CASE REPORT

Repeated Administrations of Rituximab along with Steroids and Immunosuppressive Agents in Refractory Steroid-resistant Nephrotic Syndrome

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Received : August 26, 2015;
Initial review: December 19, 2015;
Accepted: October 04, 2016.

Background: A recent randomized control trial in children with steroid-resistant nephrotic syndrome revealed that two doses of rituximab did not reduce proteinuria. **Case characteristics:** A 14-month-old boy developed refractory steroid-resistant nephrotic syndrome due to focal segmental glomerulosclerosis. **Observation:** The patient achieved complete remission 11 months after disease onset following eight doses of rituximab combined with steroids and cyclosporine. **Message:** Long-lasting B cell depletion with repeated rituximab administrations may be required to achieve complete remission in patients with steroid-resistant nephrotic syndrome and massive proteinuria.

Keywords: *Cyclosporine, Focal segmental glomerulosclerosis, Treatment failure.*

The chimeric monoclonal anti-CD20 antibody rituximab (RTX) has recently emerged as a therapeutic option for refractory steroid-resistant nephrotic syndrome (SRNS). Bagga, *et al.* [1] reported the efficacy of treatment with four doses of RTX in five patients with nephrotic syndrome resistant to treatment with high-dose corticosteroids, alkylating agents, and calcineurin inhibitors [1]. In another study, a single dose of RTX was not effective in inducing remission in children with SRNS [2]. Furthermore, a recent randomized control trial in 31 children with SRNS revealed that two doses of RTX did not reduce proteinuria at three months [3]. We report the case of a child with refractory SRNS due to focal segmental glomerulosclerosis (FSGS) who achieved complete remission 11 months after disease onset, following repeated administration of RTX.

CASE REPORT

A previously healthy 14-month-old boy diagnosed with idiopathic nephrotic syndrome was initially admitted to another hospital with generalized swelling and significant weight gain. Perinatal history was normal and family history was negative for renal disease. Despite treatment with high-dose prednisolone (2 mg/kg/day), he developed acute kidney injury and was referred to our center. Physical examination revealed generalized edema, abdominal distention, and a blood pressure of 106/63 mmHg. Laboratory findings were as follows: blood urea nitrogen 46 mg/dL, serum creatinine 0.34 mg/dL, sodium 125 mmol/l; potassium 4.1 mmol/l, calcium 7.9 mg/dL, phosphorous 4.7 mg/dL, total protein 3.6 g/dL, albumin 1.8 g/dL, total cholesterol 526 mg/dL, and serum IgG 93 mg/dL. Urinalysis by dipstick revealed 3+ occult blood and 4+ protein. Urinary protein/creatinine ratio (U-P/C) was 156.9 and the 24-h urinary protein excretion was 21 g (2 g/m^2/h). After two weeks of hemodialysis, the patient's renal function improved. However, persistent heavy proteinuria for >4 weeks with high-dose PSL led to a diagnosis of SRNS; renal biopsy showed features of FSGS and electron microscopy showed diffuse foot process effacement (>80%). Genetic mutation for *NPHS2* and *WT1* was negative. We treated the patient with intravenous methyl-prednisolone (20 mg/kg/day for 3 consecutive days per week) for 3 weeks, followed by cyclosporine (CsA; 6-7 mg/kg/day) and alternate-day prednisolone (1.5 mg/kg). However, the patient developed AKI again, which prompted the decision to switch from CsA to mycophenolate mofetil, and to initiate peritoneal dialysis. After 4 weeks of peritoneal dialysis, the renal function recovered and the patient was re-treated with CsA. However, massive proteinuria (11-18 g/day, U-P/C 120-200 g/g) persisted, and the patient required albumin infusions for more than two months. Therefore, we treated the patient with a combination of 2-weekly doses of RTX (375 mg/m^2) and additional intravenous dose of methylprednisolone. However, there was no significant reduction in proteinuria, and complete B cell depletion

(CD19 cell 0%) was not achieved, despite administration of the two doses of RTX. The serum RTX levels just after the first and second dose were 232.1 and 223.6 µg/mL, respectively; thereafter, the levels fell very quickly and were 5.1 and 2.6 µg/mL at 7 days after the first and second dose, respectively. We administered two additional doses of RTX followed by intravenous methyl-prednisolone and a second course of high-dose prednisolone (2 mg/kg/day), leading to complete B cell depletion and a subsequent marked decrease in proteinuria (<1 g/day, U-P/C 1-10 g/g). This treatment strategy resulted in the discontinuation of albumin infusions without the development of edema. At 54 days after the complete B cell depletion with fourth RTX infusion, re-emergence of CD19 cells (0.7% of total lymphocyte count) was detected and 4 more RTX infusions were added (total 8 doses), which maintained a long-term B cell depletion for the next four months. The serum RTX levels just after the fifth dose was 274.4 µg/mL. In contrast to the rapid decrease in the serum RTX levels following the first and second dose, at 10 days after the fifth dose, the patient had sustained the serum RTX levels at 75.4 µg/mL. At two months after the last (eighth) RTX infusion (11 months after the disease onset), he finally achieved complete remission and prednisolone was gradually tapered off. At the age of 3 years and 5 months, he maintained in complete remission with cyclosporine monotherapy despite the re-emergence of CD19 cells.

DISCUSSION

Despite the increasing use of RTX in children with refractory nephrotic syndrome, very little information is available on its pharmacokinetics, particularly in SRNS. In this case, we observed that the serum RTX levels declined more rapidly during a phase of massive proteinuria, indicating the need of its repeated administration at shorter intervals in patients with refractory SRNS. We previously reported that the mean serum half-life of RTX in patients with steroid-dependent nephrotic syndrome (SDNS) during a proteinuria-free period was 14.6 days [5], and the mean duration from the RTX administration until B cell was detectable was 5.1 months [6]. Counsilman, *et al*. [7] reported a very short (<1 day) serum half-life of RTX in a 10-year-old patient with SRNS, during a phase of nephrotic-range proteinuria [7]. Considering the potential losses through urine, more frequent dosing of RTX may be required to maintain the serum RTX levels, particularly in patients with SRNS.

Although RTX is regarded as a relatively safe treatment for children with idiopathic nephrotic syndrome, various adverse events such as late-onset neutropenia, hypogammaglobulinemia, and increased risk of infections, have been rarely reported [8]. Although our patient did not have neutropenia and bacterial infections after RTX therapy, despite a lack of significant proteinuria, severe hypogammaglobulinemia (184 mg/dL) requiring intravenous gammaglobulin developed at two months after the last (eighth) RTX infusion.

We conclude that long-lasting B cell depletion with repeated RTX administrations at shorter intervals may be required to achieve complete remission in children with SRNS and severe proteinuria. Studies are needed to determine the optimal doses of RTX and suitable concomitant immunosuppressive agents for refractory SRNS.

Acknowledgement: Chugai Pharmaceutical Co, Ltd. (Tokyo) for the measurement of serum rituximab concentrations.
Contributors: Both authors have contributed to patient management and manuscript writing.
Funding: None; *Competing interests*: None stated.

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