Successful Treatment of Congenital TTP With a Novel Approach Using Plasma-derived Factor VIII

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Summary: We describe a 19-year-old boy who was diagnosed with congenital thrombotic thrombocytopenic purpura (cTTP) at 7 months of age. He was subsequently treated with fresh frozen plasma infusions every 3 to 4 weeks for the next 15 years at which point he developed significant hypersensitivity reactions to fresh frozen plasma. He required immunosuppressive therapy with systemic desensitization in the intensive care unit but did not tolerate this regimen and suffered debilitating adverse effects. On the basis of the observations from United Kingdom, he was started on a trial with Koate, a plasma-derived factor VIII concentrate with ADAMTS-13 activity that is commercially available in the United States. He tolerated Koate without any complications and attained a target platelet count of > 100,000/μL. He has now been in remission for 36 months and responds to exacerbations of cTTP with additional doses of Koate. For patients with cTTP who are intolerant to plasma infusions, therapy with select plasma-derived factor concentrates with ADAMTS-13 activity may represent a reasonable alternative therapy.

Key Words: cTTP, plasma-derived factor VIII, ADAMTS-13

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Congenital thrombotic thrombocytopenic purpura (cTTP) or Upshaw-Schulman syndrome (OMIM 274150) is a rare microangiopathic disorder characterized by deficiency of a protease, ADAMTS-13. This deficiency leads to the accumulation of ultralarge von Willebrand factor (vWF) multimers that induce extensive platelet aggregation and multiorgan microthrombi. Onset of symptoms may occur during infancy with recurrent episodes of hemolytic anemia and thrombocytopenia or later with life-threatening thrombosis.[1]

Small, frequent infusions of fresh frozen plasma (FFP) (10 to 15 mL/kg) can partially correct the ADAMTS-13 deficiency and induce remission.[2] However, prophylactic plasma infusions require frequent hospital visits and are associated with risk for transfusion reactions and pathogen exposure. Recombinant ADAMTS-13 is not licensed for clinical use.[3–4] At present, there is no alternative to plasma replacement for cTTP.

Reports from the United Kingdom have described successful responses to treatment with plasma-derived factor VIII concentrates.[5–7] We describe a case of cTTP successfully treated with plasma-derived factor VIII concentrate, commercially available within the United States.

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CASE REPORT

A 19-year-old Latin American male presented at birth with respiratory distress, hyperbilirubinemia, disseminated intravascular coagulation, and renal failure. The etiology was unclear. He was treated with 2 exchange transfusions followed by phototherapy. He also received FFP and broad-spectrum antibiotics, improved, and was discharged at 3 weeks of age.

At 7 months of age, he presented with hemolytic anemia and thrombocytopenia. A von Willebrand panel revealed unusually large vWF multimers. A diagnosis of cTTP was suspected and a trial with FFP produced clinical recovery. Subsequent testing revealed absent ADAMTS-13 activity, confirming a diagnosis of cTTP. There was no family history of cTTP.

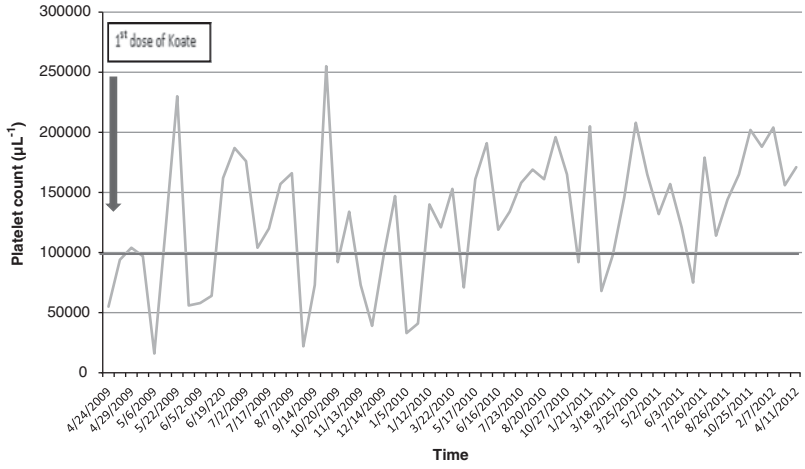
Over the next 14 years, he was treated with FFP transfusions every 3 to 4 weeks to maintain a platelet count > 100,000/μL. At 14 years of age, he was hospitalized for acute exacerbation of TTP and renal insufficiency. Subsequently, his transfusion requirement for FFP increased to every 2 weeks to maintain a platelet count > 100,000/μL.

By 15 years of age, he had developed progressively worsening hypersensitivity reactions to FFP. He presented with a generalized urticarial rash and hives despite the use of multiple medications before infusion. The Allergy and Immunology service was consulted and recommended aggressive immunosuppressive therapy to help control these reactions.

Despite these premedications, systemic steroids, and a trial with cryo-poor FFP, he continued to have debilitating hypersensitivity reactions. Ultimately, he required admissions to the pediatric intensive care unit, systemic desensitization, together with high-dose methyprednisolone to control his symptoms. Consequent to the use of high-dose steroids, he developed severe and disabling tactile hallucinations, which resolved upon discontinuation of the medications.

Facing an intolerable desensitization procedure, the family agreed to a trial with a plasma-derived factor VIII concentrate, Koate (Talercris). This product is one of 2 factor VIII products commercially available in the United States with reported ADAMTS-13 activity. He was started at a dose of 30 U/kg, which he received in a monitored setting and he tolerated the infusions without allergic reactions. His platelet count increased from 55,000 to 94,000/μL within 24 hours after infusion. His platelet response to subsequent Koate administrations is shown in Graph 1. After a single infusion, the ADAMTS-13 activity level increased from 2% to 8% 4 hours after infusion. In addition, a vWF panel showed vWF ristocetin cofactor at 143%, factor 8 level at 162%, and the presence of normal multimers, although the vWF antigen was elevated at 212%. During the first 4 weeks of this therapy, his platelet counts were monitored closely and dosing was adjusted to every 5 to 6 days to maintain trough platelet counts at > 100,00/μL. He tolerated Koate infusions well without any complications. Five months after starting therapy, he developed a febrile illness associated with exacerbation of his TTP symptoms and responded to additional Koate doses.

He has now been in remission for 36 months. His current management schedule involves Koate administration at doses between 30 to 35 U/kg every 3 to 4 days with a target platelet count > 100,000/μL, with additional dosing every 2 days for febrile illness or thrombocytopenia. He has been able to self-administer the medication at home. He has had no signs of thrombotic or renal complications.



GRAPH 1. Platelet count (per μL) after starting treatment with Koate with goal platelet count of 100,000/μL.

He reports a dramatic improvement in his quality of life. He is now in 11th grade and participates in track events without difficulty.

DISCUSSION

Small increments in ADAMTS-13 activity are sufficient to stabilize the clinical course in patients with cTTP.[7] FFP replacement has been the accepted standard of care. However, repeated FFP infusions are frequently associated with serious complications, as illustrated in this case.

It has been suggested that certain plasma-derived factor VIII concentrates may contain small amounts of ADAMTS-13.[7] In patients with congenital-relapsing TTP, case reports from the United Kingdom have described patients with variable responses to intermediate-purity plasma-derived factor VIII concentrates.[5–7] In 2002, Lester et al[6] reported the successful treatment with intermediate-purity plasma-derived factor VIII concentrate BPL 8Y in a 14-year-old girl with cTTP, who had previously required FFP transfusions every 2 weeks for 10 years. Most recently in 2006, Scully et al[5] described the use of BPL 8Y as a prophylactic and therapeutic agent in 7 children with cTTP with excellent outcomes.

Allford et al[7] measured levels of ADAMTS-13 in several plasma-derived factor VIII products and recombinant factor VIII. Among the list was a high-purity factor VIII product, Koate (Talecris) that tested at 100% activity for ADAMTS-13 activity. On the basis of the fact that Koate had 100% activity, was commercially available in the United States, and that a similar product, BPL 8Y, had successfully been used to treat cTTP,[5–6] we chose to offer our patient a therapeutic trial with this agent.

After a single infusion with Koate, the ADAMTS-13 activity level increased from 2% to 8% after infusion and sustained platelet count increase were observed. Even small increments in protease activity have shown clinical benefit.[7] Importantly, acute exacerbations associated with febrile episodes were well controlled with additional doses of Koate.

This report has several potential challenges. First, this represents a single success story utilizing a specific plasma-derived product available in the United States. The standard of care for cTTP remains FFP infusions. Others have suggested that plasma-derived factor VIII concentrates do not have sufficient ADAMTS-13 to treat TTP. However, these observations were made in patients with acquired TTP.[8] We would agree that this approach is not an appropriate consideration for acquired TTP. Second, this is an off-label application of this specific product. We cannot comment about the suitability of other plasma-derived factor VIII products. The potential long-term complications remain unknown. Plasma treatment generally has maintained its effectiveness for as long as 20 years in most patients without any reports of secondary ADAMTS-13 antibody formation.[2] What is not known is whether the long-term use of Koate could lead to factor VIII inhibitor formation. We are monitoring for this possibility. Finally, extensive monitoring of factor VIII activity and vWF panels was not performed. Elevated factor VIII activity and ristocetin cofactor levels are potentially prothrombotic. However, we have closely monitored the patient's clinical status and platelet counts as indicators of response. Our patient has done extremely well, with platelet counts > 100,000/μL and has shown no clinical signs of thrombosis for the 36 months that he has been on this replacement therapy.

CONCLUSIONS

We report an alternative treatment approach for a patient with cTTP who was intolerant of FFP infusions. Recombinant purified ADAMTS-13 is now undergoing preclinical studies. Until it is available for clinical use, the use of a selected intermediate-purity or high-purity factor VIII concentrate (Koate) may be an acceptable alternative therapeutic agent in patients with cTTP who are unable to tolerate conventional plasma replacement.

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