

BRIEF REPORT

Treatment of acquired thrombotic thrombocytopenic purpura without plasma exchange in selected patients under caplacizumab

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Abstract

Background: Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare, life-threatening autoimmune thrombotic microangiopathy. Current standard of care is therapeutic plasma exchange, immunosuppression, and caplacizumab, an anti-von Willebrand factor nanobody, which is effective in treating aTTP episodes.

Patients/Methods: Here we report on seven episodes of aTTP treated without plasma exchange in six female patients in Germany and Austria. Two episodes were initial presentations of aTTP; in five instances, patients experienced a relapse. In four episodes, moderate to severe organ dysfunction was observed; three cases presented with a mild course. All patients received caplacizumab immediately once aTTP was suspected or diagnosed, and plasma exchange was omitted based on shared decision making between patient and the treating physicians.

Results: We observed a rapid and robust increase of platelet counts already after the first dose of caplacizumab, leading to a doubling of platelet counts within 17 hours (median), platelet counts normalized (>150 G/L) after median 84 hours. Lactate dehydrogenase, as a surrogate parameter of organ damage, improved in parallel to the platelet counts, indicating resolving microangiopathy.

Conclusions: In conclusion, in selected cases of acute bouts of aTTP, it seems feasible to delay or omit plasma exchange if platelet counts increase and organ function is stable after start of caplacizumab therapy.

KEYWORDS

purpura, thrombotic thrombocytopenic, ADAMTS13 protein, plasma exchange, caplacizumab, platelet count

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1 | INTRODUCTION

The acquired (or autoimmune) thrombotic thrombocytopenic purpura (aTTP) is a rare life-threatening disease, characterized by severe thrombocytopenia, microangiopathic hemolytic anemia, and organ dysfunction. It is caused by autoantibodies against a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13 (ADAMTS13), resulting in the persistence of ultralarge von Willebrand factor multimers and microvascular platelet aggregation. The novel nanobody caplacizumab was approved for the treatment of aTTP in 2018 after positive results from the HERCULES and TITAN trials.^{1,2} It targets the A1-domain of von Willebrand factor, prevents platelets adhesion and thus limits the pathogenic process of microthrombi formation and endothelial dysfunction, and prevents organ damage. Until the introduction of caplacizumab, glucocorticoids, immunosuppressants, and plasma exchange were the mainstay of aTTP treatment, reducing mortality from > 90% (if untreated) to 10% to 15%.³ Caplacizumab was shown to significantly reduce the time to platelet count normalization and the composite key secondary outcome of aTTP-related death, recurrence, and major thromboembolic events.¹ However, with the advent of this potent novel drug and in view of potentially life-threatening procedure-associated complications, the role of plasma exchange in the treatment of aTTP remains to be reevaluated.⁴⁻⁶ Recent reports have shown that plasma exchange-free treatment is feasible, but have limitations because ADAMTS13 activities were not reported at the time when caplacizumab was first administered, or the aTTP episode was rather mild.^{7,8}

2 | METHODS

Here we report on seven episodes of aTTP, treated without plasma exchange, in six patients in Germany and Austria. Data were accessed retrospectively.^{9,10} Laboratory parameters (blood cell counts, serum chemistry) were measured with local standard methods. For measurement of ADAMTS13 activity and quantification of anti-ADAMTS13 antibodies, various methods were used as locally available (ie, chromogenic ELISA techniques, FRET-S-VWF73 assay, or anti-ADAMTS13-IgG antibody ELISA or Bethesda-assay, respectively). Statistical analysis and graphics were compiled using GraphPad Prism v8.0 (GraphPad Software).

3 | RESULTS AND DISCUSSION

Here, we report on six patients with an acute episode of aTTP treated with caplacizumab but without plasma exchange that were identified retrospectively from a cohort of 60+ patients treated with caplacizumab at 30+ different medical centers across Austria and Germany between 2018 and 2020.^{9,10} All six patients were white females between 31 and 75 years of age (Table 1). There was no uniform protocol for TTP diagnosis and treatment and the use of caplacizumab, plasma exchange, or immunosuppression. Therefore,

Essentials

- Caplacizumab and plasma exchange are still standard of care for autoimmune TTP.
- Seven episodes of aTTP in 6 patients were treated with caplacizumab but without plasma exchange.
- Prompt normalization of platelet counts and resolving organ dysfunction were observed.
- Plasma exchange is not always a mandatory requirement in aTTP management.

this collection of patients is heterogeneous in many aspects. All patients received caplacizumab immediately once aTTP was suspected or diagnosed, and plasma exchange was omitted based on shared decision making between patient and the treating physicians because of poor venous access ($n = 2$), oligosymptomatic presentation ($n = 4$), and refusal of consent to plasma exchange ($n = 1$).⁸ Patients and/or relatives were informed about the characteristics of their disease and the advantages and disadvantages of possible and available treatment options including central venous line placement and plasma exchange therapy. The new options, caplacizumab and rituximab, were also explained in detail as was that rituximab is not explicitly approved for aTTP. Two of seven episodes (28.6%) were initial presentations of aTTP, whereas in five instances patients experienced a relapse (71.4%). Based on organ damage markers and clinical presentation (Table 1), four of seven episodes were of moderate to severe affection, whereas three cases presented with a mild course (B, C, F). Detailed reports of the cases are included in Table 2.

Caplacizumab was given as a first 10 mg intravenous (IV) injection followed by daily 10 mg subcutaneous injections. We observed a rapid and robust increase of platelet counts after the first dose of caplacizumab (Figure 1), which led to a doubling of platelet counts within 17 hours (median; minimum 6, quartile 1 [Q1] 6, Q3 48, maximum 72 hours) in all patients. In cases where such data were available, a platelet count increase could even be noted within some hours after the first IV administration of caplacizumab (see cases A, E, F, G), underscoring the rapid action of the drug. The median time to tripling of platelet counts was 22 hours (minimum 6 hours, Q1 17 hours, Q3 96 hours, maximum 120 hours). Platelet counts normalized (>150 G/L) after median 84 hours (minimum 48 hours, Q1 57 hours, Q3 96 hours, maximum 96 hours). Lactate dehydrogenase (LDH) as a surrogate parameter of organ damage improved in parallel to the platelet counts, indicating resolving microangiopathy. All patients recovered without sequelae or treatment-related adverse reactions, especially without bleeding complications. All patients received immunosuppressive therapy with corticosteroids; rituximab was administered in four of seven instances. Caplacizumab was continued until recovery of ADAMTS13 activity in six cases; no recovery during the observation time was noted in one case. Time to recovery of ADAMTS13-activity to $\geq 10\%$ was 18 days (median) and to $\geq 20\%$ 25 days (median). Caplacizumab was continued for 14 days (median)

TABLE 1 Patient characteristics

	Patient 1 (A)	Patient 2, 1st episode (B)	Patient 2, 2nd episode (C)	Patient 3 (D)	Patient 4 (E)	Patient 5 (F)	Patient 6 (G)	Median (IQR)	Percent (%)
Age at diagnosis, years	25	31	31	46	34	62	75	40.0 (31.8-58)	
Sex	Female	Female	Female	Female	Female	Female	Female		6/6 (100%)
Relapse of known TPP	No	Yes	Yes	Yes	No	Yes	Yes		5/7 (71.4%)
BMI, kg/sqm	27.7	37.0	37.0	35.9	25.7	25.0	32.8	30.3 (26.2-35.1)	
Race	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian		6/6 (100%)
Reason for omission of plasma exchange	Patient refused central line	Oligo-symptomatic and patient decision	Oligo-symptomatic and patient decision	Oligo-symptomatic patient decision	Poor venous access	Oligo-symptomatic and patient decision	Poor venous access		
Neurologic symptoms	Facial paresthesia, aphasia	None	None	None	Aphasia, cephalgia, large acute infarction, multiple small non-recent infarctions	None	Yes, unspecified		3/7 (42.9%)
Renal involvement	Proteinuria, high creatinine	None	None	Proteinuria, high creatinine	Proteinuria, high creatinine	None	Proteinuria		4/7 (57.1%)
Cardiac Involvement	None	None	None	None	High troponin (>5 x ULN)	None	High troponin (>2 x ULN)		2/7 (28.6%)
Initial platelet count, G/L	17	62	63	10	7	76	5	17 (8.5-62.5)	
Initial LDH, U/L	902	298	305	828	632	283	1336	632 (301-865)	
Maximum anti-ADAMTS13 inhibitor, unit as indicated ^a	73 U/mL	99 U/mL	57 U/mL	99 U/mL	4 BU/mL	45 U/mL	7.27 BU/mL		
No. of caplacizumab doses	13	8	8	109 (ongoing) ^b	11	10	26	11 (9-19.5)	
Additional Treatments	GC, RTX	GC	GC	GC, RTX	GC, RTX	GC	GC, RTX		GC: 100% RTX: 57.1%

Note: Please note that two independent episodes of aTTP were reported for patient 2. Troponin elevation defined as a value above the upper limit of normal during the reported time frame.

Abbreviations: BMI, body mass index; GC, glucocorticoids; IQR, interquartile range (25%/75% quartiles); RTX, rituximab.

^aDifferent assays were used, including Bethesda method and anti-ADAMTS13 IgG ELISA.

^bAt the time of submission of the manuscript, the patient continued on alternate day caplacizumab dosing. The number reported indicates the number of doses until the submission of the manuscript.

TABLE 2 Individual case histories

Case	
A	Admitted to an external hospital with facial paresthesia, aphasia, and petechial bleeding. MRI ruled out stroke. Laboratory results suggested TMA (platelets 17 G/L, hemoglobin 7.5 g/dL, LDH 902 U/L, schistocytes 4.6%, haptoglobin not detectable and creatinine 63.7 μ mol/L). The patient was informed about benefits and risks of PEX and decided against the procedure. Five and 6 hours after the first IV dose of caplacizumab, the platelet count increased to 30 and 35 G/L, respectively, and normalized within 3 days. The diagnosis of aTTP was confirmed by severe ADAMTS13 deficiency and presence of autoantibodies.
B	Presented in August 2019 with relapsing aTTP (initial diagnosis in November 2011). She reported minor hematomas and bruising for a few days. LDH was 298 U/L, platelets 62 G/L, ADAMTS13 activity below detection limit, ADAMTS13 inhibitor 99 U/mL. No signs of myocardial or neurological involvement were found. Caplacizumab and steroids were started; no plasma exchange was performed. Platelets increased to 134 G/L within 48 hours and 342 G/L within 96 hours. Clinical symptoms and thrombocytopenia improved subsequently.
C	In the same patient, a relapse of aTTP was detected during a routine visit in February 2020. She complained of some abdominal pain. LDH was 250 U/L, platelets 92 G/L, ADAMTS13 activity below detection limit, ADAMTS13 inhibitors 55 U/mL. No signs of myocardial or neurological involvement were found. Caplacizumab and steroids were started; no PEX was performed. Platelets increased to 171 G/L within 48 hours and 379 G/L within 96 hours. Clinical symptoms and thrombocytopenia improved subsequently.
D	Presented with relapsing aTTP, the initial episode had occurred 18 years earlier. Two weeks before presentation, she had noted fatigue, gingival bleeding, and hematomas. Upon presentation, LDH was 828 U/L, platelets 10 G/L, and schistocytes found in the blood smear. Severe ADAMTS13 deficiency and the presence of autoantibodies (99 U/mL) confirmed the diagnosis of aTTP. There were no signs of myocardial or neurological involvement, but marked albuminuria. Caplacizumab and steroids were started immediately. Five hours after caplacizumab administration, platelets increased to 19 G/L, and to 24 G/L after 9 hours. Therefore, plasma exchange was omitted. During days 1 to 3, vWF activity was measured and was suppressed below the detection limit. Clinical symptoms, thrombocytopenia, and markers of microangiopathic hemolysis improved subsequently. Rituximab was administered on day 3 and 25.
E	Reported to a hospital because of back pain at the end of November 2019, but no laboratory tests were done. At the end of December 2019, she complained of fatigue, persisting back pain, and general weakness. At that time, she had thrombocytopenia, anemia, and elevated LDH and creatinine. A first cerebral MRI was performed at the end of January 2020, showing cerebral ischemia. The patient was admitted to a neurological department for further workup. At that time, she was confused, had undulating aphasia and paraphasia. A contrast MRI showed multiple nonrecent bihemispheric ischemic lesions, and a large acute left temporoparietal ischemic lesion. At that time, blood tests were still suggestive for TTP, showing also elevated troponin and impaired kidney function, and a hematologist (P.K.) was consulted. The first dose of caplacizumab was given IV, followed by daily 10 mg subcutaneously, and an ADAMTS13 test confirmed the diagnosis (severe deficiency, inhibitor 2.1 BU/mL). After 12 hours, the platelet counts had increased from 7 to 28 G/L, so the planned PEX was canceled. Steroids and rituximab were started, and the patient's organ functions consecutively improved. Platelet counts normalized after 6 doses of caplacizumab, and LDH after 11 doses. After dose 13 and a second infusion of rituximab, ADAMTS13 had normalized. The patient was transferred to a neurological rehabilitation unit and does well now.
F	During a routine visit, a relapse of aTTP was detected, initial episode had occurred in March 2004 with 11 consecutive relapsing episodes. Upon presentation, LDH was 283 U/L, platelets 76 G/L, and ADAMTS13 activity below detection limit, and ADAMTS13 inhibitors 38 U/mL. No signs of myocardial or neurological involvement were found. Caplacizumab and steroids were started, no plasma exchange was performed. Platelets increased to 167 G/L within 48 hours and to 209 G/L within 96 hours. Clinical symptoms and thrombocytopenia improved subsequently.
G	Presented with relapsing aTTP, the initial episode had occurred in October 2014 and needed 42 PEX treatments. The patient complained about fatigue and slight fever episodes for a few weeks. She also noticed episodes with tingling of the lips and arms, and on the day of admission she collapsed. LDH was 1336 U/L, platelet count 5 G/L, schistocyte count 35/1000 erythrocytes. ADAMTS13 activity was 7.6%, anti-ADAMTS13 IgG antibodies (ELISA) were not detectable (7.27 U/mL). The patient immediately received 10 mg caplacizumab and steroids. The scheduled PEX could not be started because of poor venous access; we refrained from central venous catheter insertion because the patient was anticoagulated with edoxaban on the day of admission. After 4 hours, platelet count had increased (9 G/L) and LDH decreased (928 U/L). The next day, platelet count had increased to 46 G/L. On days 4 and 11 the patient received rituximab 375 mg/m ² , steroids were tapered. The patient's condition improved quickly; she could be dismissed after 1 week.

and stopped when ADAMTS13 had increased (cases A, B, D, E, G) or platelet counts reached supra-normal levels (cases C, F).

The robust and rapid rise of platelet counts and waning of microangiopathic hemolysis demonstrated in the seven episodes argue in favor of plasma exchange-free treatment regimens of aTTP in a subset of meticulously selected patients. Until further data from randomized trials become available, such regimens remain off-label and should be considered only in case of contraindications against plasma exchange and/or after thorough discussion of the risks and advantages with the patient. Plasma exchanges remain the mainstay of aTTP treatment in severely symptomatic patients

or those that do not rapidly respond to glucocorticoid and caplacizumab treatment. We suggest that plasma exchange-free treatment of aTTP may be considered in patients without severe and acute life-threatening organ dysfunction or in situations with limited or no immediate availability of plasma exchange. Such patients need close (multiple times daily) monitoring of organ function and platelet count response. This approach emphasizes the importance of an immediate first IV injection of caplacizumab once the diagnosis of aTTP has been established. The administration of the drug should not be delayed by transferring the patient to specialized medical centers. We still recommend contacting local experts and

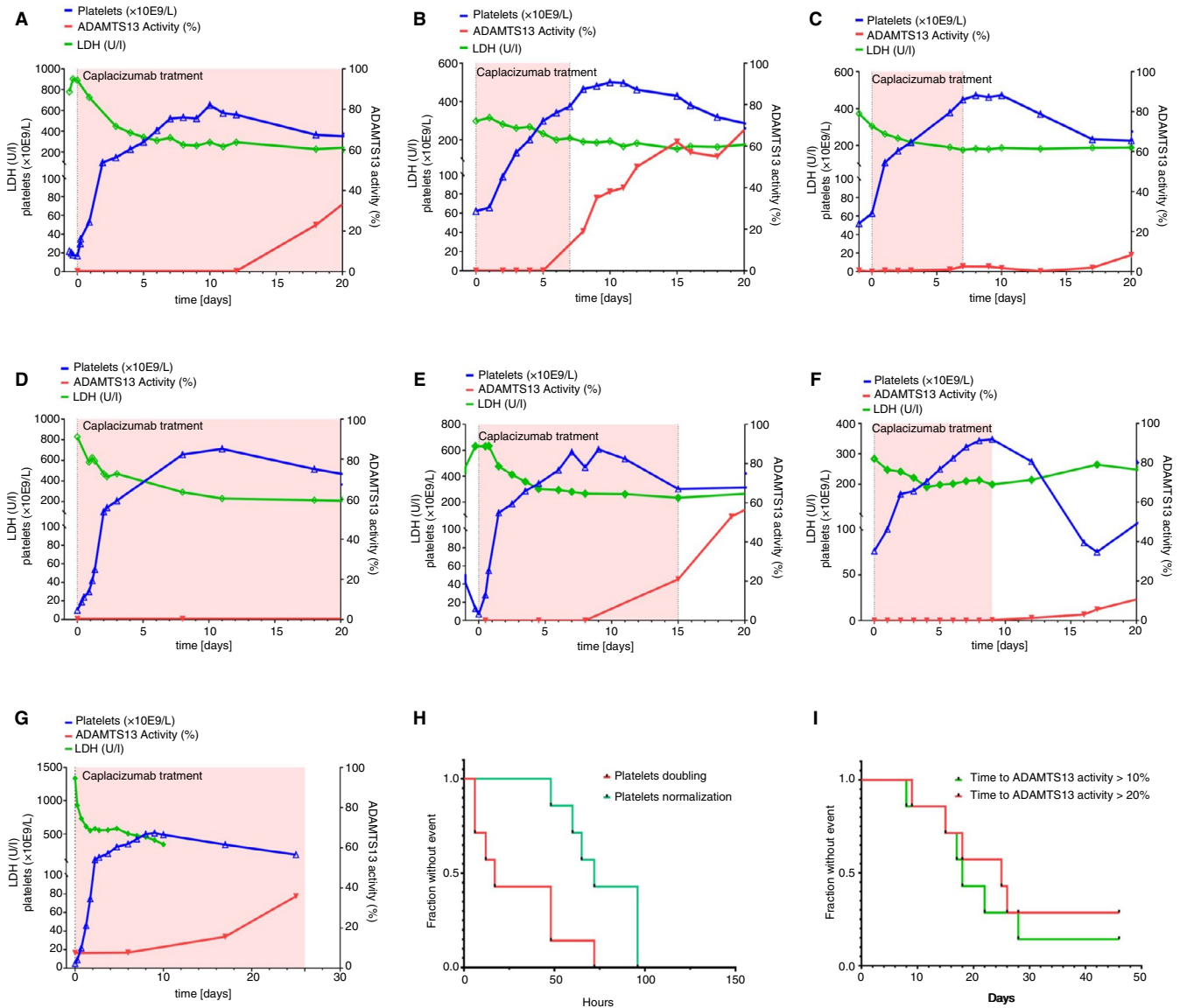


FIGURE 1 Response of aTTP episodes to caplacizumab without plasma exchange. A-G, Course of laboratory parameters of individual patients. Pink area represents the duration of caplacizumab treatment. Further treatments (glucocorticoids, rituximab) are shown in Table 1. H, Kaplan-Meier curve showing fractions without the indicated event (doubling and normalization of platelet counts). I, Kaplan-Meier curve showing fractions without the indicated event (recovery of ADAMTS13 activity to >10% and >20%)

discuss transferring patients to specialized hospitals experienced in the treatment of aTTP, with immediate availability of plasma exchange as a rescue therapy. The causal therapy of aTTP, however, is to eliminate potential triggers and initiate immunosuppressive therapy to treat the underlying autoimmune process. Steroids are widely used but rituximab, albeit off-label in this indication, has demonstrated a significant reduction in relapse rates and mortality.¹¹ Caplacizumab therapy should be continued until ADAMTS13 activity has recovered to >10% in two consecutive measurements, indicating resolved autoantibody production. Thereafter, consequent monitoring in short intervals is highly recommended. Moreover, the significant costs of caplacizumab in comparison to plasma exchange may pose an obstacle to a widespread adoption of

a plasma exchange-free approach but need to be weighed against potential benefits. Randomized clinical trials comparing aTTP therapy with and without plasma exchange are urgently needed.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Linus A. Völker, Paul T. Brinkkoetter, and Paul N. Knöbl drafted the manuscript, calculated statistics, and prepared the figures; all authors were involved in patient management, data collection, and proofreading. The manuscript has been read and approved for submission to JTH by all authors.

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