Difficulties in the treatment of an Infant with Hemophilia B

Dear Editor,

Hemophilia B is a X-linked recessive bleeding disorder which occurs as a result of Factor IX (FIX) deficiency (1, 2). In some patients with hemophilia, antibody (inhibitor) and allergic reaction may develop against FIX protein which is administered for treatment (3). While antibody develops against the factor administered in approximately 15-25% of the patients with severe hemophilia A, this rate is much lower in patients with hemophilia B (3%). Life-threatening allergic reactions may develop in 50% of the patients who have inhibitor (4).

There is no efficient treatment which can be used to prevent allergic reaction developing secondary to antibody response. In this case report, the difficulties in treatment of an infant with severe hemophilia B who developed antibody and allergic reaction against FIX treatment have been discussed.

Our patient was diagnosed with hemophilia B after investigations performed because of severe hemorrhage which developed following circumscision at the age of five months. At presentation, the bleeding tests revealed an activated partial thromboplastin time (aPTT) of 104 seconds and a FIX level of 1%. A concentrate containing FIX protein obtained from 9 doses of plasma was used to stop bleeding. When the patient was 14-month old, he was rehospitalized because of head trauma. His cranial ultrasonography and brain tomography findings were found to be normal. FIX concentrate (Replenine®) was initiated at a dose of 80 IU/kg by way of slow intravenous infusion because of head trauma. However, anaphylactic reaction (diffuse urticaria, blushing in the face, cough, dyspnea, cyanosis) developed during infusion of factor concentrate. Dexamethasone, antihistaminic and adrenaline were administered for treatment. In the following administrations, his treatment was switched to Berinine® which is another FIX concentrate with prophylactic administration of antihistaminic and steroid. A similar anaphylactic reaction developed in the third minute of infusion of this new concentrate and treatment was immediately discontinued. Antihistaminic, dexamethasone and adrenaline were administered again. In the follow-up visit one month later, aPTT was found to be 134 s, the FIX level was found to be 0.1% and the amount of inhibitor was found to be 1.7 BU. As a result of mutation study, CGA>TGA (R252X) mutation was demonstrated in exon 8, n.30875, codon 252. Non-human-derived recombinant active FVIIa (rFVIIa - Novo Seven®) was given for severe bleedings in the following periods because of development of antibody.

Allergic reaction may occur against FIX protein in patients with hemophilia B who have developed antibody in contrast to hemophilia A (5). Follow-up and treatment of hemorrhage is difficult in patients with hemophilia who are allergic against external FIX protein and develop FIX-related antibody. Antibodies are involved in morbidity and mortality related with bleeding. FIX concentrates are not appropriate, because these patients develop antibody and allergy against FIX concentrates. Since treatment with active prothrombin complex concentrate (aPCC) involves FIX, it may result in allergic reaction similarly (6). Development of recombinant FVIIa provided an appropriate treatment option for patients with hemophilia who develop inhibitor. However, no consensus has been made in relation with treatment with aPCC and rFVIIa in FIX patients who have developed antibody (7). In our own individual experience, it was observed that

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hemostasis control was provided with aPCC treatment during surgery in patients with hemophilia B who developed antibody (8). It should be kept in mind that the cost of recombinant FVIIa concentrates is high and they carry a risk of thrombosis. Therefore, inhibitor elimination and desensitization treatment should be considered in these patients (9). Elimination of antibody is considerably difficult and treatment success is poor in patients with hemophilia B who are allergic against Factor IX concentrates and who develop antibody. Immune tolerance induction (ITI) treatment which is commonly used in patients with hemophilia A to eliminate antibody and is successful is generally ineffective in these patients. It is recommended that patients with high-risk in terms of development of antibody (patients with complete gene loss) should be identified with molecular analyses at the time of first diagnosis and monitored closely in the beginning of treatment (5). In patients with hemophilia B, it is recommended that the first 10-20 treatments should be administered in hospital in terms of allergy and family members should be trained in terms of the risk of anaphylaxis (10).

In conclusion, we aimed to emphasize the difficulties in follow-up of patients with severe hemophilia B who develop allergic reaction and inhibitor against FIX concentrates. Since life-threatening allergic reactions against Factor IX concentrates may develop, the initial administrations in treatment of patients with newly diagnosed hemophilia B should be definitely performed in hospital environment. Recombinant FVIIa is the only appropriate option for treatment of hemorrhage in these patients. Despite a need for inhibitor elimination and desensitization treatment, there is no current application in this area and further studies are needed.

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