Introduction

Hemophilia is a severe bleeding disorder, which can result in significant morbidity and mortality. Bleeding episodes are effectively treated by replacing the deficient factor; however, it is common for patients to develop inhibitors to factor VIII (FVIII) or IX, which leads to uncontrollable and life-threatening bleeding events [1]. The hemophilia patients with inhibitors have difficulty in controlling bleeding; and therefore experience more critical conditions compared to the hemophilia patients without inhibitors. For the cases of severe hemophilia A, the incidence rate of inhibitor is 15-50% (average is about 30%) [2,3]. In such cases, coagulation factor supplementation does not work. Currently, two bypassing agents are available for treating hemophilia patients with inhibitors: activated prothrombin complex concentrates (APCCs) and recombinant activated factor VII. Despite the use of bypassing agents, the best treatment is to remove the antibody using immune toler-
ance induction (ITI) [1-3]. Rituximab (Basel, Roche) can be used in particular. There was a report from overseas in 2004, regarding the use of Rituximab for hemophilia patients with high inhibitor titers [4]. After that, many attempts have been made using monotherapy or combination therapy with Rituximab [5-8]. In the present study, the authors co-administered Rituximab to a 5-year-old patient with hemophilia A while using ITI and investigated its effects and availability though this treatment was a failure as a result. We discuss the case in addition to providing a review of the literature.

Case Report

A 5-year-old boy was referred to our hospital due to severe hemophilia A with inhibitor. In his past medical history, after his first hospitalization at another university hospital due to swelling in his right knee at about 15 months of age, he was diagnosed with severe hemophilia A. There was no history of hemophilia or hemorrhagic disease in his family. At that time, the coagulation factor test showed FVIII <1% and a large deletion of exon 1-22 on FVIII mutation study. He was treated with a FVIII concentrates, Recombinate® (Deerfield, Baxter), after being diagnosed with severe hemophilia A. He had high-titer inhibitor (211.12 Bethesda Units (BU)) at around 17 months of age. After that, he was treated with APCCs, FEIBA™ (Deerfield, Baxter), for bleeding control. However, there were repeated episodes of bleedings within joints, and also a large amount of hemoptysis was developed four months before the patient visited us. Thus, he was transferred to our hospital to receive ITI to remove the inhibitors.

Laboratory findings: The values from peripheral blood tests showed leukocytes 10,600/μL, hemoglobin 12.5 g/dL, hematocrit 37.9%, platelet count 481,000/μL, prothrombin time (PT) 11.9 seconds (0.91 INR), and activated partial thromboplastin time (aPTT) 166.2 seconds. Also, the coagulation factor test showed FVIII <1% and a FVIII inhibitor titer of 44 BU. The biochemical blood test results were within the normal range. The immunoglobulin (Ig) test showed the following results: IgG 927 mg/dL (345-1,236), IgA 71 mg/dL (14-159), IgM 108 mg/dL (43-207), IgE 7.3 IU/mL (0-230), CD4 25% (35-51), and CD19 15% (5-25).

Treatment and progress: He had a previous inhibitor titer higher than 200 BU before ITI and a large exon deletion from a gene mutation, which are known to be poor prognostic factors of ITI. Therefore, we decided to co-administer a high-dose of FVIII concentrates (Immunate® (Deerfield, Baxter), 100 U/kg/day, daily) and Rituximab (375 mg/m²/dose). Rituximab (375 mg/m²/dose) was administered for more than five hours per session, weekly for four weeks (the induction period) and then monthly for five months. After the last time of co-administering of Rituximab and ITI, the inhibitor titer of the coagulation factor was decreased to the borderline level (Fig. 1). Also, there was a decrease in the frequency of joint bleeding.

In spite of the continued high dose coagulation factor concentrate administration, the patient’s inhibitor titer in-

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**Fig. 1.** The Change of inhibitor titers. After immune tolerance induction with Rituximab, the inhibitor titer had been decreased to the borderline level. However, the administration of intravenous immunoglobulin for his hypogammaglobulinemia again increased the inhibitor titer.
The Use of Rituximab with ITI

Fig. 2. The Change of immunoglobulin levels (A) and lymphocyte subset panels (B). After immune tolerance induction with Rituximab, his laboratory findings showed hypogammaglobulinemia (IgG 422 mg/dL, IgA 27 mg/dL, IgM 20 mg/dL, IgE 4.2 IU/mL, and CD19 0%) (Fig. 2), and repeated manifestations of fever, sinusitis, and otitis media though he had performed as immunization schedule, including S. pneumoniae. Thus, we stopped co-administration of Rituximab and ITI, after sixth infusion of additional Rituximab. Then, we administered intravenous immunoglobulin (IVIG, 400 mg/kg) once, in the 23 months after the initiation of co-administration of Rituximab and ITI. After the administration of IVIG, the patient’s Ig level was slightly improved (Fig. 2A). However, after 8 months since the initiation of the additional treatment, the inhibitor titer was 240 BU, which increased to 510 BU after 9 months, any additional administration of Rituximab was difficult due to the side effects shown on the immunodeficiency findings along with the findings of the increased inhibitor titer, so we decided to stop the continuous administration of FVIII concentrates. There was an increase in the inhibitor titer along with the repeated hemorrhasis, and we are currently observing the patient’s progress while administering APCCs.

Discussion

After the success of removing antibodies by the continuous administration of a coagulation factor, for the first time in 1977, ITI was effective in approximately 60-80% of patients with severe hemophilia A [8]. Recent Korean study showed that complete removal rate of inhibitors was 83% [9]. Currently, ITI is the only effective treatment for removing the antibody. If ITI is successful for hemophilia with inhibitors, it would enable them to use coagulation factors and overcome incomplete bleeding control of bypassing factors, it also makes the prophylaxis with coagulation factor concentrates possible and reduces the cost of treatment. The type of F8 gene mutation in the patient is important in predicting the response of ITI. Also, it is known that pa-
tients with lower initial antibody titer or lower antibody titer during ITI have a better success rate with ITI. If hemophilia patients with inhibitors have poor prognostic factors for ITI, other immunomodulatory therapy can be used. ITI is often performed in conjunction with other treatments, including the use of Rituximab, plasmapheresis, or the combined use of extracorporeal adsorption and cyclophosphamide. Among of them, Rituximab, a humanized monoclonal anti-CD 20 antibody, was approved by the FDA in 1997 [10]. It induces selective expression of B cells by binding to CD20 antigens and increases the death of B cells. With this mechanism, Rituximab shows the efficacy for the treatment of various B cell-mediated diseases including B cell lymphoma and thrombocytopenia, and autoimmune diseases such as autoimmune hemolytic anemia [10-12]. There are several reports on its various uses for hemophilia patients with inhibitors [4,5]. In our case, co-administration of Rituximab and ITI contributed to the inhibitor titer by decreasing it to <5 BU in the severe hemophilia patient with a high inhibitor titer. In additions, a great decrease in bleeding frequency was also observed. Under this treatment, the combined use of coagulation factor concentrates increased the removal of antibody by forming immune complexes or through the process of activating, collecting, and sensitizing antibodies generated by B cells [13]. However, despite the use of Rituximab in this case, the inhibitor titer increased again eight months after the treatment. Collins PW reported a similar result as that seen in our case, where a success rate of 58% was achieved by co-administering Rituximab while undergoing ITI [14]. However, there was one recurrence out of six patients with severe hemophilia A who had a negative inhibitor titer level. In general, Rituximab temporarily reduces the B cell fraction in peripheral blood after its administration. However, the stem cells which do not express CD20 still exist and are unaffected by the treatment. Therefore, reconstruction of the B cell fraction occurs again 6-9 months after the completion of the treatment. On the other hand, the effect of the antibody-mediated immune deterioration is not significant in the antibody-producing plasma cells, since they do not express CD20 [15].

Although it was reported that hypogammaglobulinemia occurs in only around 10% of cases after Rituximab treatment, the cause and mechanism of the recovery period of the B cell fraction and the onset of hypogammaglobulinemia have not yet been elucidated [15,16]. Our case also showed the continuous decrease of antibody levels including IgG and IgM from the pediatric patient through Rituximab administration, due to the decrease of antibody levels including IgG and IgM (Fig. 2). However, the immune deterioration of the patient, which is caused by a decrease in immunoglobulin, brought further complications, recurring infections. The long-term clinical effects and results of Rituximab are not known yet, which is a limitation in the comparison of Rituximab and other immunosuppressants with respect to their advantages and disadvantages in the management of hemophilia patients with high inhibitor titers. Therefore, further modulations of the regimen and more long-term follow-up studies are necessary.

The authors observed the possibility of antibody removal through the co-administration of Rituximab with ITI, for a patient with severe hemophilia A and high inhibitor titer who had a poor prognosis for antibody removal with ITI. Along with the periodic measurements of the inhibitor titer during the treatment with/or of Rituximab, we found that the importance of measuring Ig levels was crucial with respect to infection. Thus, we present this case in addition to our literature review.

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References

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