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Recombinant ADAMTS13: An Enzyme Replacement Therapy for the Management of Congenital Thrombotic Thrombocytopenic Purpura

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Abstract

Congenital thrombotic thrombocytopenic purpura (cTTP) is a rare autosomal recessive condition that causes deficiency of the von Willebrand factor (vWF)-cleaving metalloprotease, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13). Traditionally, cTTP has been managed with plasma infusions, whether in the acute or prophylactic settings; however, there are various limitations and risks associated with this treatment modality. Recombinant ADAMTS13 (rADAMTS13) is the first FDA-approved product for management of cTTP. A phase III study compared rADAMTS13 to standard of care in which patients initially received prophylactic rADAMTS13 or plasma therapy, then crossed over to the alternative therapy. Patients receiving prophylactic rADAMTS13 had no acute cTTP events and lower rates of cTTP manifestations compared to standard of care. This article reviews the pharmacology, pharmacokinetics, efficacy, safety, dosing, administration, and implications for advanced practitioners of rADAMTS13 for the management of cTTP.

Congenital thrombotic thrombocytopenic purpura (cTTP), previously known as hereditary thrombocytopenic purpura or Upshaw-Schulman syndrome, is an autosomal recessive condition that causes deficiency of the von Willebrand factor (vWF)-cleaving metalloprotease, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13; Kremer Hovinga & George, 2019). The ADAMTS13 enzyme is

responsible for cleaving ultra-large vWF multimers into smaller, less hemostatically active peptides. Severe ADAMTS13 deficiency (ADAMTS13 activity < 10%) causes unregulated circulation of ultra-large vWF multimers leading to increased platelet adhesion and aggregation. Characterized as a form of thrombotic microangiopathy (TMA), cTTP precipitates microvascular thrombosis with organ ischemia, consumptive thrombocytopenia, and microangiopathic hemolytic anemia (MAHA; Alwan et al., 2019). Thrombotic thrombocytopenic purpura (TTP) is estimated to affect 2 to 6 people per million per year (Scully et al., 2008). Of all TTP episodes, cTTP accounts for 2% to 10%, with the remainder of cases being the acquired, immune-related form (Alwan et al., 2019).

Congenital TTP occurs due to a mutation of the *ADAMTS13* gene located on chromosome 9q34. More than 200 causative genetic mutations spanning the entire exon have been identified in patients with diagnosed cTTP (Asmis et al., 2022; von Krogh et al., 2016). Congenital TTP most often presents in early childhood and during pregnancy, and accounts for a significant portion of pediatric and obstetric patients with TTP (Sukumar et al., 2021). Patient age is useful in preemptively differentiating between the two forms of TTP.

Clinical presentation may be indistinguishable from immune TTP or they may differ considerably. Some distinct differences include symptoms in early childhood (i.e., neonatal jaundice), early onset preeclampsia during pregnancy, or abdominal pain with excessive vomiting after heavy alcohol intake (Kremer Hovinga & George, 2019). Historically, TTP presenting symptoms were characterized by a clinical "pentad" consisting of fever, MAHA, thrombocytopenia ($< 30 \times 10^9$/L), neurological deficits, and renal insufficiency. More recent data suggest the presence of MAHA and thrombocytopenia alone should prompt further investigation for the diagnosis of TTP. Other laboratory findings include increased serum lactate dehydrogenase (LDH), undetectable haptoglobin, increased serum indirect bilirubin, increased reticulocyte count, and schistocytes on peripheral blood smear. Microthrombi formation can precipitate organ dysfunction that includes seizures, stroke, acute kidney injury, and myocardial infarction (Hollifield et al., 2020; Sukumar et al., 2021).

If TMA is suspected, an ADAMTS13 activity level should be obtained, and an ADAMTS13 activity < 10% confirms the diagnosis. Further laboratory workup is needed to differentiate cTTP from the immune-mediated form and determine appropriate treatment. The presence of anti-ADAMTS13 IgG inhibitory autoantibodies is diagnostic for the more prevalent form, acquired TTP (aTTP). If autoantibodies are negative, genetic sequencing should be conducted to confirm cTTP (Sukumar et al., 2021).

Traditionally, cTTP has been treated by increasing plasma ADAMTS13 levels with infusion of 10 to 15 mL/kg/day of plasma for management of acute cTTP episodes. Following a single plasma infusion, ADAMTS13 activity will return to baseline within 5 to 10 days due to the half-life of ADAMTS13 (2.5–5.4 days). Administration of prophylactic plasma infusions every 2 to 3 weeks may be indicated for chronic prophylaxis depending on symptom burden and platelet count (Sukumar et al., 2021). However, frequent plasma infusions can be burdensome and increase the risk of transfusion-related reactions, thrombotic events, volume overload, alloimmunization, and potential blood-borne pathogens (Choosing Wisely, 2024; Reutter et al., 2001).

As an alternative option and in order to assuage the burden of care with plasma, plasma-derived factor VIII/von Willebrand factor concentrates have been tested for ADAMTS13 activity (Peyvandi et al., 2013). Among available options, the concentrate product Koate-DVI (antihemophilic factor [human]) contains a relatively high amount of ADAMTS13 that may be clinically relevant and therefore utilized for prophylactic dosing (Grifols Therapeutics, 2022). Unfortunately, the consideration of Koate-DVI and other products containing ADAMTS13 is frequently limited by financial access (third party coverage for an off-label indication) and thrombotic risk secondary to supratherapeutic coagulation factor levels.

ADAMTS13, recombinant-krhn (apadamtase alpha, Adzynma; Takeda Pharmaceuticals) is a novel human recombinant ADAMTS13 (rADAMTS13) product recently approved by the US Food and Drug Administration (FDA) for prophylactic or on-demand enzyme replacement therapy in adult and pediatric patients with cTTP, marking

the first FDA approval for a medication aimed at cTTP management. Due to the rarity of this disease and lack of alternative FDA-approved treatment options, the FDA new drug application for rADAMTS13 was granted priority review, fast track status, orphan drug designation, and awarded a pediatric disease priority review voucher (Takeda Pharmaceuticals, 2023). The objective of this review is to evaluate the pharmacology, pharmacokinetics, efficacy, safety, dosing and administration, and implications for the advanced practitioner of rADAMTS13 in the treatment of cTTP.

PHARMACOLOGY

Recombinant ADAMTS13 is a purified bivariant human recombinant enzyme expressed in Chinese hamster ovary cells using recombinant DNA technology. Replenishment of endogenous ADAMTS13 with rADAMTS13 allows restoration of cleavage of ultra-large vWF multimers into smaller proteins and thus clinical and laboratory resolution of thrombotic microangiopathy signs and symptoms. As expected, vWF antigen and ristocetin cofactor activity were shown to transiently decrease by 15% to 25% from baseline for 1 to 2 days following IV administration of rADAMTS13 due to increased cleavage of ultra-large weight vWF multimers with high hemostatic activity. Ultimately, this decreases platelet adhesion and aggregation, microthrombi formation, hemolysis, and end-organ dysfunction. The use of rADAMTS13 circumvents the risks associated with plasma transfusions and provides a treatment option to those unable or unwilling to receive blood products (Takeda Pharmaceuticals, 2023; Scully et al., 2017).

CLINICAL EFFICACY

A global, multicenter, prospective, randomized, active-controlled, open-label phase III trial with two crossover periods was conducted to compare the safety and efficacy of prophylactic rADAMTS13 to standard of care (SOC) plasma infusion in patients with cTTP (Scully et al., 2024). The study design for this phase III trial is depicted in Figure 1. Patients were randomly assigned to receive prophylactic rADAMTS13 once weekly or once every other week or SOC for months 1 to 6 (phase III, period 1), crossing over to the alternate treatment for months 7 to 12 (phase III, period 2). All patients then had the opportunity to enter phase IIIb (period 3) continuation of the trial where prophylactic rADAMTS13 was administered during months 13 to 18. In both the phase III and IIIb studies, patients could receive on-demand rADAMTS13 as rescue therapy as needed for acute TTP events. The primary endpoint was acute TTP events in patients receiving rADAMTS13 or SOC prophylaxis. An acute TTP event was defined as a decrease in platelet count of ≥ 50% from baseline or a platelet count < 100,000/μL and an elevated lactate dehydrogenase (LDH) > 2 times baseline or upper limit of normal. The primary outcome was the incidence of acute TTP events throughout all three periods. Secondary endpoints included manifestations of subacute TTP (defined as thrombocytopenia or MAHA with organ-specific signs and symptoms of TTP), treatment-emergent adverse events, and immunogenicity.

The trial enrolled 48 patients with severe cTTP (ADAMTS13 activity < 10%) during the phase III crossover study (periods 1 and 2). The age of study participants ranged from 3 to 68 years (median 33 years). Most patients were Caucasian (67%) and female (58%). Forty-seven (98%) patients received prior treatment with either fresh frozen plasma (FFP; 69%), solvent/detergent-treated plasma (23%), or FVIII-vWF concentrates (6%). Eight (17%) patients experienced an acute TTP event within 12 months prior to screening.

No acute TTP events occurred in those receiving prophylactic rADAMTS13 during the study. A total of eight acute TTP events were reported in seven patients. Five of those patients (median age: 20.0 years; sex: 3 male, 2 female) were randomized to receive either SOC or rADAMTS13 during phase III, periods 1 and 2. Two of the five patients who experienced acute TTP events were randomized to receive rADAMTS13, and three were randomized to SOC. Of the five randomized patients, 1-hour post-infusion plasma ADAMTS13 activity levels were between 80% to 270% and 10% to 48% in those who received rADAMTS13 and SOC, respectively. One event also occurred during phase III in a patient receiving prophylactic SOC with FFP during period 1. The last event occurred prior to receiving prophylactic rADAMTS13 during the screening process for the phase IIIb continuation study and was treated with rADAMTS13. All three

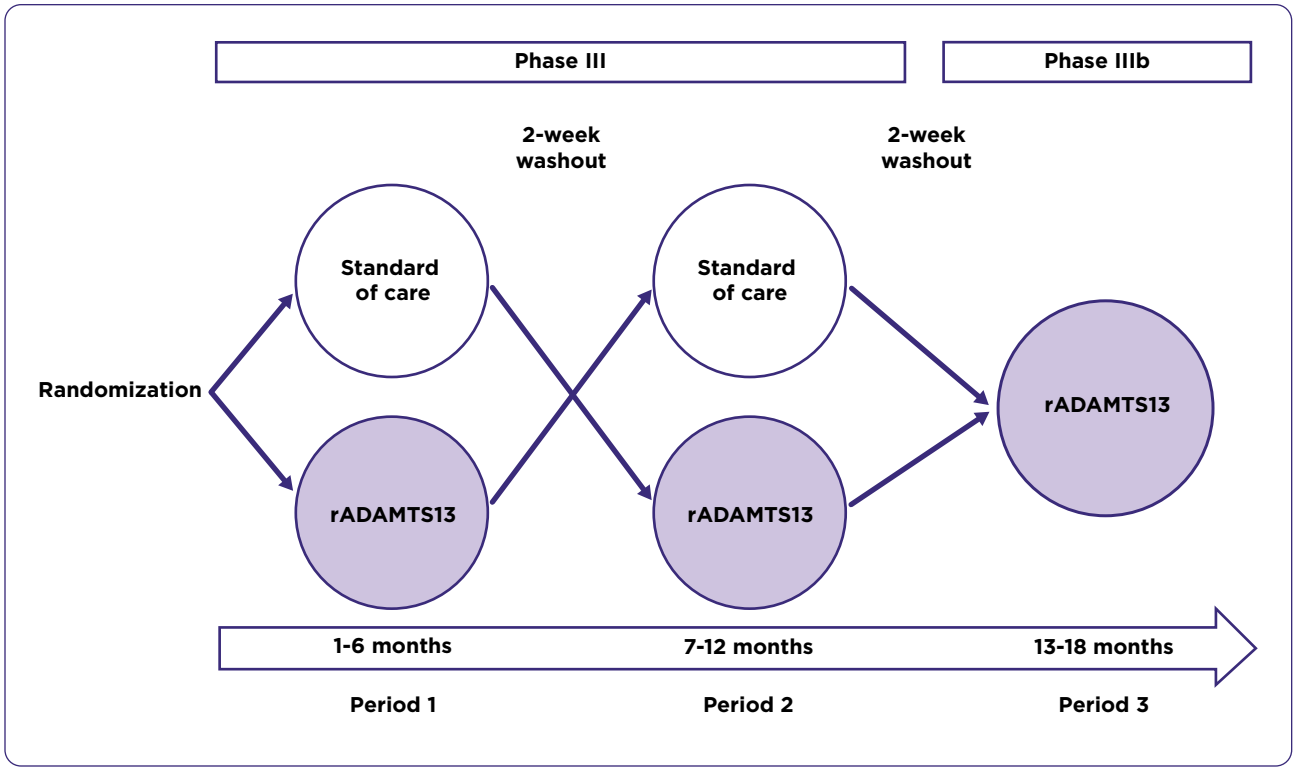

Figure 1. Recombinant ADAMTS13 phase III/IIIb study design. rADAMTS13 = recombinant—a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13.

acute TTP events treated with on-demand rADAMTS13 resolved without the need for additional plasma therapy. Over the first 3 days of treatment, the three patients treated with rADAMTS13 had a mean platelet count increase of more than fivefold while the four patients treated with SOC had an approximately threefold increase (Table 1).

There were no episodes of subacute TTP in the rADAMTS13 prophylaxis arm during periods 1 and 2, but two patients had two subacute TTP events during period 3, of which one patient received two supplemental doses of FFP and two doses of rADAMTS13. Four patients had a total of five subacute TTP episodes in the SOC arm during periods 1 and 2, and a total of seven supplemental doses were given: two of FVIII-vWF concentrate, one of FFP, and four of rADAMTS13 (Table 1). There were 30 episodes of thrombocytopenia in nine patients who were receiving rADAMTS13 compared to 75 episodes in 19 patients in the SOC arm. The mean (SD) annualized event rate of thrombocytopenia in patients receiving rADAMTS13 was estimated to be 2.0 (4.7). There were seven episodes in five patients that developed MAHA in the rADAMTS13 arm compared to 20 events in 11 patients in the SOC arm. The rADAMTS13 mean (SD) annualized MAHA event rate was 0.38 (1.03).

SAFETY

Treatment-emergent adverse events were reported in 10.3% of patients in the rADAMTS13 arm compared to 50% in the SOC arm (Scully et al., 2024). No severe adverse events were reported and no patients receiving rADAMTS13 developed ADAMTS13 neutralizing antibodies. The most common adverse effect from rADAMTS13 use was headache (31%). Other common adverse effects were diarrhea (16.7%), migraine (14.6%), abdominal pain (12.5%), nausea (12.5%), upper respiratory tract infection (12.5%), dizziness (10.4%), and vomiting (10.4%). Although no hypersensitivity or immunogenicity occurred during the study, there is a potential risk for these adverse events. Patients with life-threatening hypersensitivity reactions to rADAMTS13 should avoid future use. There are

Table 1. Thrombotic Thrombocytopenic Purpura Events Recorded During the Phase III/IIIb Study

	Prophylaxis Group	Acute TTP events	Treatment	Platelet Count, × 10^3 L		LDH, U/L	
				Event start	Event end	Event start	Event end
Phase III: Periods 1 and 2	rADAMTS13	–	–	–	–	–	–
	SOC	Patient 1[a]	SOC	104	279	454 (2.41 × BL)	194 (1.03 × BL)
		Patient 2[a]	rADAMTS13	84	270	236 (1.1 × ULN)	205 (0.96 × ULN)
		Patient 3[a]	rADAMTS13	24	155	598 (2.43 × ULN)	278 (1.13 × ULN)
		Patient 4, event 1[a]	SOC	23	62	685 (2.78 × ULN)	320 (1.30 × ULN)
		Patient 4, event 2[a]	SOC	23	101	652 (2.65 × ULN)	323 (1.31 × ULN)
		Patient 5[a]	SOC	20	276	458 (2.04 × ULN)	263 (1.17 × ULN)
		Patient 6	SOC	65	150	211 (1.06 × ULN)	187 (0.94 × ULN)
Phase IIIb: Period 3	rADAMTS13[b]	Patient 7	rADAMTS13	20	546	1027.4	282.4

	Prophylaxis group	Subacute TTP events	Treatment
Phase III: Periods 1 and 2	rADAMTS13	–	–
	SOC	Patient 1	Not reported
		Patient 2	Not reported
		Patient 3	Not reported
		Patient 4, event 1	Not reported
		Patient 4, event 2	Not reported
Phase IIIb: Period 3	rADAMTS13	Patient 5	–
		Patient 6	Two doses of FFP and two doses of rADAMTS13

Note. TTP = thrombotic thrombocytopenic purpura; rADAMTS13 = recombinant—a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; SOC = standard of care; LDH = lactate dehydrogenase; FFP = fresh frozen plasma.
[a]Patients who were randomized to receive SOC or rADAMTS13.
[b]Event occurred in the screening period prior to patient starting rADAMTS13 prophylaxis in phase 3b.

limited data in evaluating safety in patients 2 years of age or younger, as the youngest patient included in the phase III/IIIb trial was 3 years old (Takeda Pharmaceuticals, 2023).

DOSING AND ADMINISTRATION

Recombinant ADAMTS13 is supplied as a sterile, nonpyrogenic, preservative-free powder in a single-dose vial containing 500 IU or 1,500 IU nominal units (Takeda Pharmaceuticals, 2023). Each kit comes with 5 mL of sterile water for injection for reconstitution. The FDA approved prophylaxis dose is 40 IU/kg once every other week administered as a slow intravenous infusion. Dosing may be adjusted based on clinical response to 40 IU/kg once weekly. The recommended on-demand treatment dosing is 40 units/kg on day 1 followed by 20 units/kg on day 2 and then 15 units/kg once daily until resolution of acute TTP. Monitoring of ADAMTS13 activity should be considered to tailor dosing and to screen for potential immunogenicity and inhibitor development. The setting in which

rADAMTS13 is administered is likely to depend on the clinical indication. Prophylaxis may be administered in the home, since rADAMTS13 is available as a kit intended for patient preparation and self-administration. On-demand treatment is likely to be administered in a health-care facility during an acute TTP exacerbation.

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

Recombinant ADAMTS13 is the first and only product currently FDA-approved for prophylaxis and on-demand treatment of cTTP. In the ongoing phase III/IIIb trial, investigators demonstrated successful prophylaxis using weekly or biweekly rADAMTS13 infusions, with no patients experiencing an acute TTP event. Peak activity levels of ADAMTS13 were up to five times higher after administration of rADAMTS13 compared to plasma-based therapies (Scully et al., 2024). The trial also demonstrated a significant reduction in secondary composite endpoints as well as a favorable safety profile. There were no reports of immunogenicity after administration of rADAMTS13, and on-demand dosing was shown to resolve acute TTP events effectively. Pharmacokinetic data suggest that rADAMTS13 provides three- to fourfold longer duration of ADAMTS13 values above 10% compared to plasma, which may correspond to a reduction in infusion frequency compared to plasma prophylaxis.

Historically, the mainstay of therapy for cTTP treatment and prophylaxis has been human plasma-based therapy, which has several limitations. These limitations include frequent administrations in a monitored health-care setting and adverse reactions, including allergic reactions, volume overload, thrombosis, alloimmunization and potential blood-borne pathogen exposure. In contrast, rADAMTS13 is largely devoid of these complications and can be administered at home on a weekly or biweekly basis. Additionally, rADAMTS13 provides a viable treatment alternative for patients who decline human blood products. Considering these advantages of rADAMTS13 over plasma, rADAMTS13 could be offered as prophylaxis to all cTTP patients to prevent acute TTP episodes and the negative sequelae of frequent plasma infusion (Sukumar et al., 2021).

A key implication for advanced practitioners managing patients receiving rADAMTS13 is patient education. Particularly for patients using rADAMTS13 for prophylaxis and self-administering, patient education related to preparation, administration, and storage of rADAMTS13 will be critical. Detailed instructions on preparation and administration of rADAMTS13 are available in the prescribing information. Recombinant ADAMTS13 should be stored at a refrigerated temperature of 36 to 46 degrees F; however, it can be stored at room temperature for a period of up to 6 months. Once stored at room temperature, it should not be returned to refrigeration (Takeda Pharmaceuticals, 2023).

A substantial proportion of cTTP patients first manifest cTTP symptoms during pregnancy, which can lead to adverse pregnancy outcomes (Gounder & Scully, 2024). Therefore, further evaluation of rADAMTS13 is warranted in this patient subpopulation. Two patients included in the phase III study were found to be in the first trimester of pregnancy while receiving rADAMTS13 prophylaxis (Dadoun et al., 2024). One of these pregnancies resulted in miscarriage approximately 2 months following drug exposure, which was deemed unrelated to rADAMTS13. The second pregnancy resulted in a full-term labor without complications. Another patient was managed prophylactically throughout her pregnancy with fresh frozen plasma and then Koate-DVI (following an anaphylactic event to the plasma). At 35 weeks gestation this patient presented with an acute TTP event, and she was initially managed with intensively dosed Koate-DVI with minimal improvement before switching to rADAMTS13. She was given 40 units/kg daily on days 2 through 5 after presentation, resulting in platelet recovery and an induced, uncomplicated, vaginal delivery. After delivery, she received rADAMTS13 20 units/kg followed by 15 units/kg daily until postpartum day 3. She then continued rADAMTS13 40 units/kg weekly for 6 weeks postpartum before transitioning to every other week prophylaxis. Two additional patients received on-demand rADAMTS13 due to cTTP complications during pregnancy through the manufacturer's compassionate use program: one during each of the final two trimesters of pregnancy. Both pregnancies resulted

in healthy neonates with no emergent safety concerns from rADAMTS13 exposure. There are currently no data evaluating the safety of rADAMTS13 in lactating mothers.

CONCLUSION

Data from recent clinical trials support the use of rADAMTS13 as a preferred first-line therapy for cTTP prophylaxis and for the treatment of acute cTTP episodes. Recombinant ADAMTS13 offers many advantages over plasma infusion, including increased efficacy and duration of action. In addition, rADAMTS13's improved safety profile allows for the avoidance of many of the negative consequences of lifelong plasma infusion.

Disclosure

Dr. Moore reports advisory board participation with Incyte, GSK, Genentech, and Sanofi. Dr. Arnall reports advisory board participation with GSK. The remaining authors have no conflicts of interest to disclose.

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