Rituximab Followed by Mycophenolate Mofetil in Children With IgM Nephropathy

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IgM nephropathy presents with refractory nephrotic syndrome and its treatment is a significant challenge for pediatricians. We present two patients with IgM nephropathy and frequently relapsing nephrotic syndrome treated with rituximab and subsequently mycophenolate mofetil. Both showed complete remission, which 24 to 30 months later, was still maintained. The role of mycophenolate mofetil therapy in maintaining remission after successful treatment of rituximab in IgM nephropathy needs to be examined.

Key Words: *IgM nephropathy, Management, Mycophenolate mofetil, Rituximab.*

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Immunoglobulin M nephropathy often presents with refractory nephrotic syndrome which may respond to steroid treatment [1,2], though long-term remission of proteinuria was achieved in only 14% patients, indicating the need for a more effective treatment [1,3]. Rituximab, a chimeric monoclonal antibody directed against the CD20 cell surface receptor expressed on B cells, is successful for treatment of refractory idiopathic nephrotic syndrome [4]. We report two patients with IgM nephropathy and frequently relapsing nephrotic syndrome who responded to the combination therapy of reduced-dose rituximab followed by mycophenolate mofetil.

CASE REPORTS

Case 1: This 14-month-old boy was hospitalized for steroid sensitive nephrotic syndrome with but frequentrelapse. Complete remission was achieved 12-days after cyclosporine A therapy and maintained for the next 10 months. The proteinuria recurred after an episode of pneumonia. The patient later showed seven relapses within one year, associated with hypertension, hirsutism and gingival hyperplasia. Renal biopsy showed mesangial proliferation and IgM deposits in the mesangium.

Therapy with cyclosporine was stopped and he was administered two doses of rituximab (375 mg/m^2/week for 2 weeks). Complete remission was sustained and peripheral CD19 cell count dropped from 277/mm^3 to 20/mm^3, but increased to 458/mm^3 four months later. At that time, mycophenolate mofetil (20 mg/kg/day) was given as maintenance therapy. The patient has been on remission for more than 2 years. CD19 positive lymphocyte count has ranged between 863~1037/mm^3 recently. At last follow-up, his serum creatinine was 0.39 mg/dL, and 24-hr urinary protein was 98.5 mg.

Case 2: This 3-year-old had frequent relapses in the first year of onset. The kidney biopsy revealed mesangial proliferation with IgM mesengial deposits on immunofluorescence examination and deposits electron dense deposits on electron microscopy. She was administered tacrolimus at a dose of 87 µg/kg/day, and had complete remission after 15 days, which was maintained for 15 months. The trough level of tacrolimus ranged from 4.5 to 8.1 ng/mL. Following stoppage of tacrolimus she had two relapses despite low-dose prednisone (0.5 mg/kg/day).

We administered two dose of rituximab (375 mg/m^2/week for 2 weeks). Complete remission was sustained two weeks later when CD19/20 positive B lymphocytes were no longer detected. Mycophenolate mofetil (17.5 mg/kg/day) was added 6 months after rituximab administration when CD19 count recovered to 52/mm^3. Two years after the last dose of rituximab, complete remission was maintained and no adverse events were observed during follow-up. The patient had abdominal discomfort for three days during the initial stage of mycophenolate mofetil therapy, but disappeared thereafter. At last follow-up, her serum creatinine was 0.46mg/dL and 24-hr urinary protein was 112.7 mg.

The variation of CD19 positive cell count and the time for mycophenolate mofetil administration in both patients is shown in ***Fig.* 1**. The research was approved by the Ethics Committee of the University.

DISCUSSION

IgM nephropathy is shown to have a unsatisfactory response to steroids and more frequent relapses than minimal change disease. [1] Betjes, *et al.* [5] described a recurred IgM nephropathy patient after kidney transplantation, in whom two doses of rituximab lead to complete and long-term remission.

WHAT THIS REPORT ADDS?

- Combined therapy with rituximab and mycophenolate mofetil is effective in sustaining remission in patients with IgM nephropathy.
- Recovery of B-cells is not associated with relapse of nephrotic syndrome.

The optimal dose of rituximab in idiopathic nephrotic syndrome is not established. The standard protocol consists of 4-doses of 375 mg/m^2 administered at weekly interval. This multi-dose regimen, however, may cause hypersensitivity reactions and is expensive [6]. Several prospective studies have reported that lower doses also lead to CD19+ cell depletion and remission of proteinuria in idiopathic nephrotic syndrome [7-8]. Gulati, *et al*. [9] reported 24 patients with steroid dependence who received 2 infusions of rituximab. Remission was sustained in 20 (83.3%) patient at 12 months follow-up. Both of the present patients had favorable response to two dose infusion of rituximab, and no further doses was administered.

Rituximab has a significant steroid-sparing effect in idiopathic nephrotic syndrome, however, patients are likely to relapse with recovery of CD20+ cells. It is proposed that additional therapy with mycophenolate mofetil sustains remission, without the need to administer repeat dose of rituximab. Ito, *et al*. [10] reported, in prospective cohort study, the efficacy of combined therapy of rituximab followed by mycophenolate mofetil. During 1-yr follow-up, 6 of nine patients did not relapse, implying that maintenance therapy with mycophenolate mofetil is useful in sustaining for remission. Similar results were seen in the two patients in the present study.

Meanwhile, it is possible that the clinical remission in many idiopathic nephrotic syndrome patients can continue for a long time after the recurrence of B-cells. Kamei, *et al.* [11] reported that B cell recovery need not result in relapses. In the present study, remission was sustained despite recovery of B cells after rituximab therapy. This study suggests that rituximab may be a therapeutic option for the treatment of patient with IgM nephropathy. The potential role of mycophenolate mofetil therapy in maintaining remission after successful treatment with rituximab needs to be prospectively examined.

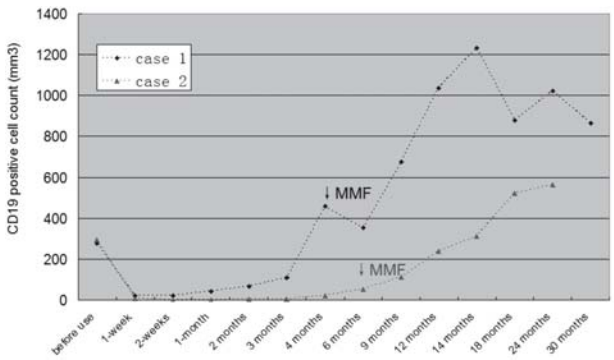

FIG. 1 *Variation of CD 19 positive B cells in the two patients during follow-up. The time of initiation of therapy with mycophenolate mofetil (MMF) is shown by vertical arrows.*

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