ADVANCES IN HEMATOLOGY

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Recombinant ADAMTS13 Concentrate in Thrombotic Thrombocytopenic Purpura

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H&O What is thrombotic thrombocytopenic purpura (TTP), and how common is it?

SC TTP is a disorder in which small vessel thrombosis occurs throughout the body in multiple organs. In the immune-mediated form of TTP, patients develop an antibody against the ADAMTS13 protease, which is needed to cleave ultra-large von Willebrand factor (VWF) multimers down to the correct size to avoid spontaneous microvascular thrombosis. In the congenital form, patients are born without the protease.

TTP is a rare blood disease. The standard estimates are that immune-mediated TTP affects 3 to 4 people per million and congenital TTP affects 1 to 2 people per million, although research by Seidizadeh and colleagues that was presented at the 2023 American Society of Hematology Annual Meeting suggests that the rates of congenital TTP may be higher than previously thought.[1]

H&O How is it diagnosed?

SC The first sign of TTP is often thrombocytopenia on a complete blood count test. Signs and symptoms related to widespread microthrombotic disease may also be present, including fever, neurologic signs, fatigue, and abdominal pain. The platelet count is often less than 30,000 platelets per mL of blood. The next step is typically a peripheral blood smear to look for schistocytes. The presence of these fragmented red blood cells raises a high suspicion of TTP, either immune-mediated or congenital. Diagnosis requires testing for the ADAMTS13 protease, which is more readily available these days.

H&O What has been the standard management of congenital TTP?

SC The standard management of congenital TTP is the replacement of ADAMTS13. The most common treatment used to be a plasma infusion every 1 to 2 weeks, although in some cases, a product approved to treat patients with hereditary factor VIII deficiency (Koāte, Kedrion Biopharma) that contains some ADAMTS13 was used. However, since the US Food and Drug Administration approved a recombinant ADAMTS13 product (Adzynma, Takeda) in November 2023 that delivers a higher and more sustained level of ADAMTS13, this has become the new standard treatment for congenital TTP.

H&O What are the advantages of recombinant ADAMTS13?

SC Recombinant ADAMTS13 is much better tolerated than plasma infusions, which often lead to fatigue and other nonspecific symptoms that limit their frequency. The infusion time is shorter, at less than an hour vs 5 or 6 hours. Patients who receive recombinant ADAMTS13 have a choice between visiting a clinic and receiving a visit from a home nurse, whereas plasma infusions

require visiting a clinic. The most important advantage of recombinant ADAMTS13 is its ability to achieve greater ADAMTS13 activity for a longer period than with plasma.

H&O What is the difference between prophylactic treatment and acute treatment?

SC We can use recombinant ADAMTS13 for both prophylactic and acute treatment of TTP in patients with the congenital form of the disease, so the treatment is the same. Regular prophylactic treatment is used to prevent symptoms and acute chronic TTP episodes, which is distinct from acute treatment for an acute chronic TTP episode.

H&O Could you discuss the research that led to the approval of recombinant ADAMTS13?

SC The study that served as the basis for approval was a phase 3 trial in which patients served as their own controls after an initial pharmacokinetic phase.[2] Patients received either recombinant ADAMTS13 at 40 U per kg or their prestudy treatment, which included fresh frozen plasma, pooled solvent/detergent-treated plasma, or a factor VIII/VWF concentrate, at the same intervals as before the study. After 6 months, patients crossed over to the other treatment for 6 months. In a phase 3b continuation study, patients received 6 months of open-label treatment with recombinant ADAMTS13.

> Some preliminary data suggest that recombinant ADAMTS13 can be used in acquired TTP.

The researchers found that acute TTP events occurred in none of the patients during prophylactic treatment with recombinant ADAMTS13 (n=37), and in 1 patient receiving standard therapies (n=38). No subacute TTP events occurred in the patients receiving prophylactic treatment with recombinant ADAMTS13, whereas 5 subacute TTP events occurred in 4 patients receiving standard therapies. In the phase 3b continuation study, 2 patients receiving prophylactic treatment with recombinant ADAMTS13 had 2 subacute events.[3]

In addition, the median time to the ADAMTS13 activity staying above 10% was about 5 days in the recombinant ADAMTS13 group vs only 2 days in the standard-of-care arm. Although the target ADAMTS13 activity will likely need to be higher than 10%, this is the minimum level that is believed to protect against the development of acute chronic TTP events.[4]

H&O What adverse events (AEs) were seen with recombinant ADAMTS?

SC The most common AEs associated with recombinant ADAMTS13 in this trial, occurring in more than 5% of patients, were headache, diarrhea, migraine, abdominal pain, nausea, upper respiratory tract infection, dizziness, and vomiting. In results that Dr Marie Scully reported at the 2023 International Society on Thrombosis and Haemostasis Congress that were later published in the *New England Journal of Medicine*, treatment-related AEs were reported in 10.3% (n=39) of patients receiving recombinant ADAMTS13 and 50.0% (n=40) of those receiving standard therapy. There were no serious AEs related to recombinant ADAMTS13, and no patients receiving it developed neutralizing antibodies to ADAMTS13, which was encouraging.[4,5]

H&O Is there still a role for older TTP treatments?

SC Yes, we can still use plasma-based treatments if recombinant ADAMTS13 is unavailable for some reason. But given the choice between the 2 approaches, I would always choose recombinant ADAMTS13.

H&O Although the approval of recombinant ADAMTS13 is just for congenital TTP, can physicians use it for immune-mediated TTP?

SC Some preliminary data suggest that recombinant ADAMTS13 can be used in immune-mediated TTP. This involves using an extra-high dose to overcome the antibody that neutralizes the patient's own ADAMTS13 and combining the agent with immunosuppressive therapy. Although these data have not been presented or published, they are expected to be published in the next 6 months.

H&O What other studies are being conducted in immune-mediated TTP?

SC The ongoing phase 3 MAYARI study is looking at the use of caplacizumab (Cablivi, Sanofi) without first-line plasma exchange in immune-mediated TTP (NCT05468320), and a phase 2 study is looking at the

use of recombinant ADAMTS13 with little or no plasma exchange (NCT05714969).

H&O What assays are used to measure ADAMTS13 activity?

SC There are many assays that can be used to measure the patient's ADAMTS13 protease. The 2 main types commonly used are based on fluorescence resonance energy transfer (FRETS) or enzyme-linked immunosorbent assay (ELISA). Many sites will have these assays available in-house, but if not, samples can be sent to a reference laboratory for analysis. These assays all measure ADAMTS13 inhibitors and activity.

H&O What further research is needed on recombinant ADAMTS13?

SC The licensing study that served as the basis for approval measured acute episodes and subacute events, but we need to see longer-term outcomes because patients with congenital TTP are at increased risk for strokes, heart disease, and chronic kidney disease. What is the blood level of ADAMTS13 that is required to prevent these complications? We need longer-term studies to look at these questions.

It would also be helpful to have a way of dosing this medication that does not require intravenous administration. One approach that has been studied is subcutaneous dosing. If approved, this method would make it easy for patients to self-administer the agent as often as needed, so if the optimal interval is every 3 days, that can be done easily. We do not know at this point what the goal is, however.

H&O What are cost issues associated with switching to recombinant ADAMTS13?

SC This is an expensive medication, costing an estimated $250,000 per year. It is certainly life-changing for patients, however. This agent represents a tremendous advance. The biggest difference may be for patients who do not live near an infusion center.

Disclosures

Dr Cataland has served as a consultant to Takeda, Sanofi, and Roche.

References

1. Seidizadeh O, Cairo A, Mancini I, et al. Estimating the population-based prevalence of congenital thrombotic thrombocytopenic purpura using large-scale sequencing data [ASH abstract 693]. *Blood*. 2023;142(suppl 1).
2. Adzynma [package insert]. Lexington, MA: Takeda; 2023. https://content.takeda.com/?contenttype=PI&product=ADZ&language=ENG&country=USA&documentnumber=1.
3. Coppo P, Patwari P, Mellgård B, et al. Recombinant ADAMTS13 prophylaxis in patients with congenital thrombotic thrombocytopenic purpura: interim analysis from phase 3b continuation study. Presented at: International Society on Thrombosis and Haemostasis Congress; June 24-28; Montreal, Canada. Abstract OC 14.4.
4. Scully M, Antun A, Cataland SR, et al; cTTP Phase 3 Study Investigators. Recombinant ADAMTS13 in congenital thrombotic thrombocytopenic purpura. *N Engl J Med*. 2024;390(17):1584-1596.
5. Scully M, Windyga J, Mellgård B, et al. Phase 3 prospective, randomized, controlled, open-label, multicenter, crossover study of recombinant ADAMTS13 in patients with congenital thrombotic thrombocytopenic purpura. Presented at: International Society on Thrombosis and Haemostasis Congress; June 24-28; Montreal, Canada. Abstract OC 14.1.