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Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura

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ABSTRACT

BACKGROUND

Acquired thrombotic thrombocytopenic purpura (TTP) is caused by aggregation of platelets on ultralarge von Willebrand factor multimers. This microvascular thrombosis causes multiorgan ischemia with potentially life-threatening complications. Daily plasma exchange and immunosuppressive therapies induce remission, but mortality and morbidity due to microthrombosis remain high.

METHODS

Caplacizumab, an anti–von Willebrand factor humanized single-variable-domain immunoglobulin (Nanobody), inhibits the interaction between ultralarge von Willebrand factor multimers and platelets. In this phase 2, controlled study, we randomly assigned patients with acquired TTP to subcutaneous caplacizumab (10 mg daily) or placebo during plasma exchange and for 30 days afterward. The primary end point was the time to a response, defined as confirmed normalization of the platelet count. Major secondary end points included exacerbations and relapses.

RESULTS

Seventy-five patients underwent randomization (36 were assigned to receive caplacizumab, and 39 to receive placebo). The time to a response was significantly reduced with caplacizumab as compared with placebo (39% reduction in median time, P=0.005). Three patients in the caplacizumab group had an exacerbation, as compared with 11 patients in the placebo group. Eight patients in the caplacizumab group had a relapse in the first month after stopping the study drug, of whom 7 had ADAMTS13 activity that remained below 10%, suggesting unresolved autoimmune activity. Bleeding-related adverse events, most of which were mild to moderate in severity, were more common with caplacizumab than with placebo (54% of patients vs. 38%). The frequencies of other adverse events were similar in the two groups. Two patients in the placebo group died, as compared with none in the caplacizumab group.

CONCLUSIONS

Caplacizumab induced a faster resolution of the acute TTP episode than did placebo. The platelet-protective effect of caplacizumab was maintained during the treatment period. Caplacizumab was associated with an increased tendency toward bleeding, as compared with placebo. (Funded by Ablynx; ClinicalTrials.gov number, NCT01151423.)

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Acquired thrombotic thrombocytopenic purpura (TTP) is a potentially life-threatening thrombotic microangiopathy resulting from systemic microvascular thrombosis and leading to profound thrombocytopenia, hemolytic anemia, and organ failure of varying severity.[1] Acquired TTP is caused by a severe deficiency of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) due to the presence of inhibitory autoantibodies.[2] Decreased ADAMTS13 activity leads to an accumulation of ultralarge von Willebrand factor multimers, which bind to platelets and induce aggregation.[3] These microthrombi cause tissue ischemia and organ dysfunction (commonly involving the brain, heart, and kidneys), resulting in early death[4,5] or in long-term complications, such as cognitive deficits, depression, and arterial hypertension, and a shortened life expectancy.[6-10]

A Quick Take is available at NEJM.org

Treatment of acquired TTP consists of rapid initiation of plasma exchange to remove autoantibodies and ultralarge von Willebrand factor multimers and to replenish ADAMTS13. Immunosuppressive therapy (e.g., glucocorticoids and rituximab)[1,11] inhibits autoantibody formation. Although the survival rate among patients with acquired TTP exceeds 80%,[12] patients remain at risk for microthrombotic complications until remission is achieved. Rapid-onset therapy designed to prevent further microthrombus formation by targeting the binding of platelets to ultralarge von Willebrand factor multimers is a potential approach to the treatment of acquired TTP.

Caplacizumab, an anti–von Willebrand factor humanized single-variable-domain immunoglobulin (Nanobody, Ablynx), targets the A1 domain of von Willebrand factor,[13] preventing interaction with the platelet glycoprotein Ib-IX-V receptor.[14] In the phase 2 TITAN study, we evaluated the potential of caplacizumab for treating acquired TTP.

Methods

Study Design and Oversight

We conducted a single-blind, parallel-design, randomized, placebo-controlled study at 56 sites worldwide (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The study was approved by the ethics committee at each participating site. All participants provided written informed consent in accordance with the Declaration of Helsinki. An independent data and safety monitoring board reviewed safety data during the trial. The single-blind design was necessary because the results of an assay of von Willebrand factor–ristocetin cofactor activity, a pharmacodynamic marker, were available to the study investigators.

The sponsor, Ablynx, designed the study with input from the principal investigator (the first author) and the other authors. The conduct of the study and the verification and analysis of the data were the responsibility of the sponsor. The investigators and research teams gathered the data and agreed to maintain confidentiality. The results were critically evaluated and interpreted by all the authors, who reviewed and revised the manuscript. The manuscript was prepared by Ablynx with assistance from a professional writer at SGS Belgium, funded by Ablynx. The sponsor and all the authors made the decision to submit the manuscript for publication. All the authors vouch for the accuracy and completeness of the data and for the fidelity of this report to the study protocol, which is available at NEJM.org.

Study Population

Adults with an acute episode of acquired TTP were eligible for the study if they had a platelet count of less than 100,000 per cubic millimeter, without active bleeding, and required plasma exchange (Table S1 in the Supplementary Appendix). Patients were assigned in a 1:1 ratio to active treatment or placebo with the use of a computerized randomization schedule.

Treatments

In addition to standard-of-care treatment for acquired TTP (daily plasma exchange and immunosuppressive therapy), patients received an intravenous loading dose of caplacizumab (10 mg) or placebo anytime from 6 hours before to 15 minutes before the start of the first plasma exchange performed after enrollment. Throughout the plasma-exchange treatment period, including tapering and plasma exchanges performed for exacerbations, the study drug (10 mg) was administered subcutaneously daily within 30 minutes after the end of each exchange. Once-daily subcutaneous administration of the study drug (10 mg) was continued for 30 days after the last plasma exchange. The maximum duration of study-drug administration was 90 days.

END POINTS

The primary end point was the time to confirmed normalization of the platelet count (i.e., time to a response). Normalization was defined as a platelet count that was 150,000 per cubic millimeter or higher, and confirmation consisted of a repeat platelet count at 48 hours that was 150,000 per cubic millimeter or higher and a lactate dehydrogenase level that was no more than twice the upper limit of the normal range. Key secondary end points included exacerbations, defined as recurrent thrombocytopenia within 30 days after the end of daily plasma exchanges that required reinitiation of daily exchanges; relapse, defined as a TTP event occurring more than 30 days after the end of daily plasma exchanges[15]; complete remission after the initial course of daily plasma exchange (i.e., plasma exchange given for the presenting acquired TTP episode), defined as confirmed normalization of the platelet count and absence of exacerbation; duration and volume of plasma exchange; mortality; and safety. Exploratory end points were evaluated, and post hoc analyses were performed (see the Supplementary Appendix). Platelet counts and laboratory tests for safety assessments were performed at the local laboratories, whereas ADAMTS13 activity, antidrug antibodies, and pharmacokinetic and pharmacodynamic characteristics were analyzed at central or specialty laboratories. ADAMTS13 activity was analyzed with the use of a fluorescence resonance energy transfer (FRET) assay for a synthetic 73-amino-acid von Willebrand factor peptide (VWF73).[16] Von Willebrand factor antigen was measured with the use of the immunoturbimetric method (STA-Liatest, Diagnostica Stago), with 5.0 μg of caplacizumab per milliliter added to the diluent to overcome drug interference. Factor VIII clotting activity was measured with a chromogenic assay (COAMATIC FACTOR VIII, Chromogenix), and von Willebrand factor–ristocetin cofactor activity was measured with a platelet-aggregation assay (vW Select, Bio/Data Corporation). All results were expressed as percentages of normal plasma. Total drug and antidrug-antibody levels were evaluated with the use of assays developed and validated in-house (see the Supplementary Appendix), with antidrug-antibody levels evaluated by means of a tiered screening-confirmation-titration assay.

STATISTICAL ANALYSIS

The planned sample of 110 patients was based on a log-rank test with a power of 80% to detect a 44% reduction in the median time to a response with caplacizumab as compared with placebo, at a one-sided alpha level of 2.5%, assuming a 15% dropout rate. The primary end point was evaluated with the use of a Kaplan–Meier analysis stratified for the absence or presence of one plasma-exchange session before randomization, with a one-sided log-rank test used to assess superiority at a 2.5% significance level. No adjustment was made for multiple comparisons for any of the end points that were analyzed. All efficacy analyses were performed on the intention-to-treat population (comprising all patients who were randomly assigned to a study group), and safety and immunogenicity analyses were performed on the safety population (comprising all patients who received at least one dose of the study drug). Exacerbations and relapses of TTP are discussed here as secondary efficacy outcomes, not as serious adverse events.

RESULTS

PATIENTS

We enrolled patients in the study from October 2010 to January 2014, when the sponsor prematurely halted recruitment because of persistent recruitment challenges (and not because of an analysis of the data). Seventy-five patients underwent randomization (with 36 assigned to the caplacizumab group and 39 to the placebo group) (Fig. S1 in the Supplementary Appendix). Demographic and baseline clinical characteristics were similar in the two study groups (Table 1, and Table S2 in the Supplementary Appendix). All patients still in the study in January 2014 finished the assigned study treatment and attended at least the 1-month follow-up visit before the study was formally ended in March 2014.

PRIMARY END POINT

A total of 69 patients had not undergone a plasma-exchange session before enrollment. Among these patients, the median time to a response was 3.0 days (95% confidence interval [CI], 2.7 to 3.9) in the caplacizumab group and 4.9 days (95% CI, 3.2 to 6.6) in the placebo group. Six patients had undergone a plasma-exchange session before enrollment; among these patients, the median time to a response was 2.4 days (95% CI, 1.9 to 3.0) in the caplacizumab group and 4.3 days (95% CI, 2.9 to 5.7) in the placebo group. On the basis of the strati-

Table 1. Baseline Characteristics and Therapy in the Intention-to-Treat Population.*

Characteristic	Caplacizumab (N=36)	Placebo (N=39)	Total (N=75)
Mean age (range) — yr	41 (19–72)	42 (21–67)	42 (19–72)
Female sex — no. (%)	24 (67)	20 (51)	44 (59)
Race — no. (%)†			
White	32 (89)	34 (87)	66 (88)
Black	4 (11)	5 (13)	9 (12)
Presenting episode of TTP — no. (%)			
Initial	24 (67)	27 (69)	51 (68)
Recurrent	12 (33)	12 (31)	24 (32)
Mean platelet count (range) — per mm^3‡	21,100 (2000–70,000)	28,000 (5000–84,000)	24,600 (2000–84,000)
Mean LDH (range) — U/liter§	1277 (240–3874)	1270 (247–4703)	1274 (240–4703)
ADAMTS13 activity — no. (%)			
<10%	28 (78)	30 (77)	58 (77)
≥10%	2 (6)	6 (15)	8 (11)
Missing data	6 (17)	3 (8)	9 (12)
PE tapering — no. (%)	11 (31)	11 (28)	22 (29)
Glucocorticoids during daily PE — no. (%)	32 (89)	36 (92)	68 (91)
Rituximab during daily PE — no. (%)¶	2 (6)	9 (23)	11 (15)

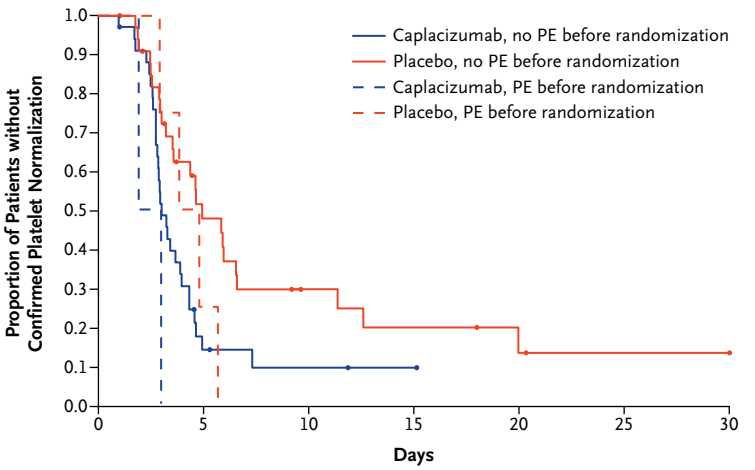
* Baseline was defined as before the first administration of the study drug. The intention-to-treat population comprised all patients randomly assigned to a study group, including three patients who did not receive the assigned study drug. There were no significant differences between the study groups in the listed baseline characteristics except as noted below. LDH denotes lactate dehydrogenase, PE plasma exchange, and TTP thrombotic thrombocytopenic purpura.
† Race was determined by the investigator.
‡ Data on platelet count were available for 72 patients (35 in the caplacizumab group and 37 in the placebo group).
§ Data on LDH were available for 69 patients (34 in the caplacizumab group and 35 in the placebo group).
¶ The proportion of patients who received rituximab during daily PE differed significantly between the two groups ($P<0.05$). The imbalance may have been a site effect, since one site used rituximab as part of the standard of care starting on day 2 of daily plasma exchange, and this site recruited seven patients, five of whom were randomly assigned to the placebo group.

fied log-rank test, caplacizumab significantly reduced the time to a response, as compared with placebo (39% reduction in median time to response; event rate ratio, 2.20; 95% CI, 1.28 to 3.78; P=0.005) (Fig. 1 and Table 2, and Table S3 in the Supplementary Appendix). (Because an event [time to confirmed platelet response] in this trial is linked with a positive outcome, "event rate ratio" is used instead of the typical "hazard ratio," with similar interpretation.) In the post hoc analysis restricted to the 58 patients with baseline ADAMTS13 activity of less than 10%, the median time to a response was 3.0 days (95% CI, 2.7 to 4.3) with caplacizumab and 4.6 days (95% CI, 3.0 to 5.9) with placebo, resulting in an event rate ratio of 1.63 (95% CI, 0.92 to 2.92). Eight patients had baseline ADAMTS13 activity that was 10% or higher, and we did not analyze the primary outcome in this subgroup because of the small number of patients. Data on ADAMTS13 activity at baseline were missing for 9 patients.

SECONDARY EFFICACY END POINTS

Exacerbations, Relapses, Remission, and Mortality

Data from the 1-month follow-up visit, available for 63 patients (Fig. S1 in the Supplementary Appendix), were analyzed for the secondary end points. Complete remission after the initial course of daily plasma exchange (i.e., plasma exchange given for the presenting acquired TTP episode) was observed more frequently in the caplacizumab group (81% of patients) than in the placebo group (46% of patients). Three caplacizumab-treated patients had exacerbations, as compared with 11 patients in the placebo group. After cessation of the study drug, 8 patients in the caplacizumab group had a relapse during the 1-month follow-up period (with 7 of them having a relapse within 10 days after cessa-



No. at Risk

Caplacizumab, no PE before randomization	34	4	2	1	0	0	0
Placebo, no PE before randomization	35	13	6	4	2	1	1
Caplacizumab, PE before randomization	2	0	0	0	0	0	0
Placebo, PE before randomization	4	1	0	0	0	0	0

Figure 1. Time to Confirmed Normalization of Platelet Count in the Intention-to-Treat Population.

Censored observations are represented by dots. Data for any patient still at risk at 30 days were censored at 30 days. PE denotes plasma exchange.

tion of the study drug), as compared with no patients in the placebo group (Table 2, and Table S3 in the Supplementary Appendix). Two deaths occurred during the study, both in the placebo group; one death was due to severe, refractory TTP, and the other was due to cerebral hemorrhage.

ADAMTS13 Activity in Relation to Exacerbation or Relapse

All available data up to the 12-month follow-up visit were considered for this post hoc evaluation. Three caplacizumab-treated patients had an exacerbation, and all 3 had baseline ADAMTS13 activity of less than 10%. At the time of the exacerbation, ADAMTS13 activity was still less than 10% in 2 of the 3 patients and was 39% in the remaining patient (Fig. 2). Eleven patients in the placebo group had an exacerbation; baseline ADAMTS13 activity was less than 10% in 10 of them and was 90% in the remaining patient. For 9 of the 11 patients, data near the time of the exacerbation were available: ADAMTS13 activity was less than 10% in 7 patients, 11% in 1 patient, and 100% in the patient with baseline activity of 90% (Fig. 2).

Eleven caplacizumab-treated patients had at least one relapse. In 7 of these 11 patients, the relapse occurred within 10 days after the study drug had been stopped. Baseline ADAMTS13 activity was less than 10% in 7 of the 11 patients with relapses; the other 4 had missing baseline data but had values of less than 10% during the treatment period. In all 7 patients with a relapse within 10 days after the study drug had been stopped, ADAMTS13 activity was less than 10% during treatment, including shortly before the end of treatment (Fig. 2). In the 4 patients who had a relapse 30 to 175 days after the study drug had been stopped, ADAMTS13 activity increased to values of 10% or higher (range, 15 to 70%) near the end of the treatment period (Fig. 2). Three patients in the placebo group had a first relapse 161 to 356 days after cessation of the study treatment, all of whom had baseline ADAMTS13 activity of less than 10%. Near the end of the study drug treatment period, 2 of the 3 patients had ADAMTS13 activity above 10% (74% and 81%) (Fig. 2).

Twenty-two caplacizumab-treated patients did not have an exacerbation or a relapse. Baseline ADAMTS13 activity was less than 10% in 19 of them. Of the remaining 3 patients, 1 had a baseline value of 10%, 1 had a baseline value of 39% but had values that were less than 10% later during the treatment period, and 1 had missing

Table 2. Primary and Secondary Efficacy End Points in the Intention-to-Treat Population.

End Point	Caplacizumab (N = 36)	Placebo (N = 39)
Primary end point		
Time to response: caplacizumab vs. placebo		
Event rate ratio (95% CI)*	2.20 (1.28–3.78)	
P value†	0.005	
Patients with no PE before randomization		
Median time to response (95% CI) — days	3.0 (2.7–3.9)	4.9 (3.2–6.6)
Confirmed response — no. (%)	29 (81)	24 (62)
Data censored at 30 days — no. (%)	5 (14)	11 (28)
Patients with one PE before randomization		
Median time to response (95% CI) — days	2.4 (1.9–3.0)	4.3 (2.9–5.7)
Confirmed response — no. (%)	2 (6)	4 (10)
Data censored at 30 days — no. (%)	0	0
Secondary end points		
Exacerbation of TTP — no. (%)‡	3 (8)	11 (28)
Relapse — no. (%)		
During 1-mo follow-up period	8 (22)	0
During 12-mo follow-up period§	11 (31)	3 (8)
Complete remission after initial daily PE — no. (%)¶	29 (81)	18 (46)
Mean no. of PE days (range)		
During daily PE period	5.9 (3–15)	7.9 (2–35)
During overall study-drug treatment period	7.7 (3–21)	11.7 (2–43)
During the first 30 days of follow-up	10.2 (4–29)	11.7 (2–43)

* The event rate ratio (i.e., the hazard ratio) is based on a stratified Cox proportional-hazards regression model with one PE session before randomization (yes or no) as a covariate.
† The P value, from a one-sided log-rank test of superiority at a 2.5% significance level, is based on an analysis stratified for the presence or absence of one PE session before randomization. An observation was censored if it did not meet the defined interval of 30 days after the first study-drug administration.
‡ An exacerbation was defined as an episode of thrombocytopenia that occurred between 1 and 30 days after the last daily PE session and required reinitiation of daily PE treatment.
§ Relapse was defined as a new episode of thrombocytopenia, and a new episode was defined as one that occurred more than 30 days after the last daily PE session.
¶ Complete remission after the initial course of daily PE (i.e., plasma exchange given for the presenting acquired TTP episode) was defined as a confirmed normalization of the platelet count (i.e., confirmed response) and an absence of exacerbations.

baseline data but had a history of recurrent TTP. All 3 had a response to therapy. ADAMTS13 values just before the end of the treatment period were available for 17 of the 22 patients: in 14 of these 17 patients, ADAMTS13 activity increased to levels of 10% or higher (range, 13 to 100%) (Fig. 2).

In the 24 patients in the placebo group who did not have an exacerbation or relapse, baseline ADAMTS13 activity was less than 10% in 18 patients. Baseline values for ADAMTS13 activity were missing for 1 patient (who was withdrawn from the study because of ineligibility) and were 10% or higher in 5 patients. Of these, 1 had a baseline value of 10% and 1 had a value of 13% during the treatment period. Both had a response to plasma exchange. The remaining 3 patients had ADAMTS13 activity values well above 10% throughout the study (values at baseline: 46%, 75%, and 76%; range of values during the entire study period: 51 to 93%), and 1 of these patients had a response to plasma exchange. ADAMTS13 values just before the end of the treatment period were available for 17 of the 24 patients: in 15 of

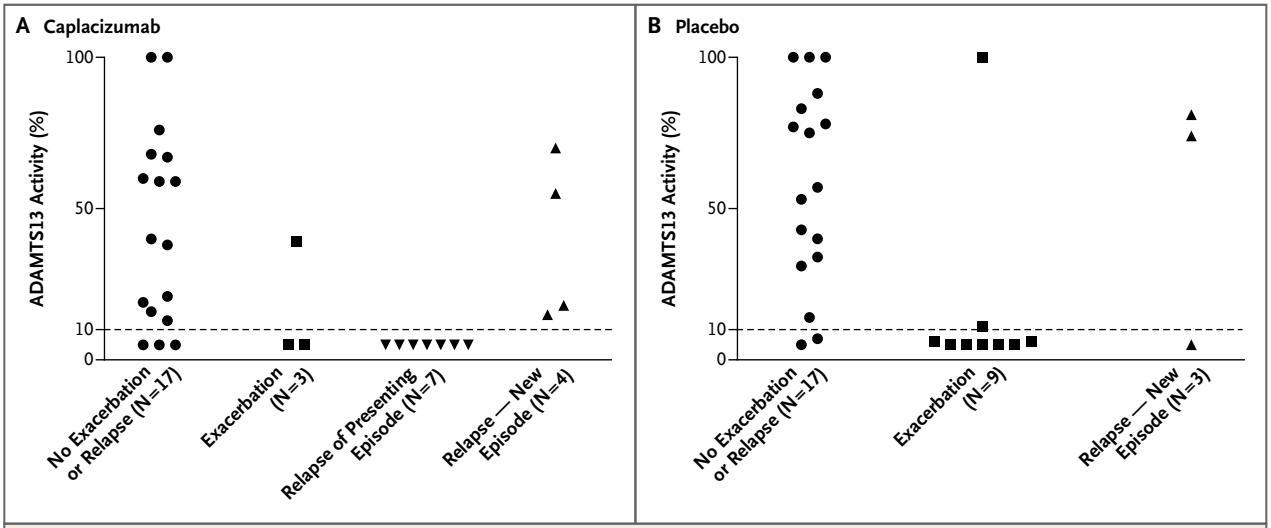


Figure 2. ADAMTS13 Activity According to Exacerbation and Relapse Status.

ADAMTS13 activity was measured with the use of a fluorescence resonance energy transfer (FRET) assay for a synthetic 73-amino-acid von Willebrand factor peptide (VWF73). Panels A and B show data for individual patients in four subgroups: patients who did not have an exacerbation or relapse, patients who had an exacerbation, patients who had a relapse of the presenting episode (defined as a relapse occurring within 10 days after cessation of the study-drug treatment in patients with ADAMTS13 activity that was <10% throughout the treatment period), and those who had a new episode (defined as a relapse occurring 30 days or more after cessation of the study-drug treatment in patients who had normalization of ADAMTS13 activity near the end of the treatment period). The data shown are for patients with available ADAMTS13 values near the end of the study-drug treatment period (range, 2 to 15 days before treatment cessation), with the exception of patients with exacerbations, for whom ADAMTS13 values obtained close to or on the day of exacerbation were used (range, 0 to 8 days preceding the exacerbation). A cutoff value of 10% for ADAMTS13 activity (dotted line) was used to define the threshold for an unresolved underlying autoimmune disorder. Patients were included in the analysis whether their baseline ADAMTS13 activity was less than 10% or 10% or higher.

these 17 patients, ADAMTS13 activity increased to levels of 10% or higher (range, 14 to 100%) (Fig. 2).

Plasma Exchange

A post hoc evaluation showed that the mean number of plasma-exchange days and the mean volume of plasma administered were lower in the caplacizumab group than in the placebo group during the period of daily plasma exchange (5.9 vs. 7.9 days, and 19.9 vs. 28.3 liters) and during the overall treatment period, including exacerbations (7.7 vs. 11.7 days, and 25.8 vs. 41.8 liters). The differences between the two groups were less pronounced during the overall study period, which included 1 month of follow-up, because of relapses after treatment (Table 2).

Pharmacokinetic and Pharmacodynamic Outcomes

The intravenous loading dose of caplacizumab ensured rapid attainment of the desired drug concentration for von Willebrand factor inhibition (Table S4 in the Supplementary Appendix). Caplacizumab rapidly neutralized its target as indicated by suppression of von Willebrand factor–ristocetin cofactor activity to a mean of less than 20% by day 1 and throughout the treatment period. Clearance of the caplacizumab–von Willebrand factor complex was increased, as compared with unbound von Willebrand factor, resulting in reduced von Willebrand factor antigen and factor VIII levels. These values returned to baseline levels within 1 week after the cessation of treatment (Fig. S2 in the Supplementary Appendix).

Organ-Damage Markers

A post hoc analysis of organ-damage markers showed that by day 2 of treatment, the percentage of patients who had lactate dehydrogenase levels that were no more than two times the upper limit of the normal range was higher in the caplacizumab group than in the placebo group (78% vs. 51%). By day 4, the percentage of patients was similar in the two groups (Table S5 in the Supplementary Appendix). The median time to normalization of lactate dehydrogenase levels was 3 days (95% CI, 3 to 4) among the 32 patients in the caplacizumab group, as compared with 4 days (95% CI, 3 to 6) among the 32

Table 3. Adverse Events and Serious Adverse Events in the Safety Population.*

Adverse Event	Caplacizumab (N=35)	Placebo (N=37)	Total (N=72)
		no. of patients (%)	
Event related to study drug†	20 (57)	5 (14)	25 (35)
Event leading to discontinuation of study drug	4 (11)	2 (5)	6 (8)
Event leading to interruption of study drug	3 (9)	4 (11)	7 (10)
Event with death as outcome	0	2 (5)	2 (3)
Bleeding-related event	19 (54)	14 (38)	33 (46)
Immune-related event	17 (49)	12 (32)	29 (40)
Serious events			
Any	13 (37)	12 (32)	25 (35)
Blood and lymphatic system disorders	1 (3)	1 (3)	2 (3)
TTP‡	0	1 (3)	1 (1)
Anemia	1 (3)	0	1 (1)
Cardiac disorders	0	1 (3)	1 (1)
Atrial fibrillation	0	1 (3)	1 (1)
Atrial flutter	0	1 (3)	1 (1)
Eye disorders: retinal hemorrhage	1 (3)	0	1 (1)
Gastrointestinal disorders	0	3 (8)	3 (4)
Abdominal pain, general	0	1 (3)	1 (1)
Abdominal pain, upper	0	1 (3)	1 (1)
Dysphagia	0	1 (3)	1 (1)
Nausea	0	1 (3)	1 (1)
Vomiting	0	1 (3)	1 (1)
Hepatobiliary disorders: elevated liver enzymes	1 (3)	0	1 (1)
Infections and infestations	3 (9)	1 (3)	4 (6)
Bacterial infection	1 (3)	0	1 (1)
Muscle abscess	1 (3)	0	1 (1)
Sepsis	1 (3)	0	1 (1)
Urinary tract infection	1 (3)	0	1 (1)
Device-related sepsis	0	1 (3)	1 (1)
Injury, poisoning, and procedural complications: traumatic fracture	0	1 (3)	1 (1)
Investigations	3 (9)	1 (3)	4 (6)
Aminotransferases increased	2 (6)	0	2 (3)
Autoantibody test	1 (3)	0	1 (1)
Liver-function test abnormal	0	1 (3)	1 (1)
Musculoskeletal and connective-tissue disorders	1 (3)	1 (3)	2 (3)
Muscle spasms	1 (3)	0	1 (1)
Pain in extremity	0	1 (3)	1 (1)
Nervous system disorders	5 (14)	3 (8)	8 (11)
Dizziness	2 (6)	0	2 (3)
Headache	1 (3)	1 (3)	2 (3)
Transient ischemic attack	1 (3)	1 (3)	2 (3)
Dysarthria	1 (3)	0	1 (1)
Paresthesia	1 (3)	0	1 (1)

Table 3. (Continued.)

Adverse Event	Caplacizumab (N=35)	Placebo (N=37)	Total (N=72)
		no. of patients (%)	
Subarachnoid hemorrhage	1 (3)	0	1 (1)
Cerebral hemorrhage	0	1 (3)	1 (1)
Facial paresis	0	1 (3)	1 (1)
Psychiatric disorders	2 (6)	0	2 (3)
Changes in mental status	1 (3)	0	1 (1)
Substance-induced psychotic disorder	1 (3)	0	1 (1)
Renal and urinary disorders: hematuria	0	1 (3)	1 (1)
Reproductive system and breast disorders	1 (3)	1 (3)	2 (3)
Metrorrhagia	1 (3)	0	1 (1)
Prostatitis	0	1 (3)	1 (1)
Respiratory, thoracic, and mediastinal disorders	2 (6)	1 (3)	3 (4)
Pulmonary embolism	1 (3)	1 (3)	2 (3)
Dyspnea	1 (3)	0	1 (1)
Skin and subcutaneous-tissue disorders	2 (6)	0	2 (3)
Allergic dermatitis	1 (3)	0	1 (1)
Hyperhidrosis	1 (3)	0	1 (1)
Vascular disorders: deep-vein thrombosis	0	1 (3)	1 (1)

* The safety population comprised all patients who received at least one dose of the study drug. A patient could have had more than one adverse event.
† A drug-related adverse event was defined as an adverse event that was thought by the investigators to be related or possibly related to the study drug.
‡ Relapses and exacerbations of TTP, although originally documented as adverse events, are not included as serious adverse events in this table but are instead reported as secondary efficacy outcomes. Events such as severe refractory TTP were coded according to the preferred term, "thrombotic thrombocytopenic purpura."

patients in the placebo group (Fig. S3 in the Supplementary Appendix).

For the subset of patients with elevated baseline levels of organ-damage markers, a trend toward a more rapid return to normal levels was observed among patients receiving caplacizumab as compared with those receiving placebo. The median time to normalization of troponin T or troponin I levels was 9 days (95% CI, 4 to 45) among 19 patients in the caplacizumab group versus 27 days (95% CI, 19 to not reached) among 17 patients in the placebo group, and the median time to normalization of creatinine levels was 4 days (95% CI, 3 to 6) among 11 patients in the caplacizumab group versus 6 days (95% CI, 3 to not reached) among 15 patients in the placebo group (Fig. S3 in the Supplementary Appendix).

ADVERSE EVENTS

A total of 541 adverse events occurring during the treatment period were reported in 34 of 35 patients receiving caplacizumab (97%), as compared with 522 adverse events in all 37 patients receiving placebo (100%). (TTP exacerbations and relapses were excluded from these counts.) Headache and epistaxis were the most common adverse events (Table S6 in the Supplementary Appendix). Most adverse events were considered to be unrelated to the study drug or unlikely to be related to the study drug. Adverse events considered to be related to the study drug were reported in 6 patients (17%) receiving caplacizumab and 4 patients (11%) receiving placebo, and events that were possibly related to the study drug were reported in 19 patients (54%) and 3 patients (8%) in the two groups, respectively. Serious adverse events were reported in 13 patients (37%) in the caplacizumab group and 12 patients (32%) in the placebo group (Table 3).

The number and percentage of patients with bleeding-related adverse events were higher in the caplacizumab group than in the placebo

group: 19 patients (54%) versus 14 patients (38%). Of 101 bleeding-related adverse events, 84 (83%) were reported as mild (i.e., usually transient, requiring no more than minimal therapeutic intervention, and not interfering with daily activities) and 14 (14%) as moderate (i.e., alleviated with additional therapeutic intervention and causing discomfort but without significant or permanent risk of harm); only 3 events (3%) were severe (i.e., interrupting daily activities, substantially affecting clinical status, or requiring intensive therapeutic intervention). Serious bleeding-related adverse events were reported in 2 patients in each study group: subarachnoid and retinal hemorrhage and metrorrhagia in the caplacizumab group and cerebral hemorrhage and hematuria in the placebo group. No patient received factor VIII or von Willebrand factor for a bleeding event. Immune-related adverse events were reported in 17 patients (49%) in the caplacizumab group and 12 patients (32%) in the placebo group. One caplacizumab-treated patient had a moderate allergic dermatitis that was reported as a serious adverse event. No other clinically significant adverse events were observed.

IMMUNOGENICITY

In the caplacizumab group, drug-induced anti-drug-antibody responses were confirmed in three patients (9%). Pharmacokinetic and pharmacodynamic profiles were not affected, indicating that there was no neutralizing activity.

DISCUSSION

This phase 2 trial showed that caplacizumab, as compared with placebo, results in a more rapid resolution of TTP episodes. As indicated by faster platelet-count normalization, caplacizumab prevents further consumption of platelets into microthrombi and the consequent progression of tissue ischemia. The platelet count is the generally accepted indicator of disease activity in acquired TTP and guides treatment decisions such as when to stop daily plasma exchange.[11] Symptoms of acquired TTP vary according to the organs affected by the tissue ischemia,[17] reflecting cardiac,[4,5,18-21] neurologic,[22] or renal[18,23] injury. The pathogenesis of acquired TTP is mediated by the production of autoantibodies against ADAMTS13, the key factor controlling von Willebrand factor–mediated platelet aggregation, and these autoantibodies are the focus of current treatment. Daily plasma exchange removes the autoantibodies and replenishes ADAMTS13 activity, thereby gradually restoring platelet counts, whereas immunosuppressive treatment acts on the underlying autoimmune process. A crucial goal of treatment is to control the pathologic microvascular thrombosis as quickly as possible because the thrombotic consequences are unpredictable and associated with high morbidity and mortality. Despite great improvement in outcomes with the use of plasma exchange, the mortality among patients with acquired TTP remains 10 to 20%.[12]

The results of our study show that caplacizumab immediately inhibits the pathophysiological mediator of the microthrombosis. Paralleling the rapid arrest of platelet consumption in the microthrombotic process, organ-damage markers appeared to resolve more rapidly in the caplacizumab group than in the placebo group, although this observation may have been confounded by the diluting effect of plasma exchange. The two deaths that occurred in the study were both in the placebo group.

The relevance of a platelet-protective effect of caplacizumab was further demonstrated by the smaller number of exacerbations in the caplacizumab group than in the placebo group during the study-drug administration period. During the 1-month follow-up period after study-drug administration, eight patients in the caplacizumab group had a relapse, and seven of those patients had a relapse within 10 days after cessation of study-drug treatment; no patients in the placebo group had relapses during this 1-month follow-up period. This between-group difference suggests that among patients who were destined to have an exacerbation, it occurred during study-drug administration in the placebo group, whereas caplacizumab may have delayed the exacerbation until after the period of study-drug administration. ADAMTS13 activity in these patients was persistently less than 10%, indicating incomplete resolution of the underlying autoimmune disorder.[12,24] This observation highlights the importance of providing immunosuppressant treatment for the immune-mediated component of the disease. ADAMTS13 activity could potentially guide decisions about the duration of caplaci-

zumab treatment, in addition to guiding immunosuppressive treatment. These results also support the use of ADAMTS13 activity as a predictive marker to identify patients at risk for relapse.[3,24-27]

On the basis of its pharmacologic effect, we expected that caplacizumab treatment would be associated with an increased risk of bleeding. Although bleeding events were observed more frequently in the caplacizumab group than in the placebo group, these events were generally mild and did not require treatment, despite the combination of a low platelet count at treatment initiation and caplacizumab-induced inhibition of von Willebrand factor.

Treatment of acquired TTP with plasma exchange and immunosuppressive therapy takes time to achieve resolution of the disease, and even when patients have a response to therapy, they are at risk for further microvasculature thrombosis, which is unpredictable in its onset, severity, and outcome. Caplacizumab, through rapid blocking of von Willebrand factor–mediated platelet aggregation, prevents further platelet aggregation more rapidly than conventional treatment alone, which could potentially prevent short- and long-term end-organ injury due to ischemia.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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