CASE REPORT

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The Use of Plasma-Derived Factor VIII in Two Patients Diagnosed with TTP

Mehmet Nur Kaya, Gül İlhan, Hasan Kaya

Department of Hematology, Mustafa Kemal University Faculty of Medicine, Hatay, Turkey

Abstract

Thrombotic thrombocytopenic purpura (TTP) develops due to increased von Willebrand factor multimers as a result of a deficiency of the a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 enzyme. It has two forms; acquired or congenital (hereditary and familial). The initial clinical manifestations of this disease have been defined as a pentad consisting of thrombocytopenia, microangiopathic hemolytic anemia, neurological findings, acute renal failure, and fever. The basis of TTP therapy consists of fresh frozen plasma (FFP) and therapeutic plasma exchange (TPE). Our cases were two patients diagnosed with congenital TTP. Plasma-derived factor 8, which is a Factor VIII concentrate, was administered to these patients at a dose of 30 U/kg/week due to the allergic reactions the patients developed during their FFP and TPE treatments, prevention of exposure to the viral agent and ineffective treatment. After this treatment, laboratory parameters improved in case 1 and clinical improvement was achieved. In case 2, however, the desired level of laboratory parameters could not be reached and no clinical improvement was achieved.

Keywords: TTP, plasma-derived factor VIII, ADAMTS-13

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare disease and its annual incidence in the United State of America is less than 4 million.[1] There are 2 forms of TTP; acquired and congenital (hereditary and familial). Acquired TTP occurs almost exclusively in adults and is an autoimmune disorder. The congenital form usually occurs in infancy or early childhood and is known as Upshaw-Schulman syndrome.[2] The initial clinical manifestations of this disease have been defined as a pentad consisting of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), neurological findings, acute renal failure, and fever. The symptoms of MAHA and the presence of thrombocytopenia are considered as indications of possible TTP. The deficiency of the a disintegrin and metalloproteinase with thrombospondin type 1 motif, member-13 (ADAMTS-13) enzyme, which is the von Willebrand factor (vWF)-cleaving protease, for the pathogenesis of TTP, or an inhibition developed against the ADAMTS-13 enzyme, was first described by Furlan et al.[3] in 1997-1998. TTP can be diagnosed via a diagnostic test which indicates the deficiency of ADAMTS-13. The acute condition of TTP is a life-threatening condition which requires urgent treatment. This treatment is usually initiated without waiting for therapeutic plasma exchange (TPE). TTP treatment is a long-term treatment which often progresses but then relapses.[4] This disease was initially treated with plasma infusions. However, subsequently, daily TPE was found to be more effective, and it has thus become the standard treatment. In this way, the overall mortality rate had decreased to less than 10%.[5] Corticosteroids are often used in addition to TPE and help control the antibodies which act as inhibitors. Cyclosporine, azathioprine, and vincristine have been included in other adjunctive treatments aimed

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ORCID IDs of the authors: M.N.K. 0000-0003-4368-3078; G.İ. 0000-0003-1616-6358; H.K. 0000-0002-2850-0862.

Address for Correspondence: Mehmet Nur Kaya
E-mail: mehmetnurkaya@yahoo.com
ORCID ID: orcid.org/0000-0003-4368-3078

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at reducing inhibitors.[6] After the relationship between ADAMTS-13 deficiency and TTP became clear, the use of recombinant ADAMTS-13, which increases ADAMTS-13 activity and reduces the level of inhibitors, was brought to the agenda. In one study carried out along these lines, ADAMTS-13 activity was found to be high in the medication called plasma-derived factor 8, which is a plasma-derived factor VIII concentrate used in hemophilia A patients.[7] In our study, we aimed to present two cases where we employed plasma-derived factor 8 treatment as an alternative treatment in congenital TTP.

CASE PRESENTATION

Case-1

A 13-year-old female was suspected of having TTP disease at the center where she presented with schistocytes in peripheral smear, and epileptic seizures [hemoglobin (Hgb): 9 g/dL (13.5-17.5 g/dL), platelet: 92,000/mcL (150,000-450,000/mcL), and lactate dehydrogenase (LDH): 567 IU/L (0-248 IU/L)]. The patient's ADAMTS-13 activity was found to be less than 10%, and the patient was diagnosed with TTP as a result. Clinical improvement was achieved in this patient who had no family history of TTP after treatment with fresh frozen plasma (FFP) and broad-spectrum antibiotics. Afterward, she was treated with FFP transfusions every 28 days for 12 years to maintain her platelet count at a level of >100,000/mcL. The patient presented to the emergency department of our hospital at the age of 25 with the complaint of speech difficulty, drowsiness, and jaundice (serum creatinine: 1.9 mg/dL (0.6-1.2 mg/dL), Hgb: 8.1 g/dL, platelet: 56,000/mcL, and LDH: 352 IU/L). Upon the detection of schistocytes in the peripheral smear, it was accepted that she had an acute exacerbation of TTP. TPE transfusions were then increased to maintain the >100,000/mcL platelet count. In this patient, who developed urticarial rash and pruritus with FFP, premedication was started. However, the patients continued to have similar complaints despite this premedication, and thus it was decided to administer plasma-derived factor 8 to the patient after obtaining off-label consent. Plasma-derived factor 8 was administered under service conditions with a dose of 30 U/kg/week. The patient tolerated the infusions without presenting with any allergic reactions. Platelet reached 151,000/mcL from 115,000/mcL 24 hours after infusion. During the first 4 weeks of this treatment, platelet counts were closely monitored and dose titration was performed to maintain the >100,000/mcL platelet count. Each week, the patient tolerated plasma-derived factor eight 1x1,500 unit infusions without any complications. The patient was able to self-administer the medication on her own at home. No thrombotic and renal complications were observed in this patient during the period of the use of this medication.

Case-2

A 31-year-old female patient presented to the hospital with a complaint of headache, weakness, and jaundice. TTP was suspected after her test results revealed Hgb: 7.8 g/dL, platelet: 64,000/mcL, LDH: 427 IU/L, serum creatinine: 1.7 mg/dL, and schistocytes in peripheral smear. The patient's ADAMTS-13 activity was found to be less than 10%, and the patient was diagnosed with TTP as a result. Plasmapheresis was performed 8 times in total on this patient, who had no family history of TTP. The patient was then followed up every 28 days by administering 3 units of FFP. The need for FFP was increased due to her low Hgb levels and the continuing thrombocytopenia, which were determined during check-ups. However, plasma-derived factor 8 was initiated instead at a dose of 30 U/kg/week due to the dose-dependent allergic effects of FFP and the necessity to treat the patient in the hospital. The plasma-derived factor 8 dose was increased to 40 U/kg/week since her platelet count could not reach >100,000/mcL, yet still the desired platelet and Hgb response could not be obtained. For this reason, plasma-derived factor 8 treatment was discontinued and 3 units of FFP treatment were continued instead once every 2 weeks.

DISCUSSION

TTP develops as a result of vWF multimers accumulating due to a deficiency of the ADAMTS-13 enzyme, which is congenitally included in the metalloproteinase family, or as a result of acquired inhibition.[8] vWF multimers have a highly prothrombotic structure and lead to platelet aggregation and multi-organ microthrombus. Symptoms may appear during infancy.[9] Recurrent hemolytic anemia can progress with attacks of thrombocytopenia or life-threatening thrombosis afterwards.[10] FFP infusions (10 to 15 mL/kg) may partially remedy the ADAMTS-13 deficiency or enable remission. However, prophylactic FFP infusions frequently require treatment under hospital conditions and also increase the risks associated with transfusion reactions and pathogens.[11] Associated allergic reactions and exposure to viral agents suggest that other treatment modalities can be applied instead of FFP transfusions, which are the standard treatment in congenital TTP. Concentrated treatments which are virally inactivated may be more appropriate, especially in a smaller volume. In the study conducted by Aledort et al.[12], 8 congenital TTP patients were administered plasma-derived factor 8 treatment without any problems. They did not present with any allergic reactions and did not require the use of a central venous catheter. It has been stated that the plasma-derived factor 8 treatment is to be titrated prophylactically to be administered in the range of 2 times per week up to once every 3 weeks.[12] Allford et al.[13], studied the ADAMTS-13 levels in plasma-derived factor VIII products and recombinant factor VIII. Plasma-derived factor 8, a product of factor VIII, was determined to yield 100% activity for ADAMTS-13 efficacy. Plasma-derived factor 8, which is used in hemophilia A patients, is a medium purity plasma-derived recombinant factor VIII concentrate. The amount of ADAMTS-13 is 900% higher in plasma-derived factor 8 compared to FFP.[13] Lester et al.[14] successfully treated a 14-year-old girl who had been diagnosed with congenital TTP and was, therefore, being treated with FFP every 2 weeks for 10 years with BPL8Y, which is another preparation with a high amount of ADAMTS-13. In another patient who was administered plasma-derived factor 8 due to TTP, the ADAMTS-13 activity level increased from 2% to 8% after a single infusion and the number of continuous platelets increased. Even a small increase in protease activity provides clinical benefits. More importantly, in fever-related attacks, a good amount of control was achieved with the administration of additional doses.[15] In case 1, effective treatment was provided with plasma-derived factor 8 as was the case in the other studies available in the literature. However, in case 2, plasma-derived factor 8 was initiated at a dose of 30 U/kg/week, then this dose was increased to 40 U/kg/week since the desired platelet count of >100,000/mcL could not be reached, and yet the desired platelet and Hgb response was still not obtained. Contrary to other cases reported in other studies available in the literature, administering even increased doses of plasma-derived factor 8 did not yield an effective treatment in case 2. Therefore, her treatment was continued with FFP and TPE. The main limitation of our study was not checking the post-treatment ADAMTS-13 levels of our cases.

We report an alternative treatment approach for a patient with TTP who was intolerant of FFP infusions. The potential advantages over the current standard use of FFP are a much smaller volume infused to the patients and a lower risk of transmission of blood-borne infections. In addition, due to the reduction of complications with, the hospitalization process is decreased and so this treatment option may be more cost-effective. However, plasma-derived factor 8 treatment did not produce any results in our second case, and this case is, in fact, the only case to date in the literature where effective treatment was not achieved with plasma-derived factor 8. Thus, the use of plasma-derived factor 8 in TTP patients should be evaluated taking into consideration these cases as well as other similar cases.

ETHICS

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.N.K., G.İ., H.K., Design: M.N.K., G.İ., H.K., Supervision: M.N.K., G.İ., H.K., Materials: M.N.K., G.İ., H.K., Data Collection and/or Processing: M.N.K., G.İ., H.K., Analysis and/or Interpretation: M.N.K., G.İ., H.K., Literature Search: M.N.K., G.İ., H.K., Writing: M.N.K., G.İ., H.K., Critical Review: M.N.K., G.İ., H.K.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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