Rituximab Treatment for Adult Patients with Focal Segmental Glomerulosclerosis

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Abstract

We present two cases with steroid-resistant nephrotic syndrome (SRNS) and two cases with steroid-dependent nephrotic syndrome (SDNS) due to focal segmental glomerulonephritis (FSGS) who were treated with a single dose of rituximab (375 mg/m²). Although the two cases with SRNS showed no response, the two cases with SDNS achieved complete remission. The patients in whom the peripheral B-cell counts subsequently increased after the administration of rituximab demonstrated a relapse. Rituximab may be an effective treatment agent for SDNS with FSGS and the peripheral B-cell count may be a useful marker in such patients for preventing disease relapse.

Key words: focal segmental glomerulosclerosis, nephrotic syndrome, rituximab

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Introduction

Focal segmental glomerulosclerosis (FSGS) is the main cause of the idiopathic nephrotic syndrome, however, the pathophysiology of FSGS still remains poorly understood. Some patients (steroid-resistant and/or steroid-dependent patients) show frequent relapses, which necessitate administration of repeated courses of prednisolone (PSL) at high doses. The adverse effects of long-term PSL treatment can be serious. A paradigm shift from such toxic 'non-specific' therapies to selective immunomodulating and immunosuppressive regimens is necessary (1).

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen which is present on B cells. Recently several case reports have suggested that rituximab may be effective in the treatment of patients with MCNS and FSGS (2-6). In this report we describe four patients with a nephrotic syndrome due to FSGS who were treated with rituximab because of failure of the standard immunosuppressive therapy or intolerance.

Case Report

Case 1

A 25-year-old woman was diagnosed as having idiopathic nephrotic syndrome (INS) when she was 13 years old in 1996. She was started on treatment with prednisolone (PSL; 60 mg/day; 1 mg/kg), however, she experienced a relapse as soon as the PSL dose was reduced to 40 mg/day, and a renal biopsy was therefore performed. Histological examination of the renal specimen revealed lesions of the collapsing variant of FSGS. Although intravenous semi-pulse methylprednisolone (mPSL) therapy (500 mg/day for three days) was administered and oral cyclosporine (CyA: AUC 0-4 1,700-2,000 ng/mL) and mizoribine (MZ: 150 mg/day) were started, they did not appear to exert any beneficial effect on the patient. She was treated with oral PSL at 60 mg/day and six sessions of low-density lipoprotein apheresis (LDL-A) were also given in 1998. However, she became progressively more resistant to steroids and was finally labeled as having

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Figure 1. The clinical course of Cases 1 to 4. PE: plasma exchange, HD: hemodialysis, PSL: prednisolone (mg/day), MMF: mycophenolate mofetil, CyA: cyclosporine, UP: urinary proteinuria (g/day), TP: total protein (g/dL), Alb: albumin (g/dL), Cr: creatinine (mg/dL).

developed SRNS when she was 18 years old in 2001. She had a urinary protein level of 6.5 g/day and deteriorated renal function (serum creatinine 1.3 mg/dL) at the onset of rituximab therapy (a single infusion of 375 mg/m²: 500 mg) in June 2008, and decreased proteinuria and improved renal function (Fig. 1) in this patient had not occurred.

Case 2

A 27-year-old woman was diagnosed as having INS when she was nine years old in 1991. Successful treatment was accomplished with standard prednisolone treatment. However, after reduction of the steroid dose, the patient experienced a relapse. She responded again to steroids, but frequent relapsing nephrotic syndrome (FRNS) and steroid-dependent nephrotic syndrome (SDNS) developed at the age of 11 years in 1993. This led to the step-by-step use of currently available medications for patients with SDNS in addition to steroid therapy, including cyclosporine (CyA), however, these treatments were not effective. A kidney biopsy in 1999 showed lesions of the perihilar variant of FSGS. In May 2009, we decided to treat her with rituximab.

We administered single-dose rituximab (a single infusion of 375 mg/m²: 500 mg). Complete remission occurred 2 weeks later and was maintained for ten months despite dis-

continuation of the steroid therapy and CyA. She developed relapses in May and September 2010, associated with an increase of the CD19/20-positive B cell count and rituximab was administered both times. In March 2011, an increase in the CD19 cell counts was again noted, and we then administered rituximab for the fourth time even though she had not demonstrated a full relapse. Thereafter, complete remission was achieved and maintained, despite eventual discontinuation of PSL and CyA (Fig. 1).

Case 3

A 21-year-old man was diagnosed as having INS when he was 12 years old in 2002. A kidney biopsy was performed because of SRNS. The histological examination of the renal specimen revealed lesions of the not otherwise specified (NOS) type of FSGS. Intravenous semi-pulse mPSL therapy and CyA were administered, with complete remission being the apparent result. Thereafter, because he developed frequent relapses and became steroid-dependent, he was started on cyclophosphamide (CPA) in October 2003 and mycophenolate mofetil (MMF) in September 2005. Because he developed SRNS again at the age of 17 years, LDL-A was undertaken in January 2007. But despite these treatments, remission was not achieved. The patient had severe proteinuria

Table 1. Patient Characteristics and Clinical Data

Case	Age	Sex	Onset (y)	U-P (g/day)	Cr (mg/dL)	variant	SDNS /SRNS	Remission	Relapse before RTX (n/y)	Relapse after RTX (n/y)	PSL before RTX (mg/day)	PSL after RTX (mg/day)
1	25	F	12	6.5	1.3	collapsing	SRNS	NO	(-)	(-)	5	0.1
2	27	F	9	9.8	0.5	perihilar	SDNS	Yes	6	1.5	20	9
3	21	M	12	13	2.1	NOS	SRNS	NO	(-)	(-)	20	30
4	26	F	10	3.6	0.4	tip	SDNS	Yes	3	0.5	29	19

U-P proteinuria (g/day); Cr creatinine (mg/dL); RTX rituximab; PSL prednisolone

and deteriorated renal function at the onset of rituximab (13 g/day and 2.1 mg/dL, respectively), thus the previous therapeutic strategies did not appear to have exerted any beneficial effect on this patient (Fig. 1).

Case 4

We report the case of a 26-year-old woman with FRNS. She was diagnosed as having INS when she was seven years old in 1992. She was started on treatment with PSL, however, she experienced a relapse as soon as the PSL dose was reduced. Although she was given CyA and CPA, they did not appear to exert any beneficial effect and she developed SDNS at the age of 11 years. She often suffered from steroid-associated toxicities, such as cataracts, depression, lumbar compression fractures and osteoporosis. A kidney biopsy in 1998 showed lesions of the tip variant of FSGS. Although MMF was also administered in 2007, remission could not be achieved.

We administered single-dose rituximab in February 2008. Complete remission occurred 2 weeks later and was maintained despite discontinuation of the steroid and CyA. In April 2010, an increase in the CD19 cell counts was noted, and then we administered a second rituximab treatment even though she had not demonstrated a relapse. Although complete remission was achieved and maintained in the patient, despite eventual discontinuation of PSL and CyA, she developed relapses in January 2011, associated with an increase in her CD19/20-positive B cell count and a third rituximab treatment was administered (Fig. 1).

Discussion

In this report, we presented four cases of FSGS treated with rituximab. The main demographic and clinical characteristics are shown in Table 1. All patients received a single dose of rituximab. In most of the previous studies, rituximab was given at a dose of 375 mg/m² body surface area once weekly for 4 weeks, because this dosage is recommended for patients with B cell lymphoma or autoimmune diseases (4, 7). However, Smith (8) reported successful treatment of an SDNS patient with a single dose of rituximab. In addition, Kamei et al (3) reported a prospective study of a single dose of rituximab for refractory SDNS. We have also successfully treated MCNS with a single dose of rituxi-

mab (9-11). Therefore, we treated the FSGS patients in the present study with a single dose of rituximab.

Rituximab administration was effective in cases 2 and 4 who had SDNS, but Cases 1 and 3 with SRNS did not show a response. Gulati et al reported the efficacy and safety of rituximab in 33 patients with SRNS and 24 patients with SDNS. Six months after rituximab therapy, 9 (27.2%) patients with SRNS showed complete remission, 7 (21.2%) had partial remission, and 17 (51.5%) had no response. Of 24 patients with SDNS, remission was sustained in 20 (83.3%) at 12 months (12).

Renal biopsies from the patients in the present study showed lesions of the collapsing variant (Case 1), perihilar variant (Case 2), NOS variant (Case 3) and tip variant (Case 4). The percentage of globally sclerosed glomeruli was 66% (Case 1), 14% (Case 2), 17% (Case 3) and 6% (Case 4). The effect of rituximab was recognized in lesions of the perihilar and tip variant, and was also demonstrated in the lower global sclerosed glomeruli. Compared with other variants of FSGS, collapsing FSGS is less responsive to steroids and other immunosuppressive drugs. According to most previous reports, the prognosis is usually poor, and patients are more likely to be in end-stage renal disease within a few years in spite of therapy (13, 14). Kaito et al reported a case with steroid- and cyclosporin-resistant collapsing FSGS who went into complete remission with a combination rituximab and steroid pulse-therapy while receiving CyA (15).

In Cases 2 and 4, the number of relapses was significantly lower (from 6 to 1.5, from 3 to 0.5) between the observed period before and after rituximab injection. No relapse of proteinuria was recorded during the B-cell depletion period. In addition, rituximab therapy allowed the prednisolone dose to be reduced in these two patients (Table 1).

In the present Case 1, a single treatment of rituximab and low dose steroid were not successful, because she demonstrated 66% global sclerosis. In Case 3, a single treatment of rituximab, CyA and low dose steroid were also not successful. This case had renal insufficiency, and demonstrated the NOS variant with 17% global sclerosis. Two patients failed to respond in spite of B-cell depletion. The reasons might be the effect of SRNS, renal insufficiency, variants of FSGS or the percentage of global sclerosis.

In conclusion, Rituximab could be one of the useful therapeutic agents for adult patients with steroid dependent

FSGS. Despite the small patient population, our results suggest that this treatment should be considered as one of the options in the management of adult patients with steroid-dependent FSGS. More studies are necessary in the future to characterize the type of patients who have FSGS and who could benefit from rituximab administration. In addition, a longer follow-up is necessary in order to evaluate possible adverse events of rituximab.

The authors state that they have no Conflict of Interest (COI).

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