Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Case Report

The Use of aPCC in Prophylaxis in a Patient with Hemophilia A with Inhibitor - Case Report

Miklasz J, Laguna P* and Matysiak M
Department of Paediatrics, Haematology and Oncology of Medical University of Warsaw, Poland

***Corresponding author:** Laguna Pawel MD, PhD, Department of Paediatrics, Haematology and Oncology, Medical University of Warsaw, 63a Żwirkii Wigury St. 02-091 Warszawa, Poland

Received: April 30, 2020; **Accepted:** June 12, 2020; **Published:** June 19, 2020

Abstract

The development of factor VIII inhibitor is a major complication of hemophilia A treatment. The treatment of choice for patients with inhibitors is immune tolerance induction. This is based on a regular administration of preparations containing factor VIII. As a result, the inhibitor is eliminated from patient's blood. We present the case of patient who is suffering from severe hemophilia A complicated by factor VIII inhibitors. The attempt to induce immunotolerance was ineffective. The patient started a bypassing therapy with activated prothrombin complex concentrate and recombinant activated factor VII on demand. He had several dozens of subcutaneous hemorrhages and joint bleeds that resulted in hemophilic arthropathy. The patient switched to aPCC prophylaxis that resulted in reduced frequency and intensity of bleedings. As a consequence of highly effective treatment and intensive rehabilitation, the quality of his life has significantly improved.

Keywords: Hemophilia A; Inhibitor; By-passing agents; aPCC

Introduction

Bleeding prevention is a foundation of hemophilia treatment. The development of inhibitors is the most important complication of hemophilia [1]. Factor VIII (FVIII) inhibitor is a polyclonal alloantibody that develops after exposure to FVIII concentrate. It develops in approximately 30% of patients with severe Hemophilia A (HA) [2], usually in early childhood, after the first few days of exposure to FVIII [3]. FVIII inhibitor is considered to be clinically significant at titer ≥0.6 BU/mL, confirmed in two separate samples. Depending on the strength of the immune response, inhibitors can be considered strong or weak, and similarly patients can be considered high or low responders, respectively [1].

In HA patients with inhibitor, bleeding frequency are not increased, and the most common location is not changed as compared to the time before inhibitor [4-10]. However, the inhibitor reduces the efficacy of the replacement therapy. This can lead to faster progression of hemophilic arthropathy and deterioration of quality of life [11].

Therefore, in addition to on demand treatment aimed to stop active bleeds, it is important to eliminate the inhibitor. The most commonly used method, effective in approximately 80% of patients, is Immune Tolerance Induction (ITI) [4]. It involves regular administration of high doses of FVIII in various schedules, from 50 IU/kg three times a week to 100 IU/kg twice daily [5].

The efficacy of ITI is monitored using inhibitor titer, usually measured once a month. Immunotherapy is considered effective when inhibitor is undetectable (<0.6 BU/mL), FVIII recovery is ≥66%, and FVIII half-life is normal (at least 6 hours after 72 hours from administration) [6]. Once immune tolerance is obtained, FVIII is administered regularly 2-3 times a week to prevent inhibitor recurrence. Failure is defined as lack or partial efficacy within 33 months of continuous therapy, lack of inhibitor reduction by 20% after the first 3 months or in subsequent measurements within 6 months from the highest inhibitor titer observed during ITI. In such case, other protocols or termination of ITI are considered.

Case Presentation

We present the history of an 18-year-old male, born of the first pregnancy, full term vaginal delivery. Family history was insignificant. After probing the nasolacrimal ducts due to obstruction in the 3 month of life, prolonged blood oozing occurred. At 6 months of age, he experienced a bleeding to the soft tissues of the hands, and a few months later - right elbow bleed. Based on coagulation workup performed at that time, HA was diagnosed (APTT 94s, FVIII <1%). At the age of 12 months, he was hospitalized due to a subcutaneous bleeding after a head injury and the first FVIII infusion was administered (25 UI/kg). He was enrolled to FVIII home therapy program. After the 6. dose, the FVIII inhibitor level was <0.4 BU/mL. Next, FVIII was administered due to minor bleeding into the buttock muscles and knee. Nine months after the initiation of FVIII therapy, he was hospitalized due to a left parietal area and soft tissues of the left upper limb bleeds, resulting in left thumb contracture.

After further 2 months, the 10. dose of FVIII was administered because of a soft tissue bleeding. Despite 2 doses of FVIII, bleeding was not resolved. FVIII inhibitor titer was 6.4 BU/mL, and Central Venous Access Device (CVAD) was implanted to allow initiation of ITI.

Vascuport was implanted under rFVIIa coverage, without hemorrhagic complications. During rFVIIa administration, extensive head and upper left limb hematomas were absorbed, and thumb paresis caused by compression resolved. Due to the presence of FVIII inhibitor, ITI was initiated at a dose of 100 UI/kg every 12 hours.

At the initiation of the ITI, the FVIII inhibitor level was 42 BU/mL. After 1 week of ITI the level increased to 245 BU/mL, and afterwards

Citation: Miklasz J, Laguna P and Matysiak M. The Use of aPCC in Prophylaxis in a Patient with Hemophilia A with Inhibitor - Case Report. Ann Hematol Oncol. 2020; 7(5): 1300.

gradually decreased. FVIII was administered at a dose of 100 IU/kg twice daily (further values of FVIII inhibitor levels. At the age of 2, he was hospitalized twice due to vascuport infection with Staphylococcus aureus and was treated with good effect with amikacin administered to the port. Two months after the last infection, thrombosis of CVAD occurred. Despite the anticoagulant treatment, the vascular port was not unclogged. The port was removed and the new one was implanted on the other side.

Despite continuous administration of high doses of FVIII twice daily, inhibitor level remained high (84-288 BU/mL). At the end of ITI, FVIII inhibitor level was 182 BU/mL.

After 18 months, ITI was ceased, and 3 months later, an increase in bleeding frequency was observed. The bleeds were treated on demand with PCC, aPCC, and rFVIIa.

At the age of 11, CVAD implanted at the age of 2 was removed because of obstruction. Between 11 and 14 years of age, he had several bleeding episodes, predominantly to the ankle, knee, and soft tissues. On-demand treatment with aPCC and rVIIa was continued.

At the age of 14, he was hospitalized because of headache accompanied by vomiting and seizures. Subarachnoid bleeding was diagnosed, treated with aPCC with good effect. Due to numerous bleeds and hemophilic arthropathy, he was referred for right elbow radiosynovectomy, and a year after - left elbow and right knee radiosynovectomy. Before these procedures, contractures and reduced joint mobility were observed. After radiosynovectomy and intensive rehabilitation, the symptoms gradually decreased. Up to the age of 15, he had several dozens of bleeds into various parts of the body, predominantly in the ankle, knee, and soft tissues.

One month after the last radiosynectomy, he was enrolled to aPCC prophylaxis program (80 IU/kg three times a week). After 4 months, the frequency of aPCC was reduced to twice a week. However, due to the right knee bleed lasting for over a month despite intensive treatment and prophylaxis, 2 months later previous schedule was resumed. At the same time, intensive rehabilitation was initiated and a spectacular reduction in the frequency and intensity of joint bleeds was observed.

At the age of 16, due to the presence of facial and scalp hemangioma, he underwent a series of laser treatments.

Up to the age of 18, he was treated in the Hematology Clinic of the Children's Clinical Hospital in Warsaw. Since the introduction of aPCC prophylaxis, he had only 1 bleeding episode (left knee) and several small soft tissue bleeds. The level of FVIII inhibitor monitored during prophylaxis remained at 18-25 BU/mL.

Currently, he began rehabilitation-kinesitherapy college. His quality of life has improved significantly since aPCC prophylaxis initiation. For the last 2 years, no joint bleeds were observed. After radiosynovectomy, the contractures withdrew and the boy regained satisfactory mobility. He regularly performs strength and aerobic training resulting in a significant fitness improvement, as well as a general increase in physical performance.

Discussion

We presented this case to draw attention to the occurrence of a FVIII inhibitor in a young 20-month-old child, as well as the inefficiency of standard induction of immune tolerance used in such patients. At the beginning of ITI, the level of FVIII inhibitor was 42 BU/mL. ITI was initiated one month after the detection of FVIII inhibitor.

The described case is an excellent illustration of the treatment of hemophilia with inhibitor, including by-passing agents such as activated prothrombin complex (FEIBA) and recombinant activated factor VII (rFVIIa). By-passing agents induce thrombin generation in the plasma, ensuring hemostasis despite the presence of FVIII inhibitor. They most common schedules for on-demand treatment are: aPCC (FEIBA) 50-100 UI/kg every 8-12 hours, rVIIa: 90-120 μg/kg every 2-4 hours or 270 μg/kg in a single dose [7]. In long-term prophylaxis, aPCC is administered at 80-100 UI/kg 3 times a week or every 48 hours, while rFVIIa is administered at 90 or 270 μg/kg every 24 hours [1]. If one of the bypassing agents is ineffective, the other should be used [11-15]. It is also possible to use these agents simultaneously or sequentially [16]. Laboratory monitoring of the treatment efficacy is based on thrombin generation curve, which is not commonly available [17]. Therefore, individual treatment modifications are based on the clinical effectiveness of the therapy.

In our patient, inhibitor titer remained high (>5 BU/mL), and spectacular improvement of clinical status was achieved only after initiation of aPCC prophylaxis. This observation was consistent with the literature data. According to Valentinno L.A., prophylactic use of aPCC contributes to reduction of bleeding episodes by 64%, and joint bleeds by 74%, compared to the effects achieved by on-demand treatment with aPCC [9]. Also, Windyga J. emphasizes that prophylactic use of aPCC improves or stabilize the orthopedic status in 85% of patients, and thus significantly improves quality of life [8]. The use of aPCC immediately after unsuccessful ITI reduces bleeding episodes frequency and provides effective protection against arthropathy [10].

The care of a patient with hemophilia with inhibitor still requires research to develop an optimal treatment regimen to improve patient's quality of life. In this respect, the role of interdisciplinary approach to the treatment process is extremely important and contributes to the improvement of both physical and emotional health, allowing to maintain high level of social functioning.

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