ORIGINAL ARTICLE

Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura

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ABSTRACT

BACKGROUND

In acquired thrombotic thrombocytopenic purpura (TTP), an immune-mediated deficiency of the von Willebrand factor–cleaving protease ADAMTS13 allows unrestrained adhesion of von Willebrand factor multimers to platelets and microthrombosis, which result in thrombocytopenia, hemolytic anemia, and tissue ischemia. Caplacizumab, an anti–von Willebrand factor humanized, bivalent variable-domain-only immunoglobulin fragment, inhibits interaction between von Willebrand factor multimers and platelets.

METHODS

In this double-blind, controlled trial, we randomly assigned 145 patients with TTP to receive caplacizumab (10-mg intravenous loading bolus, followed by 10 mg daily subcutaneously) or placebo during plasma exchange and for 30 days thereafter. The primary outcome was the time to normalization of the platelet count, with discontinuation of daily plasma exchange within 5 days thereafter. Key secondary outcomes included a composite of TTP-related death, recurrence of TTP, or a thromboembolic event during the trial treatment period; recurrence of TTP at any time during the trial; refractory TTP; and normalization of organ-damage markers.

RESULTS

The median time to normalization of the platelet count was shorter with caplacizumab than with placebo (2.69 days [95% confidence interval {CI}, 1.89 to 2.83] vs. 2.88 days [95% CI, 2.68 to 3.56], P=0.01), and patients who received caplacizumab were 1.55 times as likely to have a normalization of the platelet count as those who received placebo. The percentage of patients with a composite outcome event was 74% lower with caplacizumab than with placebo (12% vs. 49%, P<0.001). The percentage of patients who had a recurrence of TTP at any time during the trial was 67% lower with caplacizumab than with placebo (12% vs. 38%, P<0.001). Refractory disease developed in no patients in the caplacizumab group and in three patients in the placebo group. Patients who received caplacizumab needed less plasma exchange and had a shorter hospitalization than those who received placebo. The most common adverse event was mucocutaneous bleeding, which was reported in 65% of the patients in the caplacizumab group and in 48% in the placebo group. During the trial treatment period, three patients in the placebo group died. One patient in the caplacizumab group died from cerebral ischemia after the end of the treatment period.

CONCLUSIONS

Among patients with TTP, treatment with caplacizumab was associated with faster normalization of the platelet count; a lower incidence of a composite of TTP-related death, recurrence of TTP, or a thromboembolic event during the treatment period; and a lower rate of recurrence of TTP during the trial than placebo. (Funded by Ablynx; HERCULES ClinicalTrials.gov number, NCT02553317.)

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*A complete list of investigators and participating centers in the HERCULES trial is provided in the Supplementary Appendix, available at NEJM.org.

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Acquired or immune-mediated thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathy that is characterized by thrombocytopenia and hemolytic anemia. Autoantibodies inhibit activity of the von Willebrand factor–cleaving protease ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), which leads to platelet consumption in von Willebrand factor–platelet aggregates and microvascular thrombosis.[1] The ensuing tissue ischemia and multiorgan dysfunction may result in thromboembolic events and death. A diagnosis of TTP is based on clinical presentation and laboratory results and is confirmed by documentation of severe ADAMTS13 deficiency, with ADAMTS13 activity levels of less than 10%.[2] Current treatment consists of daily plasma exchange,[3] to replenish functional ADAMTS13 and remove von Willebrand factor and autoantibodies, and immunosuppressive therapy (e.g., glucocorticoids and rituximab) to suppress anti-ADAMTS13 autoantibodies.[4] Refractory disease, which develops in approximately one in six patients and is characterized by platelet counts that either do not increase at all or increase very slowly, is associated with poor outcomes.

Patients may die or have irreversible neurologic deficits before a response to treatment occurs. An episode of TTP may result in long-term consequences, such as cognitive deficits, depression, arterial hypertension, and premature death.[5] A major challenge is the persistent risk of life-threatening recurrences, which are termed exacerbations if they occur within 30 days after the last plasma exchange and relapses if they occur more than 30 days after the last plasma exchange. Most recurrences occur during the first year or two, but they can occur as late as 10 or 20 years after an episode of TTP.[6,7] Longitudinal testing has established persistent or recurrent ADAMTS13 deficiency as a strong risk factor for recurrence.[6,8-11]

Caplacizumab, a humanized, bivalent, variable-domain-only immunoglobulin fragment (Nanobody, Ablynx), targets the A1 domain of von Willebrand factor, preventing interaction with the platelet glycoprotein Ib-IX-V receptor[12] and the ensuing microvascular thrombosis. A phase 2 trial showed the efficacy of caplacizumab as compared with placebo with respect to the time to normalization of the platelet count, the incidence of recurrence of TTP during the treatment period,[13] the percentage of patients in whom refractory disease developed,[14] and the incidence of major thromboembolic events.[15] A subgroup of patients who had persistent ADAMTS13 deficiency had a relapse soon after treatment with caplacizumab was stopped, which suggests that monitoring of ADAMTS13 could be useful to guide the continuation of therapy.[13] In the phase 3 HERCULES trial (A Phase III Double-Blind, Randomized, Parallel Group, Multicenter Placebo-Controlled Trial to Study the Efficacy and Safety of Caplacizumab in Patients with Acquired Thrombotic Thrombocytopenic Purpura), we sought to confirm the potential role of caplacizumab in the treatment of TTP by comparing caplacizumab with placebo with respect to the time to normalization of the platelet count and the risk of death and complications caused by thrombotic events and organ damage. The trial also evaluated the potential of caplacizumab to reduce the risk of recurrence by allowing for treatment to continue until immunosuppressive therapy resolved the underlying autoimmune disease.

Methods

Patients

Adults (≥18 years of age) and, at some sites, children 2 to 18 years of age were eligible for participation if they had TTP that was diagnosed on the basis of clinical presentation (the presence of both thrombocytopenia and microangiopathic hemolytic anemia with schistocytes seen on blood smear) and if they had received exactly one plasma-exchange treatment. Severe ADAMTS13 deficiency was not an eligibility criterion. Patients were excluded if they had suspected thrombotic microangiopathies that were not associated with TTP, such as hemolytic uremic syndrome, or if they had congenital TTP.

Trial Design and Oversight

We conducted this randomized, double-blind, placebo-controlled trial at 92 sites worldwide (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The institutional review board or ethics committee at each participating site approved the protocol, which is available at NEJM.org, and all the patients provided written informed consent. The sponsor designed

the trial in collaboration with the external steering committee. An independent data and safety monitoring board monitored the trial. An independent adjudication committee whose members were unaware of the trial-group assignments reviewed all potential major thromboembolic events and assessed the relatedness of deaths to TTP. The results of the trial were critically evaluated and interpreted by the authors, who reviewed and revised the manuscript. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. No one who is not an author contributed to the writing of the manuscript.

TRIAL ASSIGNMENTS

Patients were randomly assigned to receive parenteral caplacizumab or placebo, in addition to standard-of-care treatment for TTP, defined in the protocol as daily plasma exchange (at 1 to 1.5 times the estimated plasma volume, until at least 2 days after normalization of the platelet count) and glucocorticoids (prednisone or prednisolone at a dose of ≥1 mg per kilogram of body weight per day during the daily plasma-exchange period and continuing for the first week after the end of the daily plasma-exchange period). Subsequently, treatment with glucocorticoids could be tapered at the discretion of the investigator, with the aim of stopping glucocorticoid treatment completely within 30 days after the last plasma exchange. Other immunosuppressive therapy was allowed in accordance with clinical practice at each site. Randomization was stratified according to neurologic involvement (baseline Glasgow Coma Scale score of ≤12 vs. >13, on a scale ranging from 3 to 15, with lower scores indicating worse mental status). Patients received an intravenous loading dose of caplacizumab (10 mg) or placebo before the start of the first plasma exchange after randomization. Subsequent doses (10 mg) were administered subcutaneously, once daily, until 30 days after the last daily plasma exchange. Administration of caplacizumab or placebo could be extended for a maximum of 28 days beyond the 30 days, guided by risk factors for recurrence of TTP, such as persistent severe ADAMTS13 deficiency, and was to be accompanied by immunosuppressive therapy that was adjusted as needed. In the event of disease recurrence (i.e., a new decrease in the platelet count that necessitated the reinitiation of daily plasma exchange) at any time during the treatment period, patients were switched to open-label treatment with caplacizumab; however, the initial trial-group assignment remained concealed. The trial included a 28-day follow-up period after the end of the treatment period. Any recurrences during this follow-up period were managed with the standard of care, without reinitiation of the trial regimen.

OUTCOME MEASURES

The primary outcome was the time to a response, which was defined as the time from the first intravenous administration of caplacizumab or placebo to normalization of the platelet count (i.e., a platelet count of at least 150,000 per cubic millimeter), with discontinuation of daily plasma exchange within 5 days thereafter. The four key secondary outcomes, which were hierarchically ranked on the basis of clinical relevance, were the following: a composite of TTP-related death, recurrence of TTP, or a major thromboembolic event during the trial treatment period; recurrence of TTP at any time during the trial, including the follow-up period; refractory TTP (defined by the lack of a doubling of the platelet count after 4 days of treatment and a lactate dehydrogenase level that remained above the upper limit of the normal range); and the time to normalization (i.e., to a level below the defined upper limit of the normal range) of three organ-damage markers (lactate dehydrogenase, cardiac troponin I, and serum creatinine). A recurrence was defined as a new decrease in the platelet count that necessitated the reinitiation of plasma exchange after normalization of the platelet count had occurred. An exacerbation was defined as a recurrence that occurred within 30 days after the last plasma exchange. A relapse was defined as a recurrence that occurred more than 30 days after cessation of plasma exchange.

Outcomes that were not part of the hierarchy included the number of days of plasma exchange and the volume of plasma exchanged, the duration of stay in an intensive care unit and in the hospital, mortality rate, pharmacodynamic and pharmacokinetic variables, and immunogenicity. Safety assessments were performed throughout the course of the trial and included evaluation of vital signs, physical examinations, clinical laboratory testing, and 12-lead electrocardiography.

Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 20.0.

ADAMTS13 activity was measured at a central laboratory at baseline, every week during the treatment period beginning with the first day after the end of daily plasma exchange, and twice during the follow-up period. In patients who had a recurrence of TTP while receiving caplacizumab or placebo, ADAMTS13 activity was measured at the time of the recurrence and then weekly beginning with the first day after plasma exchange during treatment with open-label caplacizumab.

STATISTICAL ANALYSIS

We estimated that with a sample of 132 patients, the trial would have 80% power to detect a median time to normalization of the platelet count that was 40% shorter with caplacizumab than with placebo, using a log-rank test at a 5% significance level and assuming a 10% dropout rate. We calculated that this sample size would also provide 83% power to detect a rate of the first key secondary outcome (i.e., a composite of TTP-related death, recurrence of TTP, or a major thromboembolic event during the trial treatment period) that was 20% lower in the caplacizumab group than in the placebo group, using a chi-square test with a large sample approximation and a 5% significance level. All efficacy analyses were conducted in the intention-to-treat population (which included all patients who underwent randomization), whereas the safety and immunogenicity analyses were conducted in the safety population (which included all patients who received at least one dose of caplacizumab or placebo). The time to normalization of the platelet count was compared between the trial groups with the use of a two-sided stratified log-rank test on the basis of a Kaplan–Meier analysis; the stratification factor was the severity of neurologic involvement at baseline (i.e., Glasgow Coma Scale score of ≤12 vs. >13). The time to normalization of the platelet count was also analyzed with the use of a Cox proportional-hazards regression model, with the time to normalization of platelet count as a dependent variable and treatment group and Glasgow Coma Scale category as independent variables (details on the Glasgow Coma Scale categories can be found in the protocol). The rate ratio (i.e., hazard ratio) for normalization of the platelet count estimated with the Cox model was reported along with the corresponding 95% confidence intervals. (Because the time to normalization of the platelet count is linked with a positive outcome, "rate ratio" is used to describe the result instead of the typical "hazard ratio," with similar interpretation.)

A fixed-sequence approach was applied for analyses of the key secondary outcomes that were hierarchically ordered on the basis of clinical relevance. The first three outcomes were analyzed with the use of a Cochran–Mantel–Haenszel test; the model included adjustment for baseline severity of neurologic involvement. The fourth outcome was analyzed with the use of a stratified log-rank test that was based on a Kaplan–Meier analysis, with adjustment for severity of baseline neurologic involvement and baseline lactate dehydrogenase level.

RESULTS

TRIAL POPULATION

During the period from November 2015 through April 2017, a total of 145 patients were randomly assigned to receive caplacizumab (72 patients) or placebo (73 patients). All the patients received the assigned caplacizumab or placebo, except for 1 patient assigned to the caplacizumab group who withdrew consent before receiving the first dose. Overall, 108 patients completed the trial (i.e., completed all scheduled treatment visits and had their final follow-up visit), and 36 patients who had received at least one dose of caplacizumab or placebo discontinued the trial regimen (13 in the caplacizumab group and 23 in the placebo group). The most common reasons for discontinuation were adverse events, withdrawal of consent, and physician decision (Fig. S2 in the Supplementary Appendix).

Demographic and baseline disease characteristics were generally similar in the two trial groups (Table 1). An imbalance between the groups was observed in the percentage of patients with initial as compared with recurrent TTP episodes at presentation; this finding was consistent with somewhat more severe disease in the caplacizumab group, given that initial TTP episodes tend to be more severe at presentation than recurrent episodes.

ADAMTS13 activity at baseline was below 10% in 123 patients (85%), which confirmed the clinical diagnosis of TTP. For 13 of the 20 pa-

tients who had ADAMTS13 activity of 10% or higher at baseline, the diagnosis was confirmed on the basis of a history of TTP or of ADAMTS13 activity below 10% at other time points during the trial. For 7 patients (4 in the caplacizumab group and 3 in the placebo group), the diagnosis of TTP with severe ADAMTS13 deficiency could not be confirmed.

PRIMARY OUTCOME

The median time to normalization of the platelet count on the basis of the Kaplan–Meier analysis and a stratified log-rank test was significantly shorter in the caplacizumab group than in the placebo group (Fig. 1 and Table 2). At any given time point, patients who received caplacizumab were 1.55 times as likely to have a normalization of the platelet count as patients who received placebo (rate ratio for normalization of platelet count, 1.55; 95% confidence interval [CI], 1.09 to 2.19; P=0.01).

KEY SECONDARY OUTCOMES

During the trial treatment period, a component of the composite outcome of TTP-related death, recurrence of TTP, or a major thromboembolic event occurred in 9 patients (12%) in the caplacizumab group and in 36 patients (49%) in the placebo group. This difference represented a 74% lower incidence with caplacizumab than with placebo (P<0.001) (Table 2).

During the overall trial period, including the 28-day follow-up period in which patients were no longer receiving caplacizumab or placebo, 9 patients (12%) in the caplacizumab group, as compared with 28 patients (38%) in the placebo group, had a recurrence of TTP, which represented a 67% lower incidence of recurrence with caplacizumab than with placebo (P<0.001) (Table 2). All recurrences in the placebo group occurred within 30 days (range, 2 to 25) after the end of daily plasma exchange, which met the definition of exacerbations.[16] Among the patients in the caplacizumab group who had a recurrence, 3 patients had exacerbations (2 had an exacerbation that was possibly triggered by concurrent infection and 1 had an exacerbation that was related to nonadherence to caplacizumab); the other 6 patients had a recurrence that occurred during the follow-up period (between 2 and 10 days after the end of treatment) and hence were considered to have had a relapse. In all 6 of the patients who had a relapse, the ADAMTS13 activity level was still below 10% when caplacizumab treatment was stopped, which indicated unresolved underlying autoimmune disease (Fig. 2).

Refractory disease developed in no patients in the caplacizumab group and in 3 patients in the placebo group (P=0.06) (Table 2). Normalization of the three organ-damage markers (lactate dehydrogenase, cardiac troponin I, and serum creatinine) occurred somewhat sooner in patients who received caplacizumab than in those who received placebo (Table 2, and Fig. S4 in the Supplementary Appendix).

OTHER OUTCOMES

ADAMTS13 Activity in Relation to Recurrence

A total of 129 patients (65 in the caplacizumab group and 64 in the placebo group) had normalization of the platelet count and completed the period of daily plasma exchange. In the week after daily plasma exchange ended, ADAMTS13 activity was still severely suppressed (i.e., <10%) in 57% of the patients overall (73 of 129 patients) — in 60% of the patients in the caplacizumab group (39 of 65 patients) and in 53% of the patients in the placebo group (34 of 64 patients). In total, 31 patients (3 in the caplacizumab group and 28 in the placebo group) had an exacerbation (i.e., recurrence within 30 days after the end of daily plasma exchange), 28 of whom (3 in the caplacizumab group and 25 in the placebo group) had unresolved underlying autoimmune disease, with ADAMTS13 activity levels below 10% (Fig. 2A).

Information on the ADAMTS13 activity level at the time that administration of caplacizumab or placebo was stopped was available for 120 patients (60 at the end of the period of double-blind administration of caplacizumab, 34 at the end of the period of double-blind administration of placebo, and 26 at the end of the period of open-label administration of caplacizumab). In 29 of the 120 patients (24%), ADAMTS13 was still severely deficient at the time that the caplacizumab or placebo was stopped. Among these 29 patients, 9 had a relapse during the follow-up period (Fig. 2B).

Health Care Resource Utilization

During the overall treatment period — which included, for all patients, the period of double-

Table 1. Demographic and Baseline Disease Characteristics and Concomitant Treatments for TTP in the Intention-to-Treat Population.*

Characteristic	Caplacizumab (N=72)	Placebo (N=73)	Total (N=145)
Demographic and baseline disease characteristics			
Mean age (range) — yr	45 (18–77)	47 (21–79)	46 (18–79)
Female sex — no. (%)	49 (68)	51 (70)	100 (69)
Mean body-mass index (range)†	30 (18–53)	30 (19–59)	36 (18–59)
Race — no. (%)‡			
White	47 (65)	50 (68)	97 (67)
Black	15 (21)	13 (18)	28 (19)
Asian	4 (6)	0	4 (3)
Other	3 (4)	1 (1)	4 (3)
Data missing	3 (4)	9 (12)	12 (8)
Hispanic or Latino ethnic group — no. (%)‡	4 (6)	2 (3)	6 (4)
Presenting episode of TTP — no. (%)§			
Initial	48 (67)	34 (47)	82 (57)
Recurrent	24 (33)	39 (53)	63 (43)
Median platelet count (range) — per mm^3¶‖	24,000 (3,000–119,000)	25,000 (9,000–133,000)	24,000 (3,000–133,000)
Median lactate dehydrogenase (range) — U per liter‖	449 (120–2525)	403 (151–3343)	422 (120–3343)
Median cardiac troponin I (range) — μg per liter‖	0.09 (0.01–75.96)	0.07 (0.01–7.28)	0.08 (0.01–75.96)
Median serum creatinine (range) — μmol per liter‖	77 (35–717)	82 (52–482)	80 (35–717)
ADAMTS13 activity — no. (%)‖**			
<10%	58 (81)	65 (89)	123 (85)
≥10%	13 (18)	7 (10)	20 (14)
Data missing	1 (<1)	1 (<1)	2 (1)
Glasgow Coma Scale score — no. (%)††			
≤12	6 (8)	5 (7)	11 (8)
13 to 15	65 (90)	67 (92)	132 (91)
Data missing	1 (<1)	1 (<1)	2 (1)
Immunosuppressive therapy — no. (%)			
Glucocorticoids	69 (96)	71 (97)	140 (97)
Rituximab	28 (39)	35 (48)	63 (43)
Frontline, started by trial day 3	9 (12)	16 (22)	25 (17)
During daily plasma exchange, started after trial day 3	3 (4)	7 (10)	10 (7)
After the period of daily plasma exchange	11 (15)	6 (8)	17 (12)
During daily plasma exchange among patients who had exacerbation	0	1 (1)	1 (1)
After the period of daily plasma exchange among patients who had exacerbation	0	2 (3)	2 (1)
During the follow-up period	5 (7)	3 (4)	8 (6)

Table 1. (Continued.)

Characteristic	Caplacizumab (N=72)	Placebo (N=73)	Total (N=145)
Mycophenolate mofetil	6 (8)	0	6 (4)
Hydroxychloroquine	2 (3)	1 (1)	3 (2)
Bortezomib	2 (3)	0	2 (1)
Cyclophosphamide	1 (1)	1 (1)	2 (1)
Cyclosporin	1 (1)	1 (1)	2 (1)
Other treatments for TTP — no. (%)			
Splenectomy			
Performed before the start of the trial	0	5 (7)	5 (3)
Performed during the trial	2 (3)	1 (1)	3 (2)
Immune globulin concentrate infusion	4 (6)	0	4 (3)
Immunoadsorption	1 (1)	0	1 (1)

* There were no significant differences between the groups in the characteristics listed in this table, except as noted. Baseline was defined as the period before the first administration of caplacizumab or placebo; all the patients were to have received a single plasma-exchange treatment before randomization to caplacizumab or placebo. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. TTP denotes thrombotic thrombocytopenic purpura.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Race and ethnic group were determined by the investigator.

§ The difference between the trial groups in the percentage of patients who presented with an initial episode as compared with a recurrent episode was significant ($P<0.05$).

¶ All the patients in the trial had a platelet count of less than 100,000 per cubic millimeter at screening, which met the entry criteria of the trial, with the exception of one patient in the placebo group who entered the trial with a platelet count of 100,000 per cubic millimeter; this was reported as a major protocol deviation.

‖ Normal ranges used in the trial were as follows: platelet count, 150,000 to 450,000 per mm^3; lactate dehydrogenase, 120 to 246 U per liter; cardiac troponin I, 0 to 0.059 μmol per liter; serum creatinine, 44 to 97 μmol per liter (0.5 to 1.1 mg per deciliter) (women) and 62 to 115 μmol per liter (0.7 to 1.3 mg per deciliter) (men); and ADAMTS13 activity, 50 to 130%.

** ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) is a von Willebrand factor–cleaving protease that leads to platelet consumption in von Willebrand factor–platelet aggregates and microvascular thrombosis. As a result of the requirement for previous plasma exchange, baseline ADAMTS13 activity was higher than that measured locally at the time of admission in some cases. When available, ADAMTS13 activity levels that were locally measured at the time of admission were obtained, and the lower value of the baseline and admission values is represented.

†† The Glasgow Coma Scale score is a measure of neurologic involvement; scores range from 3 to 15, with lower scores indicating worse mental status.

blind administration of caplacizumab or placebo, and, in addition, for patients who had an exacerbation and were switched to treatment with open-label caplacizumab, the period of open-label administration of caplacizumab — patients who received caplacizumab needed an average of 5.8 days of plasma-exchange treatment, as compared with 9.4 days of plasma-exchange treatment needed by patients in the placebo group, which represented a 38% shorter duration of such treatment with caplacizumab than with placebo. Accordingly, the average volume of plasma exchanged was 21.3 liters for patients who received caplacizumab as compared with 35.9 liters for patients in the placebo group, which represented a 41% lower volume with caplacizumab than with placebo. Moreover, a 65% shorter duration of care in an intensive care unit (mean, 3.4 days vs. 9.7 days) and a 31% shorter duration of hospitalization (mean, 9.9 days vs. 14.4 days) were also noted (Table 2).

Immunogenicity

Drug-induced antibodies to caplacizumab developed in 3% of the patients who received caplacizumab. No effect on either clinical efficacy or ristocetin cofactor activity was observed, and no serious adverse events were reported in these patients.

SAFETY

The median duration of exposure to caplacizumab was longer than the duration of exposure to placebo (35 days [range, 1 to 65] vs. 23 days [range, 2 to 66]). This difference is attributable to the trial

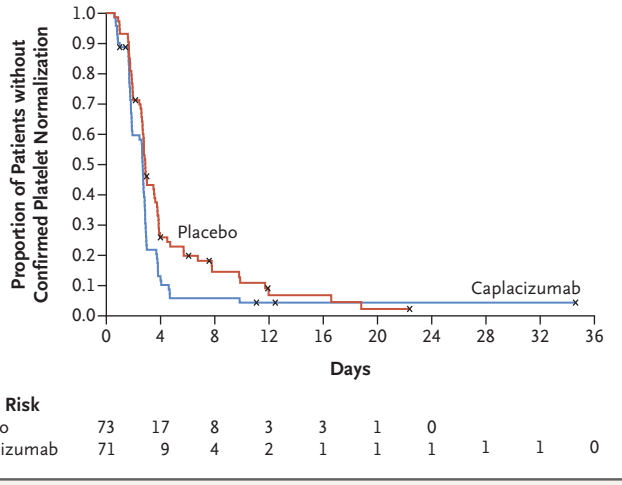

Figure 1. Time to Confirmed Normalization of the Platelet Count in the Intention-to-Treat Population.

Symbols indicate censored data.

design, which included a switch to open-label caplacizumab in cases in which a patient had a recurrence during the double-blind treatment period, and to the fact that almost all recurrences occurred in the placebo group.

The most commonly reported adverse events that occurred in at least 5% of the patients in either trial group during the double-blind treatment period are listed in decreasing order of relative risk (caplacizumab vs. placebo) in Figure 3. During the overall trial period, 68 patients (96%) in the caplacizumab group and 66 patients (90%) in the placebo group had at least one adverse event (excluding adverse events of TTP, which were considered to be secondary efficacy outcomes) (Table S1 in the Supplementary Appendix).

A total of 4 patients died during the trial, including 1 (1%) in the caplacizumab group (during the treatment-free follow-up period) and 3 (4%) in the placebo group (all during the treatment period). All 4 deaths were adjudicated as TTP-related. The cause of death in the patient in the caplacizumab group was cerebral ischemia and was assessed by the investigator as unrelated to treatment; the cause of death in the patients in the placebo group was worsening massive ischemic attack with hemorrhagic transformation in 1 patient and refractory TTP (specifically, "worsening TTP with coma and death" and "hypoxia with bleeding in the lung") in the 2 other patients. Serious adverse events (excluding serious adverse events of TTP, which were considered to be secondary efficacy outcomes) were reported in 23 patients (32%) in the caplacizumab group and in 12 patients (16%) in the placebo group during the overall trial period (Table S2 in the Supplementary Appendix). Five patients in the caplacizumab group and 9 patients in the placebo group had an adverse event that led to discontinuation of the trial regimen.

Bleeding-related adverse events were reported in 46 patients (65%) in the caplacizumab group and in 35 patients (48%) in the placebo group (Table S3 in the Supplementary Appendix). The most common such events were epistaxis and gingival bleeding; all these events resolved, most without intervention. These events were mild or moderate in severity in a majority of patients and were severe in 3 patients in the caplacizumab group (epistaxis, gingival bleeding, and upper gastrointestinal hemorrhage in 1 patient each) and in 1 patient in the placebo group (hemorrhagic transformation stroke). Serious adverse events of bleeding were reported in 8 patients (11%) in the caplacizumab group and in 1 patient (1%) in the placebo group. The most commonly reported serious adverse event of bleeding was epistaxis, which occurred in 4 patients in the caplacizumab group. One patient received von Willebrand factor concentrate as the only treatment for resolution of a severe, serious adverse event of epistaxis. No temporal relationship between the occurrence of bleeding and the duration of exposure to caplacizumab was observed.

DISCUSSION

In this phase 3 trial involving patients with TTP, the time to normalization of the platelet count was shorter among patients who had received caplacizumab than among those who had received placebo, presumably because caplacizumab prevented the consumption of platelets in microthrombi. The trial also showed that treatment with caplacizumab resulted in a lower incidence of a composite of TTP-related death, recurrence of TTP, or a major thromboembolic event during the trial treatment period and a lower incidence of recurrence during the overall trial period than placebo.

Exacerbations occurred up to 25 days after the end of plasma exchange, which supports the need for treatment with caplacizumab during the pe-

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

Outcome	Caplacizumab (N=72)	Placebo (N=73)	P Value
Primary outcome			
Time to normalization of platelet count			
25th Percentile (95% CI) — days	1.75 (1.65–1.87)	1.94 (1.70–2.64)	
50th Percentile (95% CI) — days	2.69 (1.89–2.83)	2.88 (2.68–3.56)	
75th Percentile (95% CI) — days	2.95 (2.85–3.81)	4.50 (3.78–7.79)	
Rate ratio for normalization of platelet count, caplacizumab vs. placebo (95% CI)*	1.55 (1.09–2.19)		0.01
Key secondary outcomes			
Composite of TTP-related death, recurrence of TTP, or major thromboembolic event during the double-blind treatment period — no. (%)	9 (12)	36 (49)	<0.001
TTP-related death	0	3 (4)	
Recurrence of TTP: exacerbation†	3 (4)	28 (38)	
Major thromboembolic event	6 (8)	6 (8)	
Recurrence of TTP at any time during the trial — no. (%)†	9 (12)	28 (38)	<0.001
During the double-blind treatment period: exacerbation	3 (4)	28 (38)	
During the follow-up period: relapse‡	6 (8)	0	
Refractory TTP — no. (%)§	0	3 (4)	0.06
Median time to normalization of organ-damage markers (95% CI) — days	2.86 (1.93–3.86)	3.36 (1.88–7.71)	
Other secondary outcomes¶			
Number of days of plasma exchange			
Mean (95% CI)	5.8 (4.8–6.8)	9.4 (7.8–11.0)	
Median (range)	5.0 (1.0–35.0)	7.0 (3.0–46.0)	
Volume of plasma exchanged — liters			
Mean (95% CI)	21.3 (18.1–24.6)	35.9 (27.6–44.2)	
Median (range)	18.1 (5.3–102.2)	26.9 (4.0–254.0)	
No. of days of hospitalization			
Mean (95% CI)	9.9 (8.5–11.3)	14.4 (12.0–16.9)	
Median (range)	9.0 (2.0–37.0)	12.0 (4.0–53.0)	
Patients admitted to the intensive care unit — no. (%)‖	28 (39)	27 (37)	
No. of days in the intensive care unit			
Mean (95% CI)	3.4 (2.6–4.2)	9.7 (5.3–14.1)	
Median (range)	3.0 (1.0–10.0)	5.0 (1.0–47.0)	

* Because an event (time to normalization of the platelet count) in this trial is linked with a positive outcome, "rate ratio" for normalization of the platelet count is used to describe the result instead of the typical "hazard ratio," with similar interpretation.

† Recurrence was defined as a new decrease in the platelet count after initial normalization of the platelet count, necessitating reinitiation of plasma exchange. According to the consensus terminology,[16] a recurrence within 30 days after the end of daily plasma exchange is considered to be an exacerbation, and a recurrence that occurs more than 30 days after the end of daily plasma exchange is considered to be a relapse.

‡ Four of the six patients who had a relapse during the follow-up period had received the maximum allowed extension of treatment.

§ Refractory TTP was defined as the lack of a doubling of the platelet count after 4 days of treatment and a lactate dehydrogenase level that remained above the upper limit of the normal range.[17]

¶ These outcomes were assessed during the trial treatment period.

‖ Admission to the intensive care unit for administration of plasma exchange is standard practice at some centers and is not necessarily indicative of more severe clinical presentation.

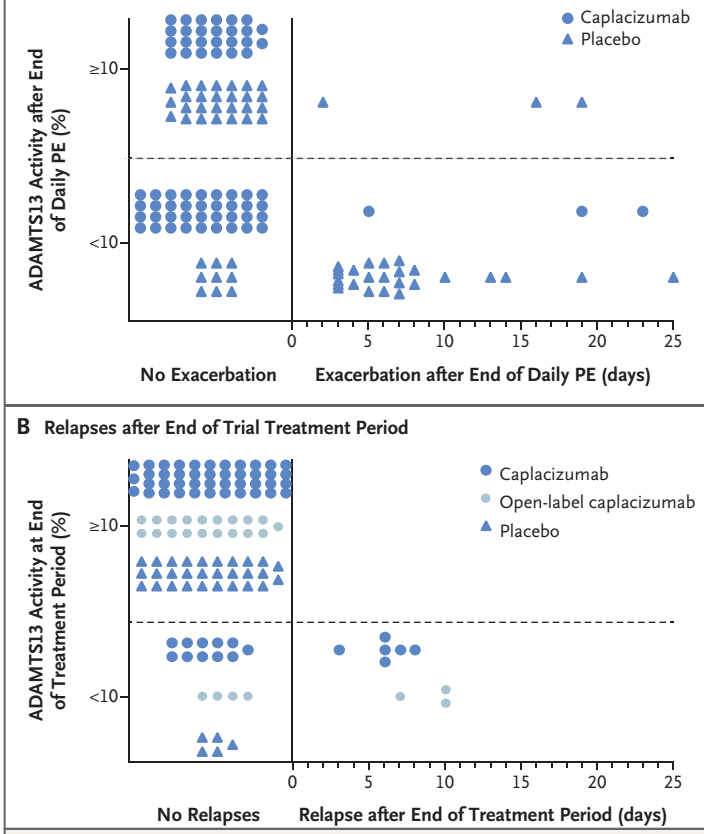

Figure 2. Recurrence Status According to ADAMTS13 Activity in the Intention-to-Treat Population.

ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) is a von Willebrand factor–cleaving protease that leads to platelet consumption in von Willebrand factor–platelet aggregates and microvascular thrombosis. Panel A shows individual-patient data on exacerbation status during the trial treatment period. Panel B shows individual-patient data on relapse status during the follow-up period (i.e., after the end of the treatment period). Recurrences are termed exacerbations if they occur within 30 days after the last plasma exchange (PE) and relapses if they occur more than 30 days after the last PE.

riod in which a patient is at risk (i.e., for at least 30 days after normalization of the platelet count is achieved). In the phase 2 trial, when caplacizumab was stopped, early relapses occurred in a subgroup of patients who had persistent severe ADAMTS13 deficiency below 10%. On the basis of these results, the current trial was designed to allow investigators to continue administration of caplacizumab or placebo under blinded conditions in patients who had evidence of persistent autoimmune activity (e.g., ADAMTS13 activity <10%) at the end of the 30-day period after the last plasma exchange. Continuation of caplacizumab or placebo was to be accompanied by adjustment of immunosuppressive therapy. This approach of extending the treatment period was validated, as evidenced by the occurrence of fewer relapses in this trial than in the phase 2 trial. The relapses that did occur were all in patients who still had severely suppressed ADAMTS13 activity below 10%. This finding suggests that monitoring of ADAMTS13 activity could be useful in guiding not only immunosuppressive treatment[18-22] but also the continuation of caplacizumab treatment beyond 30 days after stopping plasma exchange.

No patient in either the phase 2 trial or the current trial died while receiving treatment with caplacizumab. In addition, treatment with caplacizumab prevented the development of refractory disease and consequently the negative outcomes that are commonly reported in patients with refractory TTP. Normalization of markers associated with organ damage occurred sooner among patients who received caplacizumab than among those who received placebo. The effect of treatment with caplacizumab on the time to normalization of the platelet count and on the incidence of recurrence was also reflected in the fewer number of days of plasma exchange and the shorter stays in the hospital and in the intensive care unit among patients who received caplacizumab than among those who received placebo.

Caplacizumab interferes with von Willebrand factor, a key protein in hemostasis. Accordingly, it is associated with mucocutaneous bleeding that is similar to that observed in patients with von Willebrand's disease.[23] Safety results in the current trial were consistent with those reported previously,[13] including an increased risk of bleeding.

Over the past two decades, despite a better understanding of the pathophysiological characteristics of TTP,[24] treatment outcomes have not changed substantially, with recent mortality rates reported to be as high as 20%.[25] Death occurs primarily during the acute phase, as a result of uncontrolled formation of microvascular thrombi. The current treatments — plasma exchange and immunosuppression — replenish functional ADAMTS13 enzyme and control the underlying autoimmune disease but do not directly address the microvascular thrombosis. Caplacizumab blocks adhesion of von Willebrand factor multimers to platelets, a step in the formation of these thrombi.

Overall, caplacizumab showed value when add-

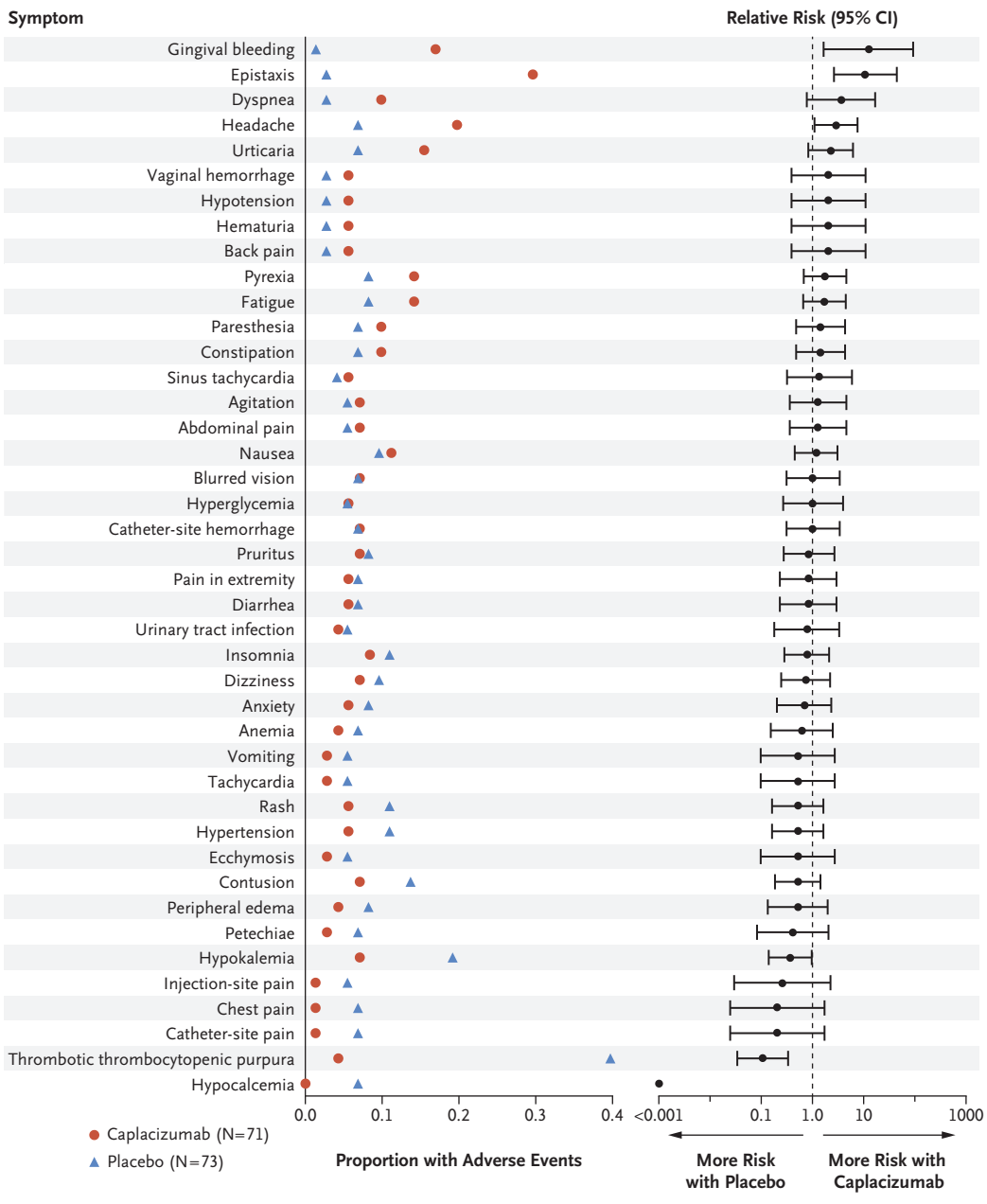

Figure 3. Adverse Events According to Relative Risk in the Safety Population.

Shown are adverse events that occurred in at least 5% of the patients in either trial group, in decreasing order of the relative risk with caplacizumab as compared with placebo.

ed to the standard treatment for acquired TTP. This added value was associated with a higher incidence of low-grade mucosal bleeding than that with placebo.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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