE with RTX in pediatric transplant recipients at four different centers across the US. This is the largest case series reported so far. We also attempted to evaluate the side-effects associated with RTX use in this condition.

Materials and methods

A retrospective chart review was undertaken for children who had recFSGS in the transplanted kidney and were treated with rituximab. Recurrence was defined as a urine protein/creatinine ratio (Up/c) of >2 without another identifiable cause. Immediate recurrence was defined as occurring within 1 week post-transplant.

Induction immunosuppression regimens for the kidney transplant were mostly Thymoglobulin™ and methylpred-nisolone except for two patients (cases 7 and 8), who were induced with basiliximab and methylprednisolone. Maintenance regimens consisted of tacrolimus and mycophenolate mofetil except for two patients; one was maintained on cyclosporine and mycophenolate mofetil (case 7) and the other on prednisone in addition to the tacrolimus and mycophenolate mofetil (case 8).

Once these children were diagnosed with recFSGS, they received TPE as indicated and tolerated. Most of these patients were also treated concurrently with an angiotensin-

converting enzyme inhibitor and/or angiotensin receptor blocker for added antiproteinuric benefit.

Children were treated with RTX 375 mg/m²/dose once weekly for 1-4 doses after having minimal or no response to TPE. The method of administration of RTX was determined by each center's protocol. Response to therapy was measured by Up/c ratio, which was the main outcome variable. Complete response was defined as Up/c less than 0.2 and partial response was defined as decrease in Up/c ratio by 50 % of baseline and in the sub-nephrotic range (Up/c <2). Side-effects were noted.

Results

Eight children (age range 5-17 years) were identified to have post-transplant recurrence of FSGS at four different centers across the United States. Six of the eight patients received living donor (LD) transplants, two received a deceased donor (DD) transplant. One patient had two transplants, the first being a LD and the second being a DD. In three of the eight cases, the diagnosis of recurrence was confirmed by an allograft biopsy. Four of the eight children had received preemptive TPE prior to transplantation.

All the cases were on TPE for a variable period of time for as little as 3 days to 61 months post-transplant before RTX was used. Complete response was seen in 2/8 (25 %) patients with normalization of Up/c ratios. Partial response was seen in four of the eight (50 %) patients. Two patients (25 %) had no response.

Cases 2, 3, and 8 had a delayed onset of response as long as 9 months after the RTX infusion. One of the non-responders, case 5, had a delayed but significant decrease in proteinuria although it is still in the nephrotic range (Up/c ratio decreased from 10 to 2.4, 17 months post-RTX) with stable serum creatinine levels.

Case 7 was the only one that did not have an immediate recurrence. He recurred about 4 years after transplant and proteinuria was resistant to TPE. He had a complete response after a single dose of RTX. He had two other episodes of recurrence, each one being a year apart, again both these episodes of recurrence responded to a single dose of RTX. After each dose of RTX, his CD 19 count decreased to <1 %, and recovery of CD19 counts did not predict a relapse. This was also seen with case 8 who had a recovery of CD19 several months after RTX but no proteinuria. No correlation was found between percent of CD19 B cells and proteinuria during the follow-up period in other patients. Recovery of CD19 counts was not associated with return of proteinuria in those who responded and CD19 depletion did not necessarily predict a response.

At last follow-up, all of the partial responders had subnephrotic range proteinuria (Up/c ratios ranging from 0.29 to 1.6). Clinical features of study participants are further delineated in Table 1.

Significant complications such as acute tubular necrosis, central nervous system (CNS) malignancy, RTX-associated lung injury (RALI) and death, were also observed in our case series.

Case 4 developed a particularly severe form of recFSGS, with massive proteinuria (U p/c >10) and oliguric allograft dysfunction on day 1 post-transplant and required initiation of TPE and dialysis. A kidney biopsy confirmed recurrence with global glomerulosclerosis and extensive foot process effacement. RTX was started on POD # 7. Urine output, Up/c ratio, and allograft function started improving 2 weeks after starting RTX, and dialysis was held. He was discharged home 3 weeks after starting RTX with an Up/c of 2.3 and a serum

creatinine of 2.2 mg/dl. A week later he became severely anemic and required packed red blood cell (PRBC) transfusion. The same night he developed nausea, vomiting, shortness of breath, and was brought to the emergency department. He was found to be hypoxemic with an oxygen saturation of 75 %. Chest X-ray showed bilateral multifocal pulmonary infiltrates, which were later confirmed on a computed tomography scan. At the time of admission, his serum creatinine was 1.6 mg/dl and Up/c ratio was 1.9, the lowest post-transplant. His condition progressively deteriorated and he went into multiorgan failure, requiring pressor support, high-frequency ventilation, and continuous veno-venous hemofiltration (CVVH). He died of hypoxemic respiratory failure 5 weeks post-RTX. No infectious agent was identified on multiple cultures. Autopsy findings of rare microthrombi in the transplanted kidney and pulmonary hypertensive changes suggested thrombotic microangiopathy. The cause of death was most likely respiratory failure. This could be a potential case of rituximab-associated lung injury although it is difficult to assign causality to RTX alone.

Case 8 had received the most number of RTX doses in our series and he developed a malignant CNS glioma 1 year after the last dose of rituximab. Complications are enumerated in Table 2.

Discussion

Recurrent focal segmental glomerulosclerosis carries a significant disease burden both in terms of medical and emotional costs. Recurrent disease can occur at any point post-transplant, and ultimately leads to graft loss [15, 16]. Rapid progression to ESRD is the most consistently reported risk factor for recurrence in the literature [2, 3, 17]. Younger age, living related donor transplant, recurrence in prior allograft and non-black race are the other factors shown to be associated with a risk for recurrence [2, 17-19]. A significant increase in urine protein excretion is the initial manifestation of recurrence. No other clinical biomarkers are currently available to diagnose recurrence. It was recently reported by Wei et al. that serum soluble urokinase receptor (suPAR) levels are elevated in subjects with primary FSGS and higher levels pre-transplant were also associated with risk of recurrent disease [20].

Therapeutic options for recFSGS are few and results are inconsistent. TPE has traditionally been used to manage the proteinuria with variable success [21-23]. TPE has to be performed 1-3 times per week and places significant burden on the family, patient, and the healthcare system. Calcineurin inhibitors and cyclophosphamide have also been used in conjunction with TPE with variable outcomes [24, 25].

Rituximab is a monoclonal antibody against the CD20 antigen and causes depletion of B-lymphocytes. Its beneficial role in decreasing proteinuria in recFSGS was serendipitously discovered while treating a pediatric transplant recipient for post-transplant lymphoproliferative disease [7, 8]. The exact mechanism of action of rituximab in recFSGS is still unclear. Various hypotheses are being proposed. FSGS is thought to be a T-cell mediated disease. B-cells co-stimulate T-cells and this may be disrupted by rituximab [14]. Others hypothesize that the permeability factor in FSGS resembles an immunoglobulin and may be produced by B-cells. A recent study reports that rituximab acts by a B-cell-independent mechanism. It attenuates the pathogenic effect of recFSGS sera on sphingolipid-related enzymes that might disrupt the actin cytoskeleton and podocyte architecture causing proteinuria [26].

A review of the published literature seems to suggest that children have a higher likelihood of responding to rituximab as compared to adults. A response was seen in 81 % of the

pediatric cases reported in the literature as compared to 50 % of adult patients [11, 27-36]. Complete remission was seen in ~66 %, and partial remission in ~14 % of the reported pediatric cases [7, 9-13, 37-39]. Our patient cohort showed a 75 % response rate with 25 % of the cases showing complete remission and 50 % showing a partial decrement in proteinuria. Araya et al. analyzed data compiled from 18 published case reports to determine factors associated with response to rituximab in recFSGS. Data from 39 patients (19 pediatric) were evaluated and it showed lower age at transplant ($p=0.014$) and normal serum albumin at diagnosis of recurrence ($p=0.01$) to be predictive of either partial or complete response to rituximab [40]. We were unable to evaluate this association in our patients because of the small sample size. Early treatment with rituximab has also been reported to be more beneficial in the literature. Sakai et al. evaluated the literature on use of rituximab in children and adults and showed that rituximab infusion was performed significantly earlier in effective cases ($n=12$, 100 ± 95 d after onset of massive proteinuria) than in ineffective cases ($n=13$, 468 ± 379 d after onset of massive proteinuria), $p=0.003$ [33]. Our study did not show this to be true with reduction in proteinuria being seen in patients who received rituximab within 1 month post-transplant as well in those who received it 3 years post-transplant. There are reports of recurrence of proteinuria after recovery of CD19 counts, but we did not observe any correlation between CD19 percent levels and the recurrence of proteinuria.

We were able to discontinue TPE in the patients with complete remission and the frequency of TPE sessions could be decreased in those with partial response. The decrease in TPE frequency did not worsen the proteinuria. All of our patients received rituximab after having minimal or no response to TPE so in those who responded it is likely because of the rituximab.

Most of the literature for rituximab use in recurrent FSGS does not report many severe adverse effects. However, complications such as infusion reactions varying from mild respiratory symptoms and hypotension to severe anaphylaxis, ulcerative colitis, CMV colitis, hepatitis, neutropenia, and persistent hypogammaglobulinemia have been reported with use of rituximab for other conditions [10, 11, 41-43].

Rituximab-associated lung injury (RALI) was a term coined by Bitzan et al. and it can include interstitial pneumonitis, alveolar-interstitial pneumonia, pulmonary fibrosis, and cryptogenic organizing pneumonia (COP). They reported two pediatric cases that developed pulmonary symptoms after receiving rituximab for primary FSGS and acute allograft rejection [44, 45]. They also reviewed the literature and found 30 adult patients, aged 58 to 69 years, who had received rituximab for B-cell malignancies, one for graft-versus-host disease and one for immune thrombocytopenia; 71 % also received concomitant chemotherapy. Eleven of 31 patients required mechanical ventilation, and nine died (29 %). Ventilation was a significant predictor of fatal outcome (odds ratio 46.7; confidence interval 9.5-229.9) [45]. Several small pediatric studies also report pulmonary-adverse events after rituximab use [41, 46].

Infections (28 %) and malignancy (11 %) are common causes of death in pediatric transplant recipients [47]. Two subjects in our case series developed complications such as RALI leading to death and a malignant glioma. Although it is hard to assign causality to RTX alone, these complications should serve as a reminder that RTX can potentially have very serious adverse effects, especially in combination with other immunosuppressive medications these children are already receiving. In most of the studies reported, the duration of follow-up has been relatively short and complications may present at a later date, indicating that close surveillance must be maintained.

Conclusions

Rituximab can be used cautiously as a treatment for recurrent FSGS. Efficacy is variable, ranging from none to complete response. Even partial reduction in proteinuria is of benefit in prolonging the life of the allograft. However, the potential toxicity of rituximab has to be kept in mind and closely monitored. Long-term, adequately powered, multicenter studies are needed to elucidate factors that may predict a favorable response, prove its sustained efficacy in those who respond, and monitor for potentially serious adverse effects.

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Table 1

Clinical features of study participants

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Gender	Male	Male	Male	Male	Female	Female	Male	Male
Race	Cau	Cau	AA	AA	Cau	Cau	Cau	Cau
Age at transplant (years)	15	12	5	16	17	14	7	15
Induction regimen	Thymo + Sol	Thymo+ Sol	Thymo + Sol	Thymo + Sol	Thymo + Sol	Thymo + Sol	Simu+ Sol	Simu + Sol
Maintenance regimen	FK+ MMF	FK +MMF	FK + MMF	FK + MMF	FK + MMF	FK + MMF	Cyclo + MMF	Pred+FK + MMF
Time to recurrence post-transplant	Immediate	Immediate	Immediate	Immediate	Immediate	Immediate	4 years	Immediate
Pre TPE Up/c	2.3	3.4	>20	>10	10	2	>25	10
Duration of TPE prior to RTX (months)	1.5	47	36	0.1 (3 days)	17	61	1.2	6
Duration to RTX post- transplant (months)	2	47	36	0.25	17	63	48	6
Total number of rituximab doses	4	4	4	4	8	1	3	10
CD 19 % (4 weeks post-RTX)	0	0	0	0	0	1	<1	<1
Response	Partial	Partial	Partial	Partial	None	None	Complete	Complete
Time to response (months)	1	9	9	0.5	12	NA	1.5	8
S. creatinine pre-RTX	1.2	1.2	0.74	4.2	2.2	1.8	1	1.2
S. creatinine 4 weeks post-RTX	0.9	1.1	1.2	1.6	2.8	1.7	0.8	1.0
S. creatinine at last follow-up	1.2	1.2	1.0	1.6	1.9	1.8	0.8	1.3
Up/c pre RTX	2.3	8.1	4.4	6.1	10	25	23	4.19
Up/c 4 weeks post-RTX	1.2	3.3	6.5	2.2	8	21	0.20	0.14
Up/c at last follow-up	0.43	0.7	0.29	1.6	2.4	11	0.10	0.12
Duration of follow-up post-RTX (months)	24	17	18	1	17	41	3	33

Can Caucasian, AA African American, *Thymo* thymoglobulin, *Sol* methylprednisolone, *Simu* basiliximab, *FK* tacrolimus, *MMF* mycophenolate mofetil, *Cyclo* cyclosporine, *Pred* prednisone, *TPE* plasmapheresis, *Up/c* urine protein creatinine ratio, RTX rituximab

Table 2

Complications associated with rituximab

	Case 4	Case 6	Case 8
Complications	RALI	ATN and AKI	CNS malignancy
Time to complication	5 weeks	Immediate	1 year
Death due to complication	Yes	No	No

RALI rituximab-associated lung injury, *ATN* acute tubular necrosis, *AKI* acute kidney injury, *CNS* central nervous system