Rituximab Treatment for Adult Purpura Nephritis with Nephrotic Syndrome

Hiroaki Ishiguro, Tatsuo Hashimoto, Mariko Akata, Shota Suzuki, Kengo Azushima, Yusuke Kobayashi, Tomohiko Kanaoka, Shinichiro Yoshida, Hiromichi Wakui, Jin Oshikawa, Kiyotaka Nagahama, Yoshiaki Inayama, Kouichi Tamura, Yoshiyuki Toya and Satoshi Umemura

Abstract

The case of a 68-year-old woman with purpura nephritis associated with nephrotic syndrome is herein described. The patient’s clinical course and the findings of a renal biopsy study revealed purpura nephritis. Following treatment with corticosteroids and intravenous cyclophosphamide accompanied by an angiotensin II type I receptor-blocker, an anti-platelet drug and an hydroxymethylglutaryl (HMG)-CoA, the proteinuria mildly decreased. Additional rituximab therapy led to a complete remission. This report describes our successful experience using rituximab to treat refractory nephrotic syndrome of purpura nephritis. Further studies are required to confirm the efficacy of rituximab as an alternative therapy for nephrotic syndrome.

Key words: purpura nephritis, nephrotic syndrome, corticosteroids, cyclophosphamide, rituximab

(Intern Med 52: 1079-1083, 2013)
(DOI: 10.2169/internalmedicine.52.9325)

Introduction

Henoch-Schönlein purpura (HSP) nephritis is a rare kidney disease; however, up to 30% of all affected adult patients develop end-stage renal disease (ESRD) during long-term follow-up (1). A recent meta-analysis concluded that data for interventions used to improve kidney outcomes are very sparse, with the exception of short-term steroids, and that there is no evidence that steroids prevent serious long-term kidney disease in HSP patients (2). Furthermore, a prospective randomized trial demonstrated that the addition of cyclophosphamide provides no additional benefits for adults with severe HSP compared to treatment with steroids alone (3). The development of other optional treatments to prevent purpura nephritis from progressing to ESRD is required.

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen present on B-cells. The efficacy of rituximab in standard treatment-refractory chronic Henoch-Schönlein purpura was recently reported in three children (4). In this report, we describe a case of purpura nephritis associated with nephrotic syndrome treated with rituximab due to the failure of standard immunosuppressive therapy.

Case Report

In April 2011, a 68-year-old Japanese woman was referred to us for an evaluation of lower limb edema, purpura and proteinuria. A clinical examination showed a regular pulse rate of 83 beats/min, a blood pressure of 132/76 mmHg, a temperature of 36.6°C and edema and purpura in the feet; however, the patient reported no complaints of any abdominal pain. A urinalysis showed protein 4+ and blood 3+ with sediment that contained 21 to 30 red cells per high-power field, 3 to 5 granular casts per low-power field and 1 to 3 red cell casts per wide field. The patient’s daily urinary protein excretion was 6.6 g/day, the protein:creatinine ratio in the urine was 10.4 g/gCr and the creatinine clearance was...
67.6 mL/min. Laboratory studies revealed the following results: hemoglobin, 12.6 g/dL; platelets, 38.3x10⁴/μL; fasting blood glucose, 128 mg/dL; creatinine, 0.58 mg/dL; blood urea nitrogen, 30 mg/dL; total cholesterol, 144 mg/dL; total protein, 4.1 g/dL; serum albumin, 1.8 mg/dL; IgG, 301 mg/dL; IgA, 144 mg/dL; IgM, 46 mg/dL; C3, 96 mg/dL; C4, 35 mg/dL; CH50, 46.2 U/mL; antinuclear antibodies, myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA), C-ANCA and rheumatoid factor were negative (Table). Computed tomography of the abdomen showed normal sized kidneys and abdominal dropsy.

A renal biopsy was performed in April 2011, which detected 65 glomeruli. Light microscopy revealed global sclerosis in three glomeruli and cellular crescents in nine glomeruli. There was mesangial proliferation and endocapillary hypercellularity in some locations (Fig. 1a, b). No evidence of vasculitis was seen in the vessels. The morphology of the tubules was almost maintained. Immunofluorescence was partially positive for IgA in both the mesangial and glomerulocapillary lesions (Fig. 1c). IgM, C3, C4 and C1q were weakly positive in the same patterns. Paramesangial and subendothelial dense deposits were found on electron microscopy (Fig. 1d).

After the biopsy, the patient was treated with half-dose pulse steroid therapy (methylprednisolone, 500 mg per day for three days) with subsequent oral steroid therapy (prednisolone, 25 mg per day, 0.6 mg/kg/day); however, the patient’s urinary protein excretion remained high. In addition, two rounds of intravenous cyclophosphamide therapy (500 mg per time) were administered, although the nephrotic state remained. Furthermore, rituximab therapy (375 mg/m² body surface area per time) was administered once weekly for four weeks and a complete remission was finally achieved and maintained after the four weeks. After a 1-year follow-up, the level of urinary protein excretion in fresh urine was under the limit of detection and the serum CD19/20-positive B-cell count remained low (Fig. 2).

**Discussion**

Henoch-Schönlein purpura nephritis is a rare kidney disease leading to ESRD. The risk of chronic kidney disease is higher in adults than in children; however, it varied from 35% to 69% in 388 patients followed up for at least five years in four published series (5-8). Although the risk is high, some patients can recover spontaneously, even those with a severe clinical and histologic presentation, while the clinical courses of other patients worsen following the initial presentation of mild symptoms. Therefore, it is difficult to develop experimental treatment protocols and interpret treatment efficacy (9). A recent meta-analysis concluded that there is no evidence that steroids prevent serious long-term kidney disease in patients with HSP (2). Moreover, a prospective randomized trial demonstrated that the addition of cyclophosphamide provides no additional benefits in adults with severe HSP compared to treatment with steroids alone (3). Recently, some case reports suggested that rituximab is a potential treatment modality for HSP (4, 10).
In this report, we presented the first case of purpura nephritis with nephrotic syndrome in an adult successfully treated with rituximab therapy. Initially, we began the treatment regimen by administering steroids intravenously (500 mg per day for three days) and orally (25 mg per day, 0.6 mg/kg/day) in accordance with the guidelines of the Japanese Society of Nephrology. After the patient was administered half-dose pulse steroid therapy, the moderate leg edema improved to a mild status and the purpura disappeared. However, the urinary protein excretion remained above 6 g/day and the cholesterol level continued to be high, approximately 350 mg/dL on average; therefore, a second regimen using intravenous cyclophosphamide (500 mg per session every 28 days for two cycles) was accepted. Additional intravenous cyclophosphamide (IV-CY) therapy lowered the cholesterol level to approximately 290 mg/dL; however, the leg edema remained mild and the nephrotic syndrome persisted. After being administered two courses of IV-CY, the patient developed loss of hair and she requested discontinue of IV-CY, even though six courses of IV-CY are widely recommended. Our department has newly initiated an advanced medical care promotion project using rituximab to treat refractory nephrotic syndrome, although the drug is not approved for nephritis and a warning of off-label use has
been issued by the Food and Drug Administration (FDA). When we presented rituximab as an alternative therapy, the patient understood that the drug was beyond the range of her health insurance and was not approved to treat nephritis and that we had developed a program for its use as an advanced medical care promotion project. She understood the risks and benefits of rituximab; therefore, we administered a third regimen using this drug in the present case. Rituximab therapy (375 mg/m² body surface area per session) was administered once weekly for four weeks according to the recommended dosage for patients with B-cell lymphoma or administered once weekly for four weeks according to the recommended dosage for patients with B-cell lymphoma or autoimmune diseases (11, 12). The successful use of single-dose rituximab therapy has been reported in some patients previously exhibiting minimal changes (13-15). In patients with membranous nephropathy, four weekly infusions are generally accepted and achieve a good response (16, 17). In this case, the patient achieved complete remission after four weeks of therapy and maintained this positive status for over one year without any additional administration of rituximab. Following the rituximab therapy, the patient’s leg edema completely disappeared and her cholesterol level decreased to approximately 220 mg/dL. In addition, no apparent adverse effects definitively related to rituximab infusion were observed. Within this period, the level of CD19/20 lymphocytes was under the detectable limit. This indicates that the effects of rituximab in reducing the amount of urinary protein is a consequence of its inhibitory actions on B-cell differentiation and immunoglobulin secretion, as documented in several recent studies (18-20), and that the level of CD19/20 lymphocytes can be used as a useful marker to predict relapse. The effects of rituximab in depleting the level of circulating CD20-positive cells continue for nine to twelve months, and additional courses of rituximab can be administered effectively and safely (21) as a result of its low immunogenicity derived from being a human component (22). Therefore, the use of rituximab therapy may help to manage nephrotic syndrome patients who are sensitive to the drug by administering a single agent easily for a longer period. However, physicians must pay attention to and address side effects. HSP is suspected to be sensitive to rituximab (4), and the drug has the potential to decrease the risk of ESRD. Further studies are needed to prove the sensitivity and efficacy of rituximab in patients with purpura nephritis. Incidentally, rituximab is associated with serious side effects such as progressive multifocal leuкоencephalopathy; therefore, it should be used carefully.

We were unable to find any case reports of the use of rituximab to treat purpura nephritis with nephrotic syndrome in an adult in the literature. This is the first report of the successful use of rituximab in a patient with purpura nephritis with steroid-resistant nephrotic syndrome.

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

References


© 2013 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html