Real-world safety and efficacy of rADAMTS13 prophylaxis in congenital thrombotic thrombocytopenic purpura: experience from Polish patients previously treated with fresh frozen plasma

Congenital thrombotic thrombocytopenic purpura (TTP), or Upshaw-Schulman syndrome, is a rare autosomal recessive disorder caused by severe ADAMTS13 deficiency, leading to accumulation of ultra-large von Willebrand factor multimers and resulting in microvascular thrombosis, platelet consumption, and microangiopathic hemolytic anemia.[1]

Traditional management has relied on replenishing ADAMTS13 levels using plasma-based therapies, including fresh frozen plasma (FFP) and selected plasma-derived factor VIII concentrates. However, these approaches pose risks such as volume overload, allergic reactions, and limited efficacy. In addition, plasma-derived factor VIII concentrates contain von Willebrand factor, which may be undesirable in the context of TTP.[2,3] Furthermore, the 2020 guidelines from the International Society on Thrombosis and Haemostasis advise against the use of factor VIII concentrates due to variability in ADAMTS13 levels.[4] Therapeutic plasma exchange and FFP infusions remain the cornerstone of TTP treatment, improving survival rates from below 20% in the pretreatment era to over 95% with treatment.[5-7]

The introduction of recombinant ADAMTS13 (rADAMTS13), specifically apadamtase alfa (Adzynma), represents a major advance. Approved by the US Food and Drug Administration (FDA) in 2023 and the European Medicines Agency (EMA) in 2024, it offers targeted enzyme replacement without the drawbacks of plasma products. Phase III trials confirmed its efficacy in both prophylactic and on-demand settings, with sustained ADAMTS13 activity, no acute TTP events, and a favorable safety profile.[8-10]

Comparative studies have shown higher and more durable ADAMTS13 activity with rADAMTS13 than with FFP, along with better tolerability. While trial data are promising, real-world evidence remains limited.[3,11] This study reviews initial real-world experience with rADAMTS13 in Poland, focusing on clinical outcomes and its potential to reduce treatment burden.

We retrospectively assessed clinical data from adult and pediatric patients with congenital TTP treated across 10 hematologic centers in Poland. All patients transitioned from FFP prophylaxis to rADAMTS13. Each center obtained rADAMTS13 after contacting the pharmaceutical company (Takeda) for compassionate use and following the required national approval process.

rADAMTS13 therapy was initiated through a shared decision-making process involving treating physicians, patients, and their parents or caregivers. Written informed consent was obtained from all families for both the use of rADAMTS13 and the publication of clinical details. All study procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Data were collected for the 12 months preceding rADAMTS13 initiation (under FFP prophylaxis) and the 12 months following its initiation. Collected variables included laboratory parameters; the number of acute, subacute, and isolated TTP events; and the number and duration of hospitalizations. Laboratory tests were performed in local accredited laboratories in accordance with applicable diagnostic standards. Definitions of TTP events were based on the rADAMTS13 clinical trial.[11]

Statistical analyses were performed using Prism, version 10.3.1 (GraphPad Software). Data were presented as means and standard deviation (SD). Normality of data distribution was assessed using the Shapiro-Wilk test. Differences between FFP and rADAMTS13 treatment periods were analyzed using the Wilcoxon matched-pairs signed rank test or the paired *t* test, depending on data distribution. Differences in the number of hospitalizations were assessed using the Mann-Whitney U test. $P<0.05$ was considered statistically significant.

Patient characteristics and prophylactic treatment dosing are presented in Table 1. A total of 23 patients were enrolled in the study, including 10 males and 13 females. Among the entire study population, there were 7 patients under 18 years of age, including 3 females and 4 males. The overall mean age was 25.7 (SD: 13.2) years, with a median age of 30 years. After transitioning to prophylactic treatment, patients received rADAMTS13 at a dose of 40 IU/kg every two weeks, except for one patient whose dosing interval was changed to once weekly due to frequent subclinical episodes already observed during previous prophylaxis with FFP. Although switching to rADAMTS13 every two weeks led to slight improvement, subclinical episodes persisted. The treating physician, therefore, decided to increase the dosing frequency to once weekly, which proved to be an effective strategy. The adherence to rADAMTS13 prophylaxis was 100%.

A significant increase in hemoglobin levels and platelet counts was observed following the switch from FFP to rADAMTS13 prophylaxis in all patients. Notably, lactate dehydrogenase (LDH) and total bilirubin levels were significantly lower during rADAMTS13 prophylaxis, while no significant

Table 1. Patients' characteristics.

N	Age, years	Sex	Age at first symptoms, years	Age at initiation of FFP prophylaxis, years	First symptoms	Weight, kg	Prophylactic FFP dose*	Total FFP dose#	Prophylactic rADAMTS13 dose
1	9	F	1	5	Thrombocytopenia, anemia, renal failure	36	1U Q3W	16U	40 IU/kg Q2W
2	12	F	1	5	Thrombocytopenia, anemia, renal failure	44	1U Q2W	23U	40 IU/kg Q2W
3	10	M	1	1	Thrombocytopenia, anemia, renal failure	28	1U Q4W	17U	40 IU/kg Q2W
4	16	M	15	15	Thrombocytopenia, anemia	63	2U Q2W	10U	40 IU/kg Q2W
5	9	M	1	4	Thrombocytopenia, anemia, renal failure	26	2U Q3W-Q4W	40U	40 IU/kg Q2W
6	3	M	1	1	Thrombocytopenia, anemia	14	Q4W**	ND	40 IU/kg Q2W
7	8	F	1	5	Thrombocytopenia, anemia	23	Q4W**	ND	40 IU/kg Q2W
8	38	M	23	23	Thrombocytopenia, anemia, renal failure, ischemic stroke, TIA	104	9-12 U Q3W-Q4W	194U	40 IU/kg Q2W
9	24	F	1	24	Thrombocytopenia, anemia, renal failure, ischemic stroke, TIA	84	3-4U Q1W	81U	40 IU/kg Q2W
10	35	F	26	28	Thrombocytopenia, anemia	81	2U Q2W-Q3W	24U	40 IU/kg Q1W
11	55	F	23	23	Thrombocytopenia, anemia, renal failure	56	4U Q2W	96U	40 IU/kg Q2W
12	33	F	3	31	Thrombocytopenia, anemia, renal failure	55	2U Q4W	24U	40 IU/kg Q2W
13	33	F	1	ND	Thrombocytopenia, anemia, renal failure	58	ND	ND	40 IU/kg Q2W
14	40	F	34	ND	Thrombocytopenia, anemia	75	ND	ND	40 IU/kg Q2W
15	38	M	3	36	Thrombocytopenia, anemia, renal failure	65	2U Q4W	ND	40 IU/kg Q2W
16	34	F	31	31	Anemia, ischemic stroke,	81	2U Q2W	ND	40 IU/kg Q2W
17	35	M	7	18	Thrombocytopenia	108	6U Q2W	150U	40 IU/kg Q2W
18	18	M	1	2	Thrombocytopenia, anemia	54	3U Q6W-Q8W	27	40 IU/kg Q2W
19	18	M	3	9	Thrombocytopenia, anemia	70	2-3U Q4W	ND	40 IU/kg Q2W
20	32	F	1	15	Thrombocytopenia, anemia	53	3U Q2W	72U	40 IU/kg Q2W
21	31	F	1	12	Anemia	73	4U Q2W	96U	40 IU/kg Q2W
22	30	M	ND	11	Thrombocytopenia, anemia	80	4U Q2W	96U	40 IU/kg Q2W
23	29	F	1	ND	Anemia	86	4U Q3W	ND	40 IU/kg Q2W

F: female; FFP: fresh frozen plasma; HUS: hemolytic uremic syndrome; M: male; ND: no data; Q1W: once weekly; Q2W: once every 2 weeks; Q3W: once every 3 weeks; Q4W: once every 4 weeks; Q6W-Q8W: once every 6-8 weeks; rADAMTS13: recombinant ADAMTS 13; TIA: transient ischemic attack; TTP: thrombotic thrombocytopenic purpura. *1 U FFP equals 200-300 mL. **No data on dosing. #Total FFP dose in the 12 months prior to initiation of rADAMTS13.

changes were observed in serum creatinine levels. Detailed laboratory results are presented in Figure 1 and *Online Supplementary Table S1*.

When stratified by age, patients both above and below 18 years demonstrated improvements during rADAMTS13 prophylaxis compared to FFP therapy, with significant increases in platelet count and hemoglobin as well as reductions in bilirubin and LDH. Creatinine levels remained stable across treatment phases. Results are summarized in *Online Supplementary Table S1*.

Following rADAMTS13 initiation, the mean number of acute, subacute, and isolated TTP events decreased in both adults (from 1.1, 1.9, and 2.9 to 0, 0, and 0.1) and children (from 0.4, 5.6, and 1.9 to 0.1, 0.1, and 0.3).

The mean number of hospitalizations and hospitalization days was significantly reduced during rADAMTS13 prophylaxis, from 17.2 to 0.7 and from 24.8 to 0.8, respectively, in the overall patient group. Hospitalizations specifically related to TTP-related disease exacerbation also declined. No significant difference was observed in the mean number of days spent in hospital due to exacerbation between FFP and rADAMTS13 prophylaxis. Similar patterns were observed in both adult and pediatric subgroups. Notably, the relatively high number of hospitalizations in the pre-rADAMTS13 period reflects the local clinical practice in Poland, where each administration of FFP for prophylaxis requires a formal hospital admission due to procedural regulations and monitoring requirements. Hospitalization-related outcomes are shown in *Online Supplementary Table S2*.

During the 12 months preceding the switch to rADAMTS13, allergic reactions were reported in 9 of 17 patients (53%), and one patient (6%) was diagnosed with transfusion-related acute lung injury (TRALI). In contrast, no adverse events were observed during the 12 months of rADAMTS13 prophylaxis.

This real-world multicenter study provides compelling evidence for the clinical benefits of switching from FFP to rADAMTS13 prophylaxis in Polish patients with congenital TTP. The observed improvements in laboratory parameters, reduction in acute, subacute, and isolated TTP events, and decreased hospitalization rates collectively highlight the effectiveness and safety of rADAMTS13 in both adult and pediatric patients.

A significant increase in hemoglobin levels and platelet counts, along with a reduction in LDH and total bilirubin, were consistent with improved disease control and a reduction in microangiopathic hemolysis. These findings were evident across the overall study population and in subgroup analyses by age. A similar observation was reported in another Polish real-world study by Łaguna *et al*. carried out in 9 children,[12] where treatment with rADAMTS13 led to an increase in platelet count, particularly in patients with low baseline levels, and a decrease in LDH levels in those with higher baseline values. Patients with congenital TTP are at increased risk of ischemic stroke, particularly between the ages of 40 and 50.[13] Early initiation of prophylactic treatment can help prevent such events by maintaining proper hemostatic balance.

Fresh frozen plasma carries a risk of immune complications, including allergic reactions and, more rarely, serious events such as TRALI.[14,15] In our study, FFP prophylaxis led to allergic responses in over half of the patients, and one patient experienced TRALI. The absence of such events during rADAMTS13 treatment underscores its improved safety and tolerability, supporting its role as a safer long-term prophylactic option in patients with congenital TTP.

Importantly, no acute TTP events were recorded during the 12-month period following the initiation of rADAMTS13 prophylaxis, and subacute or isolated manifestations were rare. Our findings are consistent with those reported in the phase III clinical trial,[11] further supporting the effectiveness of rADAMTS13 in the prophylactic setting. Notably, we adopted the same definitions for TTP events as those used in the trial, ensuring comparability of results across both clinical and real-world settings.

Although few cases of increased creatinine levels were reported in the phase III clinical trial,[11] with most values being only marginally above the protocol-defined threshold of 1.5 times the baseline value, creatinine levels remained stable

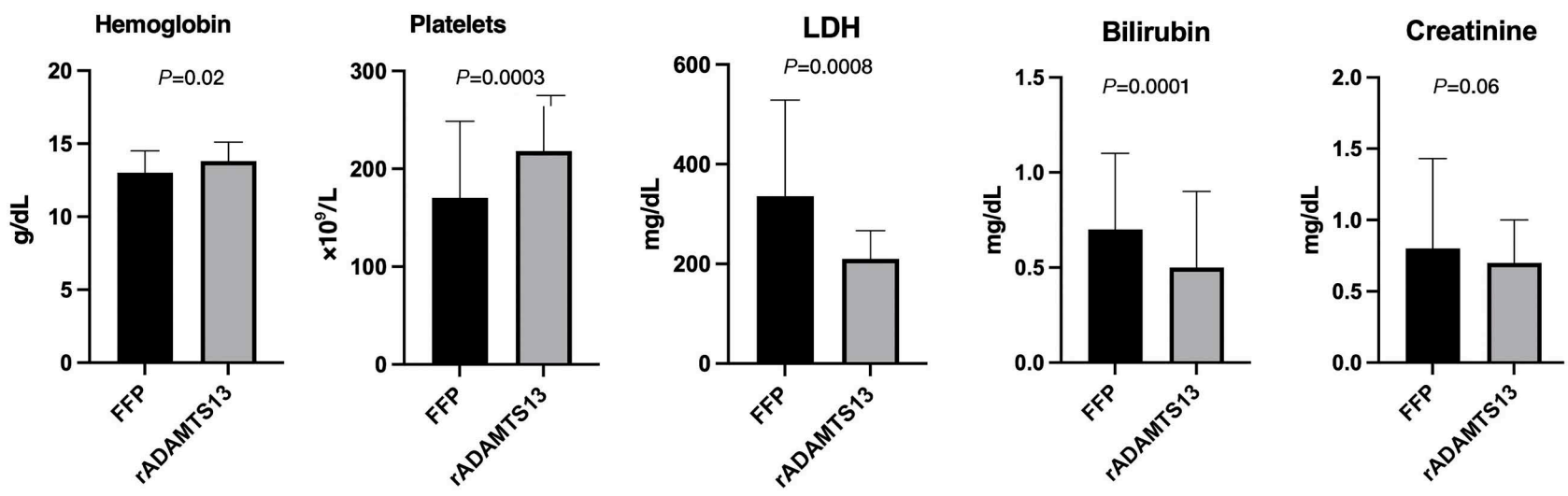

Figure 1. Changes in laboratory parameters over 12 months of fresh frozen plasma therapy and during the subsequent 12 months after switch to rADAMTS13 prophylaxis in all patients. Bars represent the mean; error bars indicate the standard deviation.

throughout the follow-up period in our study.
Another key observation was the reduction in the use of healthcare resources. The number of hospitalizations - particularly those related to disease exacerbation - declined significantly in both adults and children. For pediatric patients, this translated into fewer days missed from school and a reduced burden on caregivers, underscoring the broader benefits of rADAMTS13 beyond hematologic parameters.
The main strength of this study is the use of real-world data from a relatively large population of patients with this rare disease. However, certain limitations should be acknowledged. The partially retrospective design introduces the potential for selection and reporting bias. The small cohort size limits statistical power, particularly for subgroup analyses. Another limitation is the lack of measurements of ADAMTS13 activity during rADAMTS13 prophylaxis; however, a prospective evaluation of this parameter is planned and will be addressed in a separate study.
In conclusion, our findings provide real-world support for the use of rADAMTS13 as an effective and well-tolerated prophylactic therapy for congenital TTP, offering clear advantages over traditional FFP-based regimens.

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Contributions

JW conceived and supervised the study, developed the methodology, prepared visualizations, and drafted the manuscript. All authors contributed to data processing, validation, analysis, investigation, resources, data curation, funding acquisition, and to writing, reviewing, and editing the manuscript.

Data-sharing statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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