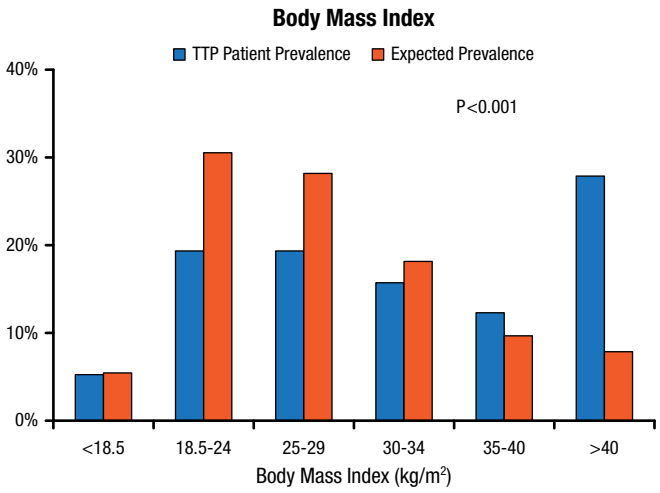
Figure 1. Prevalence of Categories of Body Mass Index Among TTP Patients and Expected Prevalence From NHANES Data Adjusted for Age, Sex, and Race



TTP, thrombotic thrombocytopenic purpura.

Reprinted from Deford CC et al. Multiple major morbidities and increased mortality during long-term follow-up after recovery from thrombotic thrombocytopenic purpura. *Blood* 2013;122(12)2023-2029. With permission from the American Society of Hematology.

Comparison of registry data with data from the US National Health and Nutrition Examination Survey (NHANES) adjusted for age, sex, and race has revealed a significantly higher body mass index for TTP registry patients as compared with the US expected values (Figure 1) [Deford CC et al. *Blood*. 2013].

The Oklahoma cohort highlights the heterogeneity in the clinical presentation of ADAMTS13 deficiency. Of 80 patients, 52% (n=42) had severe neurological abnormalities but 30% (n=24) had no neurological manifestations. Similarly, 40% (n=32) presented with renal insufficiency but 51% (n=41) had normal kidney function.

In the long term, relapse tends to occur within 3 years of remission. About one-half of the patients experienced >1 relapse. With the advances in treatment including greater use of steroids and rituximab during the initial acute episode, the recurrence rate may have been reduced; of the 34 patients diagnosed after 2005, only 18% have relapsed.

While a low ADAMTS13 level during remission may precede a relapse, the risk of relapse in patients with ADAMSTS13 deficiency is low, according to data from the Oklahoma registry (3 of 18 patients relapsed within 1 year of an ADAMTS13 activity <10%).

Pregnant women with a history of TTP are deemed to be at risk for recurrence and miscarriage [Ferrari B et al. *Blood*. 2014]. On the contrary, the Oklahoma cohort data revealed that TTP during pregnancy poses a low risk of fetal death. Women with TTP who desire to become pregnant need not be discouraged because of fetal health concerns. However, TTP is a risk factor for preeclampsia in a subsequent pregnancy (Table 1).

Table 1. Risk of Preeclampsia in Subsequent Pregnancy in Women With TTP

Occurrence per Pregnancy	TTP Frequency in the Oklahoma Cohort (n = 13)		TTP Frequency in the United States, %
	n (%)	95% CI	
Preeclampsia	5 (38)	14 to 68	2.1-3.2
Severe preeclampsia	3 (23)	5 to 54	1.0-1.2

TTP, thrombotic thrombocytopenic purpura.

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TTP is not only a life-threatening acute condition, but it is also associated with long-term sequelae including impaired cognition, depression, systemic lupus erythematosus, hypertension, impaired kidney function, and early mortality [Deford CC et al. *Blood*. 2013; Kennedy AS et al. *Transfusion*. 2009]. The cognition deficits are characteristics of diffuse, subcortical, microvascular disease [Kennedy AS et al. *Transfusion*. 2009].

Advances and Potential in Treatment of Hemophilia A

Written by Brian Hoyle

About 60% of people with hemophilia A have the severe form of the disease, which is characterized by factor VIII (FVIII) levels <1%. Intracranial hemorrhage and spontaneous bleeding require urgent intravenous administration of FVIII; however, this can cause complications including infection and thrombosis.

In an era of different recombinant FVIII treatment options, with the prospect of extended FVIII half-life, getting a better understanding of the product(s) that provide the maximum advantage for individual patients is important. Even incremental lengthening of the time of higher FVIII trough levels provides more protection from spontaneous bleeding. The goal in the treatment of hemophilia A, therefore, according to Jerry S. Powell, MD, CSL Behring, King of Prussia, Pennsylvania, USA, is to use a factor that is retained in the body longer and at higher levels than is the case now.

In hemophilia A about 30% of patients will, when exposed to normal factor VIII recognize it as foreign by the immune system. Treatment involving factor administration can help damp down the production of immune inhibitors [Nakar C et al. *Haemophilia*. 2015].

In hemophilia B, recombinant factor IX modified by pegylation has displayed a markedly extended half-life in phase 3 trials [Negrier C et al. *Blood*. 2011]. Another factor IX recombinant product fuses albumin, which is cleaved at the site of coagulation to deliver the native factor IX. A similar strategy involving recombinant FVIII (rFVIII) has been explored for the treatment of hemophilia A. Various products have been developed that feature pegylation and a recombinant fusion protein incorporating FVIII and a carboxy-terminal bound fragment crystallizable (Fc) domain of immunoglobulin G.

rFVIII-Fc features a longer half-life and decreased rate of clearance compared with the current recombinant FVIII products, independent of the level of von Willebrand Factor (vWF) [Powell JS et al. *Blood*. 2012].

Alternatives to factor replacement include FVIIIa mimetic-specific antibody, antibody to tissue factor pathway inhibitor, and the use of RNA interference technology to block antithrombin production. As with the extended half-life strategy, these alternate strategies aim for better and less frequent prophylactic treatment of hemophilia A, according to Andreas Tiede, MD, PhD, Hannover Medical School, Hannover, Germany.

The area of most robust research and development has been pegylation. The attachment of polyethylene glycol changes the physiochemical properties of the target compound and lengthens its residency in the body.

Pegylated products are approved for use with a variety of diseases, including leukemia, hepatitis C, age-related macular degeneration, rheumatoid arthritis, and Crohn disease. All feature a half-life that is extended compared with the native compound, with appreciable retention of activity [Fishburn CS. *J Pharm Sci*. 2008].

Pegylated products for hemophilia A include the B domain deleted FVIII compounds N8-GP, BAY 94-9027, and CSL 627, and the full-length FVIII backbone product BAX 855. With all, the pegylated region is removed during thrombin activation. All feature longer half-lives (about 1.5-fold increase, translating to about 18 hours for N8-GP, BAY 94-9027, and BAX 855 and about 13 hours for CSL 627) compared with recombinant FVIII [Tiede A et al. *J Thromb Haemost.* 2013].

Compared with FVIII, N8-GP displays reduced binding to lipoprotein receptor–related protein (LRP), similar potency and efficacy, and better protection from bleeding. vWF does affect the activity of N8-GP; the consequences, if any, are unknown. The compound is currently being evaluated in a phase 3 trial. BAX 855 has a similar thrombin-mediated activation rate as rFVIII but reduced binding to LRP. The reduced binding to LRP of these 2 compounds likely influences their extended half-lives. BAY 94-9027 can be monitored in serum using the one-stage activated partial thromboplastin time FVIII assay [Gu JM et al. *Haemophilia*. 2014], which could be exploited in phase 3 trials to monitor FVIII activity in patients treated with the compound. CSL 627 is similar to rFVIII in the rate of blood coagulation and performance in a mouse model of hemophilia. The compound also displays relatively increased binding to vWF. Its performance in a phase 1 assay has been promising [Coyle TE et al. *J Thromb Haemost*. 2014].

No safety issues have been evident with any of the compounds. Larger PEGs can accumulate in the body without any apparent adverse effects. Although immune response to PEG has been documented for other pegylated molecules, this has not been observed so far in vivo for the pegylated FVIII compounds.

Aside from the use of extended activity rFVIII compounds, researchers including Etienne Sokal, MD, PhD, Université Catholique de Louvain, Brussels, Belgium, are exploring stem cell therapy for relief of hemophilia. The research is grounded in the knowledge that the liver is a repository for thousands of enzymes that catalyze a wide variety of reactions. So, supplying progenitors of these cells could replace the enzyme-mediated defect of interest [Sokal EM. *J Inherit Metab Dis*. 2014].

Liver mesenchymal stem cells (MSCs) can be differentiated in vitro and used therapeutically [Khuu DN et al. *Cell Transplant*. 2013, 2011; Najimi M et al. *Cell Transplant*. 2007]. Intra-portal infusion facilitates the targeted delivery of liver MSCs to the liver [Defresne F et al. *Nucl Med Biol*. 2014].

A phase 1/2 study [NCT01765283] involving 20 pediatric patients (14 with urea cycle disorders and 6 Crigler-Najjar patients) with 3 doses of liver MSCs has indicated the safety and preliminary efficacy of treatment in restoring liver function in terms of urea production. These results have prompted studies assessing whether stem cell–mediated functional restoration can be applied to clotting factor deficiencies. The capacity of MSCs to produce FVIII has been demonstrated in vitro [Sanada C et al. *J Cell Physiol*. 2013], with correction of hemophilia and joint bleeding shown in animal models [Follenzi A et al. *Blood*. 2012; Porada CD et al. *Exp Hematol*. 2011]. Other examinations have indicated the potential of liver stem cells to target joints affected in hemophilia.

The emerging data indicate the therapeutic safety of adult liver MSCs and their capability as a vector for delivery of enzymes or proteins to affected tissues. The hope is that MSCs that express FVIII can be delivered where needed in patients with hemophilia.