EXCEPTIONAL CASE REPORT

blood advances

Management of thrombotic thrombocytopenic purpura without plasma exchange: the Jehovah's Witness experience

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Key Points

- TTP in Jehovah's Witness patients has been managed successfully without PEX.
- This experience, plus new TTP treatments, may make it possible for patients who are not Jehovah's Witnesses to avoid PEX in the future.

Introduction

Plasma exchange (PEX) has been the principal and presumed essential treatment of acquired thrombotic thrombocytopenic purpura (TTP) since publication of the randomized clinical trial documenting its effectiveness in 1991.[1] The requirement for PEX creates a crisis when a Jehovah's Witness patient presents with TTP because Jehovah's Witness doctrine is that refusal of transfusions of whole blood or any of its 4 primary components (red cells, white cells, platelets, and plasma) is mandatory.[2] Therefore, PEX cannot be performed. However, the use of albumin and other purified protein fractions is not absolutely prohibited; for these products, personal choice is acceptable.[2]

We report the successful treatment of a Jehovah's Witness patient with acquired TTP without PEX. We also systematically searched for previous published reports of TTP in Jehovah's Witness patients.

Case description

A 46-year-old white woman felt increasing fatigue for 2 weeks and noticed jaundiced sclerae 1 week before her hospitalization. However, she continued to work until the day of admission. That morning, she awoke suddenly with weakness, clumsiness, and numbness of both arms and hands and both sides of her face. She also had expressive aphasia. These symptoms were intermittent: throughout that initial day, in the emergency department and after hospital admission, they would resolve, often within 20 minutes, and then recur. During the periods when these symptoms had resolved, she was alert, oriented, and comfortable. After the first hospital day, through day 4, her neurologic symptoms did not recur.

TTP was suspected in the emergency department. The diagnosis of TTP was subsequently supported by severe thrombocytopenia and anemia with features of microangiopathic hemolysis (total bilirubin, 5.1 mg/dL; direct bilirubin, 0.6 mg/dL; direct antiglobulin test, negative; haptoglobin, $<$30 mg/dL). ADAMTS13 activity was $<$5% (testing for a functional inhibitor was not performed). Her past history included Graves disease in 2010, which was treated with radioiodine ablation, and hypertension, diagnosed in 2016.

Treatment was begun on day 1 with methylprednisolone and folic acid (Table 1). Rituximab was given on day 3. Plasmapheresis with albumin replacement (not PEX with plasma replacement) was performed on days 4 and 5, but was then stopped because of hypofibrinogenemia (46 mg/dL). Erythropoietin was begun on day 4. IV immunoglobulin (IVIg) was given on days 5 and 8.

On day 5, following apheresis and while receiving IVIg, her neurologic symptoms suddenly recurred. She felt faint and had expressive aphasia with left arm weakness. Stroke was suspected but brain computed tomography scan was normal. Later that day, her neurologic examination returned to normal. Methylprednisolone dosage was increased and the second rituximab infusion was given. Koate (Koate-DVI, antihemophilic factor [human]; Kedrion Biopharma) was given to provide ADAMTS13.[3,4] Koate contains factor VIII and von Willebrand factor; it is primarily used for treatment of hemophilia A and von Willebrand disease. After day 5, she progressively recovered with no further neurologic symptoms (except hallucinations attributed to corticosteroids, which were treated with risperidone). She was transferred to rehabilitation on day 16 because of corticosteroid myopathy. Recovery was documented by normal ADAMTS13 activity.

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Table 1. Clinical course and treatment of our Jehovah's Witness patient

Day	Hgb, g/dL	Plt, $\times 10^9$/L	Clinical course	Treatments*
1	8.4	12	Transient aphasia, bilateral arm and face numbness and weakness, hand clumsiness.	MP 375, folic acid
2	7.8	16	Neurologic symptoms resolved.	
3	7.8	24		Rituximab
4	7.5	10		Apheresis, Epo
5	6.9	9	Acute transient episode of feeling faint, aphasia, left arm weakness.	Apheresis, IVIg
6	6.0	10	Neurologic symptoms resolved; no further neurologic abnormalities.	
7	5.7	15		MP 1000, IVIg
8	—	—		MP 1000, IV iron, rituximab
9	6.6	28		MP 1000
10	—	—	Gradual improvement. Hallucinations and proximal muscle weakness attributed to corticosteroids.	Koate, prednisone 80
11	7.2	45		
12	7.7	74		Rituximab
14	9.1	96		Prednisone 40
16	9.3	109	Discharged to rehabilitation for steroid-induced proximal muscle weakness. Regained strength with physical therapy.	
19	10.0	115		Rituximab
21	11.8	90		
23	12.7	125		
28	13.0	231	Discharged to home. ADAMTS13, 99%.	
60	—	—	Return to work.	

Days begin with hospital admission on day 1.
Epo, recombinant human erythropoietin; Hgb, hemoglobin concentration; MP, methylprednisolone (and prednisone); Plt, platelet count.
*Doses, regimens: apheresis, plasmapheresis with albumin replacement; Epo, 10 000 U then 20 000 U, 3 times per week; folic acid, 1 mg per day; IVIg, 70 g (1 g/kg); IV iron, ferrous gluconate, 125 mg IV daily; Koate, 2000 U (30 U/kg), given once; MP, milligrams per day; rituximab, 375 mg/m^2.

Methods

We searched 7 databases (MEDLINE via OVID, MEDLINE via PubMed, EMBASE, Cochrane Database of Systematic Reviews, Cumulative Index to Nursing and Allied Health Literature, Web of Science, and Current Contents) through August 2017 using the medical subject heading terms "thrombotic thrombocytopenic purpura" and "Jehovah's Witness." Bibliographies of the identified articles were searched for additional reports. Searches were limited to English language.

Results and discussion

Our systematic literature search identified 12 articles; 6 described management of TTP in Jehovah's Witness patients. Two of these 6 articles were excluded because the diagnosis of TTP was not confirmed by measurement of ADAMTS13 activity or by occurrence of relapse. Among the 4 included articles, the diagnosis of TTP was supported by ADAMTS13 activity <5% in 3[5-7] and by the description of relapse in 1[8] (Table 2).

There was no consistent plan of treatment of the 5 episodes of TTP in the 4 previously reported patients, as well as in our patient. This inconsistency clearly reflects the urgency for treatment and the uncertainty regarding what treatments to use. Rituximab was used in 5 of the 6 episodes, vincristine in 3, and cyclophosphamide in 1. High-dose corticosteroids were used in 4 episodes; corticosteroids were not mentioned in 2 episodes.[8] IVIg and apheresis with albumin replacement were used in 3 patients. Koate, to provide ADAMTS13, was only used in our patient. All 5 patients recovered without PEX; 1 patient recovered twice, from both of her episodes.[8]

There are ~8 300 000 Jehovah's Witness adherents worldwide.[9] Because the incidence of TTP is ~2 patients per million in the population per year,[10] we must assume that there have been many other unpublished occurrences of TTP among Jehovah's Witnesses. Death from TTP in Jehovah's Witness patients has not been reported, only recovery. However biased these case reports may be, only reporting successful treatment, the experience with these 5 Jehovah's Witness patients suggests that TTP can be effectively treated without PEX.

From our experience, how would we treat future Jehovah's Witness patients, or our patient if she relapses? The most effective treatment may be rituximab, 375 mg/m^2 twice weekly for 2 weeks, and methylprednisolone, 1000 mg per day for 3 days, followed by more conventional corticosteroid doses, similar to the regimen used in a United Kingdom study.[11] Koate, to provide ADAMTS13,[3,4] would be repeated while thrombocytopenia persists. Erythropoietin and folic acid would be given to provide support for erythropoiesis. Additional immunosuppressive agents and apheresis with albumin replacement may not be necessary. It may be prudent to avoid IVIg because its efficacy is unknown and adverse reactions to IVIg may mimic the thrombotic,[12] neurologic,[13] and renal[14] manifestations of TTP.

This proposed regimen will change with the anticipated approval of new treatments for TTP. Caplacizumab, a nanobody that blocks von Willebrand factor interaction with platelets, can promptly prevent

Table 2. Clinical course of the 4 previously published Jehovah's Witness patients with TTP

Patient*/year/reference	Age/sex	Past medical history, presenting symptoms, laboratory data	Treatment	Outcome
1/2007/5	19/F	Previous mixed connective tissue disease treated with hydroxychloroquine and prednisone. Chest pain, headache, syncope. Hgb, 4.9; Plt <10; Cr, 1.0; LDH, 1131; ADAMTS13, <5%; Inh, <0.4 BU	MP, 1000 mg on days 1-3. Vincristine, day 3, 2 mg; days 6 and 9, 1 mg.	Plt, <10 on days 1-3; 125 on day 4; 280 on day 5
2/2015/6	41/F	Previous SLE, treated with hydroxychloroquine. Bruising, dyspnea, abdominal pain. Hgb, 6.1; Plt, 29; Cr, "normal"; LDH, 477; ADAMTS13, <5%; Inh, 1.4 BU	Dex, 40 mg days 1-4, IVIg, 1 g/kg days 1, 2, 5. Vincristine, 2 mg days 3, 8. Rituximab, 375 mg/m^2 days 3, 8, 15. Apheresis with albumin replacement days 2, 3, 6, 7. Epo, 30 000 U days 6-11.	Plt, 9-29 until 50 on day 8; 200 on day 12. Nadir Hgb, 3.2 on day 8, 6.3 on day 16. At 6 mo: Hgb, 12.6; Plt, 225; ADAMTS13, 90%
3/2015/8	58/F	First episode: Hgb, 5.4; Plt, 16; Cr, 1.2; LDH, 1605; Hpt, <10; ADAMTS13, NR Second episode: Transient aphasia, blurred vision. Hgb, 9.1; Plt, 30; Cr, 1.1; LDH, 756; ADAMTS13, NR	First episode: rituximab, cyclophosphamide Second episode: rituximab, IVIg	Both episodes: "Significant improvement within few days" (remission is assumed)
4/2017/7	22/F	Purpura. Hgb, 10.1; Plt, 12; LDH, increased; Hpt, decreased; ADAMTS13, <5%; Inh, >8 BU	"High-dose steroid," Epo, folic acid beginning day 1. Apheresis, albumin replacement: days 2, 5; cryoprecipitate replacement, days 7, 9, 10, 12, 13. Rituximab, days 3, 10, 17. Vincristine, days 6, 16. Sanguinate, days 10-13.	Discharge on day 19: Hgb, 8.8; Plt, 221

Doses, regimens: Cr, mg/dL; Hgb, g/dL; Hpt, mg/dL; LDH, U/L; Plt, $\times 10^9$/L.

BU, Bethesda unit; Cr, serum creatinine; Dex, dexamethasone; Hpt, haptoglobin; Inh, functional ADAMTS13 inhibitor; LDH, lactate dehydrogenase; MP, methylprednisolone; NR, not reported; SLE, systemic lupus erythematosus.

*Patients 1, 2, and 4: platelet count values were extrapolated from the published figures. Patient 3 was described in an abstract with minimal detail. No presenting symptoms were described for her first episode; ADAMTS13 activity was not reported. No regimens or days of administration were reported for the treatments; no outcomes were described for either episode. Patient 4: Sanguinate (pegylated bovine carboxyhemoglobin) is a product in development for patients with severe anemia (NCT02754999). For patients 3 and 4, drug doses were not reported.

microvascular thrombosis.[15] Recombinant ADAMTS13 will provide ADAMTS13 activity to decrease the concentration of ultra-large von Willebrand factor multimers.[16] These new treatments may provide a major benefit for Jehovah's Witness patients.

These observations on Jehovah's Witness patients suggest the possibility that PEX may not be an essential treatment of TTP. If PEX could be avoided, management of patients with TTP could be simpler and safer. PEX requires mobilization of specialized personnel and instruments that may not be available in many hospitals or at all times. PEX requires insertion of a central venous dialysis catheter, with its risk for hemorrhage and infection. We have systematically documented adverse reactions to PEX among Oklahoma TTP Registry patients during the past 20 years.[17,18] Three of our 78 TTP patients (4%) have died of complications of PEX: 2 from sepsis and 1 from hemorrhage caused by central venous catheter insertion.[18,19] Twelve additional patients (18%) have had sepsis with documented bacteremia, related to their central venous catheter. Three patients have had venous thrombosis at the central venous catheter site requiring systemic anticoagulation. One patient had an anaphylactic reaction to plasma with cardiac arrest; she had a complete recovery.[18]

We acknowledge that PEX is the current essential treatment of TTP. However, the successful management of Jehovah's Witness patients without PEX may provide insight for effective and safer future management of all patients with TTP.

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Authorship

Contribution: J.N.G. consulted with J.S. and S.A.S. throughout the patient's hospitalization, helped perform the systematic literature review, and wrote the manuscript; and J.S. and S.A.S. provided the primary care for the patient, including continuing follow-up, provided the patient's medical records for J.N.G., and reviewed the manuscript for accuracy and appropriate interpretation.

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References

1. Rock GA, Shumak KH, Buskard NA, et al; Canadian Apheresis Study Group. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. *N Engl J Med*. 1991;325(6):393-397.
2. Committee for Hospital Information for Jehovah's Witnesses. Religious and Ethical Position on Medical Therapy and Related Matters. https://www.jw.org/en/medical-library/strategies-downloads/religious-and-ethical-position-medical-therapy/. Accessed 8 October 2017.
3. Peyvandi F, Mannucci PM, Valsecchi C, Pontiggia S, Farina C, Retzios AD. ADAMTS13 content in plasma-derived factor VIII/von Willebrand factor concentrates. *Am J Hematol*. 2013;88(10):895-898.
4. Naik S, Mahoney DH. Successful treatment of congenital TTP with a novel approach using plasma-derived factor VIII. *J Pediatr Hematol Oncol*. 2013;35(7):551-553.
5. Dabak V, Kuriakose P, Raman S. Successful management of a Jehovah's Witness with thrombotic thrombocytopenic purpura unwilling to be treated with therapeutic plasma exchange. *J Clin Apher*. 2007;22(6):330-332.
6. Chai W, Chaudhry A, Rabinowitz AP. Successful management of thrombotic thrombocytopenic purpura in a Jehovah's Witness without plasma exchange. *J Clin Apher*. 2015;30(1):46-49.
7. Sam C, Desai P, Laber D, Patel A, Visweshwar N, Jaglal M. Pegylated bovine carboxyhaemoglobin utilisation in a thrombotic thrombocytopenic purpura patient. *Transfus Med*. 2017;27(4):300-302.
8. Kirti F, Ibarra G, Calvo AR. Treatment of a Jehovah's Witness with recurrent thrombotic thrombocytopenic purpura with rituximab [abstract]. *J Thromb Haemost*. 2015;13(S2):473. Abstract PO585-MON.
9. How many Jehovah's Witnesses are there worldwide? https://www.jw.org/en/jehovahs-witnesses/faq/how-many-jw-members/. Accessed 19 October 2017.
10. Reese JA, Muthurajah DS, Kremer Hovinga JA, Vesely SK, Terrell DR, George JN. Children and adults with thrombotic thrombocytopenic purpura associated with severe, acquired Adamts13 deficiency: comparison of incidence, demographic and clinical features. *Pediatr Blood Cancer*. 2013;60(10):1676-1682.
11. Scully M, McDonald V, Cavenagh J, et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. *Blood*. 2011;118(7):1746-1753.
12. Ovanesov MV, Menis MD, Scott DE, et al. Association of immune globulin intravenous and thromboembolic adverse events. *Am J Hematol*. 2017;92(4):E44-E45.
13. Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med*. 1994;121(4):259-262.

14. Centers for Disease Control and Prevention (CDC). Renal insufficiency and failure associated with immune globulin intravenous therapy–United States, 1985-1998. *MMWR Morb Mortal Wkly Rep*. 1999;48(24):518-521.

15. Peyvandi F, Scully M, Kremer Hovinga JA, et al; TITAN Investigators. Caplacizumab for acquired thrombotic thrombocytopenic purpura. *N Engl J Med*. 2016;374(6):511-522.

16. Scully M, Knöbl P, Kentouche K, et al. A recombinant human ADAMTS-13: first-in-human study evaluating pharmacokinetics, safety and tolerability in cTTP patients [published online ahead of print 14 September 2017]. *Blood*. doi:10.1182/blood-2017-06-788026.

17. Rizvi MA, Vesely SK, George JN, et al. Complications of plasma exchange in 71 consecutive patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic-uremic syndrome. *Transfusion*. 2000;40(8):896-901.

18. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. *Blood Adv*. 2017;1(10):590-600.

19. Kremer Hovinga JA, Vesely SK, Terrell DR, Lämmle B, George JN. Survival and relapse in patients with thrombotic thrombocytopenic purpura. *Blood*. 2010;115(8):1500-1511, quiz 1662.