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Progressive arthropathy in the course of immune tolerance induction failure in a child with hemophilia A and FVIII inhibitor – a case report

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Abstract

We present the case of an 18.5-year-old boy with hemophilia A and FVIII inhibitor detected at the age of 8 months. No persistent inhibitor eradication was achieved, despite three attempts of immune tolerance induction (ITI) with temporary inhibitor resolution and subsequent administration of 11 doses of rituximab. In spite of hemostatic treatment, rehabilitation, and radiosynovectomy, the patient suffered from recurrent bleeding episodes into almost all major joints, which resulted in the development of progressive hemophilic arthropathy. Currently, due to high frequency of bleeding episodes, the patient is being treated prophylactically and receives prophylaxis with activated prothrombin complex concentrate (aPCC).

Keywords:
hemophilia A, factor VIII inhibitor, ITI, bypassing agents

Introduction

Hemophilia A is an inherited bleeding diathesis resulting from decreased FVIII plasma activity, predisposing to an increased frequency of spontaneous bleeding episodes, mainly into joints and muscles. Hemophilia A patients receive intravenous concentrates of deficient clotting factor in order to treat bleeding episodes and prevent their reoccurrence. However, this management is associated with potentially negative immunological reaction to therapeutic FVIII due to possible development of anti-FVIII neutralizing antibodies (i.e., inhibitor). The abovementioned problem is observed mainly in patients with severe hemophilia A with an inhibitor prevalence of 10%–33% [1, 2]. A common therapy used in inhibitor eradication is immune tolerance induction (ITI) [3, 4].

Case report

Difficulties associated with the abovementioned treatment are illustrated in the presented case of hemophilia A patient who developed FVIII inhibitor. The patient was born in May 1998 (gravida 1, normal para 1). He was first hospitalized at the age of 8 months due to bleeding into the buttock. The family history of bleeding diathesis was negative. In a laboratory assessment of the patient's coagulation system, APTT was indeterminable and subsequent evaluation of FVIII levels revealed very low values (<1% of active factor) of this clotting factor. Therefore, the patient was diagnosed with severe hemophilia A. Further tests revealed mutation of FVIII in the form of intron 22 inversion.

From his first bleeding episode, the patient received on-demand FVIII concentrate in a dose of 30 U/kg of body weight (BW).

All preventive vaccinations were administered subcutaneously in association with the prophylactic use of FVIII concentrate. From the beginning of the treatment, inhibitor titer evaluation was performed during every three to five courses of FVIII concentrate therapy. At the age of 16 months, after 36 courses of FVIII concentrate, lack of hemostatic effect after FVIII treatment was stated. At that time, the FVIII inhibitor level was 6.5 BU/ml and was increasing progressively. Next, the patient was implanted with a central venous catheter (Port-a-Cath) in order to initiate ITI and attempt to eradicate inhibitor (inhibitor titer was 17 BU/ml at the time). As part of the ITI regimen, the patient received FVIII concentrate daily in a dose of 200 U/kg BW for 10 months (from September 1999 until July 2000). Unfortunately, an increase of inhibitor titer to 28 BU/ml was observed. Due to lack of factor VIII supplies and lack of response to FVIII replacement therapy, the dose was modified to 150 IU/kg BW three times per week. Regrettably, the abovementioned regimen was also ineffective and did not result in inhibitor eradication. Thus, in December 2000, after 15 months of use, we decided to withdraw this therapy. However, the patient's situation was poor as he suffered from frequent hemarthroses and progressive arthropathy, which caused a significant decrease in his quality of life (QoL). Therefore, we made an attempt to use prophylactic treatment with activated prothrombin complex concentrate (aPCC). The boy who was almost 3 years old received aPCC in a dose of 80 U/kg BW 3 times per week. This therapy was conducted from March 2001 to February 2002, when further treatment was withdrawn due to its ineffectiveness. Owing to previous therapeutic failures, we decided to use on-demand sequential treatment with two bypassing agents only, recombinant activated factor VII (rFVIIa) and aPCC, instead of the previous regimen consisting of one bypassing agent administered during bleeding episodes.

Unfortunately, the abovementioned regimen was also ineffective. In February 2005, after 6 years of hemophilia A treatment, when the patient was 7 years old, we decided to try another prophylactic regimen consisting of rFVIIa, however, this time, in trial conditions. rFVIIa was used in a dose of 90 mg/kg BW for 3 months, up to May 2005. This

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regimen resulted in a decrease in hemarthroses, yet it did not prevent their occurrence. At that time, inhibitor titer decreased to 1.5 BU/ml. For us, this small therapeutic success was an incentive for a second ITI regimen initiation. In May 2005, the second ITI regimen with FVIII concentrate (43 U/kg BW daily) was administered. After 14 months of therapy, we achieved decrease in inhibitor titer to 0.87 BU/ml. This was accompanied by a reduction in the frequency of bleeds. Unfortunately, after initial success, the inhibitor titer started to rise in the following month, reaching a level of 10 BU/ml. After the failure of the 2-year regimen, further ITI with FVIII was discontinued. In the period from June 2007 to September 2009, the patient received on-demand bypass agents (i.e., rFVIIa and aPCC).

During this period, despite the patient's participation in an additional original program of rehabilitation exercises for degenerative lesions, the frequency of bleeding episodes did not decrease. Arthropathy occurred in the right elbow joint (Pettersson score: 5 points, Colorado score: 7 points), left elbow joint (Pettersson score: 4 points, Colorado score: 6 points), left knee joint (Pettersson score: 4 points, Colorado score: 6 points), right knee joint (Pettersson score: 4 points, Colorado score: 6 points), right elbow joint (Pettersson score: 5 points, Colorado score: 7 points) and left elbow joint (Pettersson score: 4 points, Colorado score: 6 points), left knee joints (Pettersson score: 4 points, Colorado score: 6 points) and right knee joints (Pettersson score: 4 points, Colorado score: 6 points). In 2007, an Yttrium-90 (^{90}Y) synovectomy of both elbow joints was performed, leading to temporary reduction in bleeding episodes. At the beginning of September 2009, owing to inhibitor titer reduction <1 BU/ml, we decided to undertake a third attempt at ITI therapy, aiming to eradicate the inhibitor. This time, FVIII concentrate was given twice a day in a dose of 100 U/kg BW. The 2-month regimen resulted in an inhibitor titer negativization (<0.4 BU/ml). This therapeutic success resulted in a significant improvement of the patient's QoL, enabling implementation of effective rehabilitation of the locomotor system. Unfortunately, after a subsequent year of follow-up treatment, we observed an increase in inhibitor titer >21 BU/ml.

Due to the ineffectiveness of previous therapeutic measures, after obtaining the approval of the Bioethics Committee of the Medical University of Warsaw and the patient's parental consent, we decided to eradicate treatment-resistant inhibitor using rituximab 375 mg/m^2, a widely advertised therapy at the time. The first dose of the new regimen was given in October 2010, and three subsequent doses were administered in 7-day intervals. Initial results were promising. After a fifth dose of rituximab, inhibitor titer reduction to <0.4 BU/ml was obtained. Therefore, subsequent doses were given only on demand (i.e., only in the case of an inhibitor titer increase). The regimen was used for 3 years until May 2012. In total, the patient received 11 doses of rituximab. Unfortunately, the initial positive outcome of rituximab therapy was not persistent. In October 2013, after 3 years of treatment, an abrupt inhibitor titer increase of >18 BU/ml was observed. Therefore, no 12th dose of rituximab was given (Fig. 1). This was also the reason for ITI regimen discontinuation. At that time, the patient was suffering from frequent hemarthroses, again mainly into knee and elbow joints. Radiosynovectomy of these joints was performed in order to stop the bleeding and resulted in a minimal reduction of the frequency of bleeding episodes with improvement of the patient's QoL. Recurrent hemarthroses and inhibitor reoccurrence due to ineffectiveness of previous treatment, including rituximab, created a real problem concerning adjustment of further therapy of this 16-year-old patient. In April 2014, we decided to initiate daily prophylaxis with aPCC at a dose of 80 U/kg BW

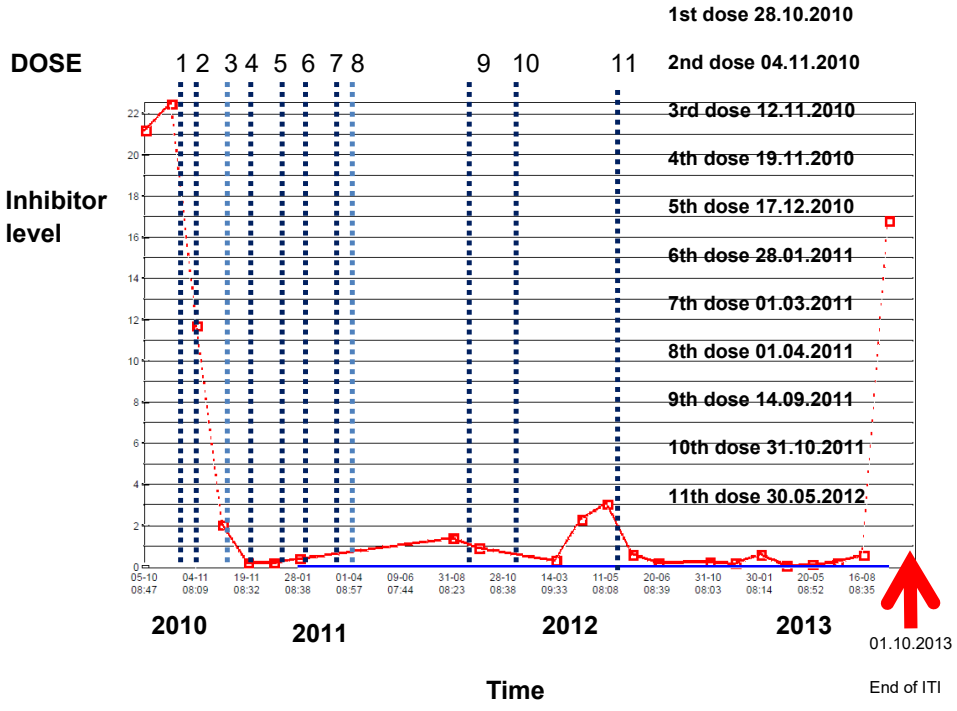

Fig. 1. Correlation between inhibitor level and subsequent doses of rituximab

in order to reduce bleeding frequency. However, every attempt to decrease aPCC administration frequency, only by 1 day per week, resulted in joint bleeding. Thence, a daily aPCC regimen was maintained. In 2014, due to recurrent bleeding episodes, a right knee joint radiosynovectomy together with prophylactic use of rFVIIa was performed. Next, treatment with aPCC was continued. Currently, the patient aged 18.5 years is capable of walking unassisted through the city and attends school regularly. He also continues daily rehabilitation of the locomotor system. In physical examination, the only abnormalities were arthropathies of elbow and knee joints. During the last assessment (December 2017), FVIII inhibitor titer was 20 BU/ml. A daily aPCC regimen from August 2014 to November 2017 resulted in no episodes of joint bleeding. Thus, we decided to reduce the number of aPCC treatment days by one per week. If in three subsequent months of therapy no episode of joint bleeding occurs, we plan to reduce frequency of treatment by another day.

Discussion

The therapy of patients with hemophilia A is based on replacement of deficient clotting factor factor, in order to prevent or stop an active bleeding episode. In most cases, this approach is effective. However, it may be associated with the risk of anti-FVIII antibody (the so-called inhibitor) development. Depending on the inhibitor level, this may limit the effectiveness of deficient coagulation factor concentrate administration [5, 6]. From the patients' point of view, this is very dramatic as the use of deficient factor concentrate is actually the only method of effective hemophilia treatment. For patients with FVIII inhibitor, one solution is the use of bypassing agents, like aPCC and rFVIIa. Patients receive one to three doses of rFVIIa in two-hour intervals; rFVIIa is given between aPCC doses that are administered every 12 hours. Significantly better results were obtained, compared to the use of one bypassing agent [6]. Therefore, in patients with hemophilia and FVIII inhibitors, the main therapeutic aim is to develop the most effective method of inhibitor eradication. In the light of current knowledge, the most powerful method is immune tolerance induction (ITI), although its effectiveness in hemophilia patients is approximately 80%. The case of an 18.5-year-old male patient with hemophilia A diagnosed at the age of 8 months presented here is a clear example of ITI ineffectiveness. According to available data, it is believed that ITI effectiveness is indicated by the speed of inhibitor titer reduction to <0.4 BU/ml, normal FVIII recovery, and normal half-life time. Our research shows that we can distinguish effective, partially effective, or ineffective ITI [6]. With regard to the ineffectiveness of previous treatment of hemophilia A patients with inhibitors, increasing literature data suggest the use of anti-CD20 antibodies (i.e., rituximab at a dose of 375 mg/m^2). Rituximab is a mouse-human chimeric monoclonal antibody manufactured with the use of genetic engineering methods. It is a glycosylated immunoglobulin containing constant human IgG1 regions and variable mouse regions composed of light and heavy chains.

Rituximab is manufactured in the culture of mammalian cell suspension (Chinese hamster ovary cells) and purified with the use of selective ion-exchange chromatography and specific methods of viral pathogens' inactivation and removal. Except for its use in oncology and rheumatology, there are also reports on its efficacy in hematological conditions, including hemophilia with treatment-resistant inhibitor [4]. Therefore, the abovementioned drug was given to our patients, yet the initial results of treatment were only temporary. In the presented case with high inhibitor titer and joint bleeding episodes, we also used another treatment option, i.e., prophylaxis with bypassing agents. It is believed that prophylactic use of aPCC can be recommended to patients with persisting inhibitor and recurrent joint bleeding episodes, when previous ITI was ineffective. This is also the case of patients not fulfilling criteria of ITI use and not giving their consent to this type of treatment.

Prophylactic use of aPCC reduces the number of bleeding episodes and may increase the effectiveness of ITI [7].

Above we have summarized all the data that can be found in literature to date. However, the question of clinical practice remains. The case we describe here indicates that despite the use of different available methods and initial successes, inhibitor eradication is not persistent. Moreover, because of the patient's young age and the consequences of recurrent joint bleeding episodes, this case is very dramatic.

Regrettably, recurrent joint bleeding episodes were the biggest problem. Perhaps, our decision on radiosynovectomy at the age of 9, when joint lesions are already significant (5 points on Pettersson scale), was made too late. Possibly, introduction of early, long-term prophylaxis with bypassing agents would be more effective.

A new therapeutic option for all hemophilia A with inhibitor is the use of Fc fusion technology (rFVIIIFc) to prolong circulation in the body. Recombinant factor VIII Fc fusion protein demonstrated rapid time to tolerization in high-risk first-time ITI patients [8].

Treatment of these disorders has focused on replacement of the missing coagulation factor to prevent or treat bleeding. New technologies and insights into hemostasis have driven the development of many promising new therapies for hemophilia and von Willebrand disease. Emerging bypass agents including zymogen-like factor IXa and Xa molecules are in development, and a bispecific antibody, emicizumab, demonstrated efficacy in phase 3 trial in people with hemophilia A and inhibitors. Tissue factor pathway inhibitor, the protein C/S system, and antithrombin are targets of novel compounds in development to alter the hemostatic balance, and new approaches using modified factor VIII molecules are being tested for prevention and eradication of inhibitor antibodies in hemophilia A [9, 10].

Results of the emicizumab test based on HAVEN 1–4 test are very promising [11, 12, 13]. HAVEN 2 was a nonrandomized, open-label trial of three dosing regimens (1.5 mg/kg BW administered weekly, 3 mg/kg every 2 weeks, and 6 mg/kg every 4 weeks) given to 88 children with hemophilia A complicated by inhibitor under the age of 12 years. These data have only been presented in an abstract form but demonstrated marked intraindividual reductions in treated bleeding events compared to their prior bypassing agent regimen. Young reported an overall 99% reduction in the annualized number of treated bleeding events compared to the prior bypassing agent regimen [14].

The benefits of emicizumab include bioavailability following subcutaneous administration, a long-acting effect allowing for reduced dosing frequency potentially as infrequent as once monthly, greater prophylactic efficacy, and benefits irrespective of the presence or absence of an inhibitor to FVIII. However, further investigations are needed.

Today, we have a problem finding correct answers to all these questions. Furthermore, we do not know whether widespread prophylactic use of recombinant coagulation factor concentrates will impact properties of newly developed inhibitors and our ability to eradicate them. Therefore, the search for new methods and treatment options for hemophilia patients with inhibitor is crucial.

Authors' contributions/Wkład autorów

PŁ – concept of work, data interpretation, preparation of the article text, verification of the entire text
MM, JC AK – concept of work, data collection and interpretation, proofreading of the whole text, verification of the entire text

All authors approved the final version of the article.

Conflict of interest/Konflikt interesu

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Etyka/Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, EU Directive 2010/63/EU for animal experiments, and Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

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