Rituximab for Treatment of Focal Segmental Glomerulosclerosis in a Child: A Case Report

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Abstract

Objective: To study the efficacy of rituximab in children with focal sclerosing glomerulonephritis (FSGS).

Case Report: Before treatment, blood biochemistry, hepatic and renal function, differential white cell counts, immunoglobulins and the complement system were assessed. Promethazine (0.5-1 mg/kg) and methylprednisolone (0.1-0.3 mg/kg) were administered intravenously 30 min and 5-10 min before the rituximab infusion. Rituximab (0.27 g) was diluted in 300 ml glucose solution and initially administered at 50 ml/hr the rate increased to 50 ml/hr every 30 min after no side effects occurred in the first hour. A second dose was given one month later. During treatment, prednisone (30mg) was taken on alternate days. Benazepril (3.3 mg) was administered every day with one chongcao capsule.

Homemade ertapenem was given three times a day. Outcome: Eyelid and limb edema declined two weeks after the first application of rituximab and resolved after the second treatment. Urinary protein levels decreased, serum albumin increased, and white cell counts, hepatic function and renal function remained constant. After 3 months of follow-up, urine protein decreased significantly, and serum albumin (35.2 g/L) and cholesterol (5.4 mmol/L) normalized. Parameters of immune activation also reduced, and the patient remained well.

Conclusion: In this case, rituximab was a safe and efficacious treatment for FSGS.

Keywords: Rituximab; Pediatrics; Sclerosing; Glomerulonephritis; Therapy

Introduction

For refractory nephropathy in children who are resistant to the classical treatment, such as steroid or immunosuppressive agents, B Cell Depletion Therapy (BCDT) may be a useful option. BCDT is specific for the removal of B cells by apoptosis; the most commonly use medicine currently is rituximab. Rituximab is an anti-CD20 human-rat mosaic monoclonal antibody that has been constructed by gene recombination technology [1,2]. It has been used in recent years in the treatment of B-cell lymphoma, rheumatoid arthritis, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, refractory nephrotic syndrome and other autoimmune diseases. The following paper reports the clinical application of rituximab in a single pediatric case with focal sclerosing glomerulonephritis (FSGS).

Case Report

A 4-yr-old male patient (17 kgs) presented to his local hospital with edematous eyelids and lower limbs without an apparent cause in October 2008. His urine protein level was 3+, with a serum albumin of 20.6 g/L and cholesterol of 13.7 mmol/L; the diagnosis of Nephritic Syndrome (NS) was made. The patient was given prednisone (35 mg) every day. One month later, his urinary protein was still positive, and white cell counts, hepatic function and renal function remained constant. After 3 months of follow-up, urine protein decreased significantly, and serum albumin (35.2 g/L) and cholesterol (5.4 mmol/L) normalized. Parameters of immune activation also reduced, and the patient remained well.

The patient was referred to Jinling Hospital for further treatment. After admission, physical examination showed edema of the lower limbs and eyelids, full consciousness, no reddened throat, swollen tonsils, or abnormalities on heart and lung auscultation. There was no pleural rub. The abdomen was soft without tenderness, and there were no abnormalities of the nervous system. Laboratory examinations revealed proteinuria at 4+, red blood cells 1200/ul, ascorbic acid +, NAG enzyme 25.1 u/g•cr, urine retinol binding protein 0.31 mg/L, urinary C3 2.71 ng/L, and urinary α2-M 2.95 ng/L. Full blood count analysis revealed white blood cell count 7.8×10⁹/L, platelets 268×10⁹/L, and lymphocytes 0.39 hemoglobin 102 g/L, platelets 268×10⁹/L. Albumin serum was 24.1 g/L, cholesterol 9.5 mmol/L, triglyceride 2.75 mmol/L, glucose 3.8 mmol/L, blood urea nitrogen (BUN) 4.4 mmol/L, creatinine (Cr) 58 mmol/L, ALT 7u/L, aspartate aminotransferase 18 u/L; IgG 0.690 g/L, IgA 0.313 g/L, IgM 0.520 g/L, IgG 0.691 g/L, IgA 0.314 g/L, IgM 0.520 g/L, IgE 21.5 Iu/ml, C3 0.899 g/L, C4 0.350 g/L, CRP <3.20, RF <20, anti-O <25 u/mL. Clotting analysis showed the following: activated thromboplastin time 27.4 seconds, fibrinogen 382 mg/dl, prothrombin time 10.6 seconds, and thrombin time 17.3

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seconds. CD3 + 75.0 %, CD4 + CD3 + 36.0 %, CD8 + CD3 + 38.0 %, Th: Ts0.95; CD19 + 127a/ul, CD19 + Gate 6.34 %, CD20 + 103a/ul, CD20 + Gate 5.15 %. B ultrasound showed no abnormal renal sonogram.

A repeated renal pathology showed the following: 19 glomeruli, where 11 showed glomerular sclerosis with hyalinization, glomerular capsule fibrosis, reduced glomerular volume, capillary lumen occlusion, part of the ball wall adhesion, tubular atrophy, dilation, and renal interstitial fibrosis. Immunofluorescence showed IgG (-), IgA (-), IgM (+++), C3 (-), and C1q (-) (Figures 1-7).

After the mechanism and dosage of rituximab was explained to the guardians of the patient, informed consent was obtained. Phenergan (0.5-1mg/kg) was injected intravenously half an hour before treatment, and dexamethasone was injected intravenously 5 to 10 minutes before treatment. Rituximab (0.27 g) was diluted in 300 ml 5% glucose solution. The initial fluid infusion rate was 50 ml/hr, and the dose was increased one hour later in the absence of side effects to 100 ml/hr. One month later, the second intravenous infusion was taken. Prednisone (30 mg) was given every other day on a gradually reducing dose, and benazepril (3.3 mg) was taken once a day, and cordyceps capsules (0.45 g) were taken three times a day with our self-produced ershenkang (a kind of traditional Chinese medicine), which was beneficial for the renal diseases.

Results
After the first infusion of rituximab, the edema of the eyelid and lower extremities decreased, and disappeared after the second intravenous infusion. There was no hydrothorax. One month after the first intravenous infusion of rituximab, serum albumin increased, cholesterol and triglycerides had no apparent change, while liver and kidney functions and blood parameters were both normal; three months after the second infusion, the blood leukocytes were 5.2×10⁹/L, (N -0.46, L-0.52) Hb-121-g/L, Plt-341×10⁹/L; serum albumin was 35.2-g/L, cholesterol was 5.4-mmol/L, triglyceride was 1.94 mmol/L,
Rituximab has been given in recurrent or chemotherapy-resistant B cell types in non-Hodgkin’s lymphoma, due to its specific inhibition of B cells, and indirect action against T cells. It has gradually been applied to other clinical immune complex diseases, such as systemic lupus erythematosus and refractory thrombocytopenic purpura, among others. In recent years, clinicians have applied rituximab to refractory renal diseases, to refractory renal diseases [3,4], although this has not been attempted in China.

In this paper, rituximab was given to a child with FSGS and, two weeks after the first intravenous infusion, edema of the eyelids and lower extremities declined. A gradual improvement in clinical and laboratory parameters was observed, and the edema resolved completely within a month of the second treatment infusion. No adverse effects of treatment were observed. The numbers of T helper cells and B lymphocytes both decreased, while the levels of other blood cells and overall liver and kidney function were not affected. The results showed that rituximab plays a role in both the humoral and cellular immune function through targeted therapy against B cells [5].

Several crucial points should be adhered to during the application of rituximab: i) rituximab should be diluted in sterile conditions in sodium chloride or 5% glucose solution to a concentration of 1 mg/ml, and the infusion bags of mixed solution should be inverted gently to prevent foaming; ii) the initial intravenous speed for the first hour of the infusion was 50 mg/hr, which then increased by 50 ml every 30 minutes. The maximum speed remained less than 300 mg/hr; iii) rituximab should be used with caution in patients with a neutrophil count of less than 5×10⁹/L and/or the platelet count was less than 75×10⁹/L patients. During treatment, the neutrophil and platelet counts should be monitored regularly; iv) if any allergic reaction occurs, the patient should be treated appropriately with standard agents, such as epinephrine, antihistamines and corticosteroids [6].

This study reports the safe and effective use of rituximab in the treatment of refractory focal sclerosing glomerulonephritis in a child. This was apparently mediated through the significant decrease in circulating B cells and it provides a new approach for patients with difficult B cell-mediated renal disease.

Table 1: The change before and after the intervention of rituximab.

| Urinary protein | Before the treatment | after the first infusion | after the second infusion |
|-----------------|----------------------|-------------------------|--------------------------|
| Urinary protein | 4+                   | 2+                      | 1+                       |
| 24-hr urinary protein (g/L) | 1.71               | 0.68                    | 0.32                     |
| Urinary NAG enzyme (u/g-cr) | 25.1                | 17.2                    | 13.4                     |
| Urinary retinol binding protein (mg/L) | 0.31               | 0.29                    | 0.32                     |
| Urinary C3 (mg/L) | 2.71                | 2.76                    | 2.8                      |
| Urinary α2-M (ng/L) | 2.95               | 2.78                    | 2.96                     |

This study demonstrates that rituximab has been effective in treating refractory focal sclerosing glomerulonephritis in a child.

Discussion

Rituximab is a chimeric IgG1 mouse/human monoclonal antibody, which is specifically designed against the CD20 antigen in the cell membrane. This antigen is located in the pre- and mature B lymphocytes, but does not exist in the hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues.