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ORIGINAL ARTICLE

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

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ABSTRACT

BACKGROUND

Atypical hemolytic–uremic syndrome is a genetic, life-threatening, chronic disease of complement-mediated thrombotic microangiopathy. Plasma exchange or infusion may transiently maintain normal levels of hematologic measures but does not treat the underlying systemic disease.

METHODS

We conducted two prospective phase 2 trials in which patients with atypical hemolytic–uremic syndrome who were 12 years of age or older received eculizumab for 26 weeks and during long-term extension phases. Patients with low platelet counts and renal damage (in trial 1) and those with renal damage but no decrease in the platelet count of more than 25% for at least 8 weeks during plasma exchange or infusion (in trial 2) were recruited. The primary end points included a change in the platelet count (in trial 1) and thrombotic microangiopathy event–free status (no decrease in the platelet count of >25%, no plasma exchange or infusion, and no initiation of dialysis) (in trial 2).

RESULTS

A total of 37 patients (17 in trial 1 and 20 in trial 2) received eculizumab for a median of 64 and 62 weeks, respectively. Eculizumab resulted in increases in the platelet count; in trial 1, the mean increase in the count from baseline to week 26 was 73×10^9 per liter ($P<0.001$). In trial 2, 80% of the patients had thrombotic microangiopathy event–free status. Eculizumab was associated with significant improvement in all secondary end points, with continuous, time-dependent increases in the estimated glomerular filtration rate (GFR). In trial 1, dialysis was discontinued in 4 of 5 patients. Earlier intervention with eculizumab was associated with significantly greater improvement in the estimated GFR. Eculizumab was also associated with improvement in health-related quality of life. No cumulative toxicity of therapy or serious infection-related adverse events, including meningococcal infections, were observed through the extension period.

CONCLUSIONS

Eculizumab inhibited complement-mediated thrombotic microangiopathy and was associated with significant time-dependent improvement in renal function in patients with atypical hemolytic–uremic syndrome. (Funded by Alexion Pharmaceuticals; C08-002 ClinicalTrials.gov numbers, NCT00844545 [adults] and NCT00844844 [adolescents]; C08-003 ClinicalTrials.gov numbers, NCT00838513 [adults] and NCT00844428 [adolescents]).

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Atypical hemolytic–uremic syndrome is a genetic, chronic, and progressive inflammatory disease that affects patients of all ages.[1,2] This syndrome is caused by defects in regulation of the complement system. These defects are inherited, acquired, or both, and they result in chronic, uncontrolled activation of the complement system[1-4] which leads to platelet, leukocyte, and endothelial-cell activation and systemic thrombotic microangiopathy.[1,5-9] Affected patients have a lifelong risk of systemic clinical complications of thrombotic microangiopathy, including damage to multiple organ systems (e.g., the central nervous system, kidneys, heart, and gastrointestinal tract).

Although plasma exchange or infusion has been used to manage atypical hemolytic–uremic syndrome and may transiently maintain a normal platelet count and lactate dehydrogenase level in some patients,[10-12] the underlying complement dysregulation and thrombotic microangiopathic processes are likely to persist.[10] Indeed, end-stage renal disease (ESRD) or death occurs in approximately 33 to 40% of patients during the first clinical manifestation of atypical hemolytic–uremic syndrome.[7,8,13] Within 1 year after a diagnosis of this syndrome, up to 65% of patients treated with plasma exchange or infusion sustain permanent renal damage, have progression to ESRD, or die.[7]

Among patients with atypical hemolytic–uremic syndrome who undergo kidney transplantation, graft failure is reported in 60 to 90% of patients within 1 year.[14,15] Combined liver and kidney transplantation may normalize complement regulation in patients with certain genetic defects,[16] but it is associated with substantial morbidity and mortality, including a mortality of 14% in the short term.[9,17,18]

Eculizumab (Soliris, Alexion Pharmaceuticals), a terminal complement inhibitor, is a humanized monoclonal antibody that binds with high affinity to the human C5 complement protein and blocks the generation of proinflammatory C5a and C5b-9.[19-25] It is approved for the treatment of paroxysmal nocturnal hemoglobinuria.[19,26-28] Previous case reports have suggested that eculizumab is effective in atypical hemolytic–uremic syndrome.[24,25] In two separate 26-week, phase 2 studies with long-term extension phases, we evaluated the efficacy and safety of eculizumab in patients with atypical hemolytic–uremic syndrome and clinical evidence of progressing thrombotic microangiopathy (in trial 1) and in patients with disease of long duration, chronic kidney damage, and prolonged treatment with plasma exchange or infusion (in trial 2). The data from these prospective trials, as well as data from a separate retrospective study (unpublished data), were used by regulatory agencies in the United States, Europe, and other countries for the approval of eculizumab in the treatment of atypical hemolytic–uremic syndrome.[29,30]

METHODS

PATIENTS

At 27 European and North American clinical sites, we enrolled patients with a diagnosis of atypical hemolytic–uremic syndrome who were 12 years of age or older and weighed 40 kg or more. Eligibility criteria differed between the studies (Fig. 1). In trial 1, patients were eligible if they had evidence of progressive thrombotic microangiopathy after four or more sessions of plasma exchange or infusion in the prior week. In trial 2, patients were eligible if they had no decrease in the platelet count of more than 25% for at least 8 weeks before they received the first dose of eculizumab and were being treated with plasma exchange or infusion at least once every 2 weeks but no more than three times per week (Fig. 1). Both studies required evidence of hemolysis (e.g., lactate dehydrogenase level at or above the upper limit of the normal range, haptoglobin level below the lower limit of the normal range, or the presence of schistocytes) and impaired renal function (creatinine level at or above the upper limit of the normal range). Identification of complement gene mutations or complement factor H autoantibodies was not required. Key exclusion criteria for both trials were ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity at or below 5% in plasma,[31] evidence of Shiga toxin–producing *Escherichia coli* infection, or prior eculizumab exposure.

STUDY DESIGN

The studies included several periods: screening (a maximum of 3 days in trial 1 and 2 weeks in trial 2), an 8-week observation period (in trial 2 only), eculizumab treatment (26 weeks and a long-term extension period), and an 8-week follow-up period if eculizumab was discontinued.

Patients received the first eculizumab dose

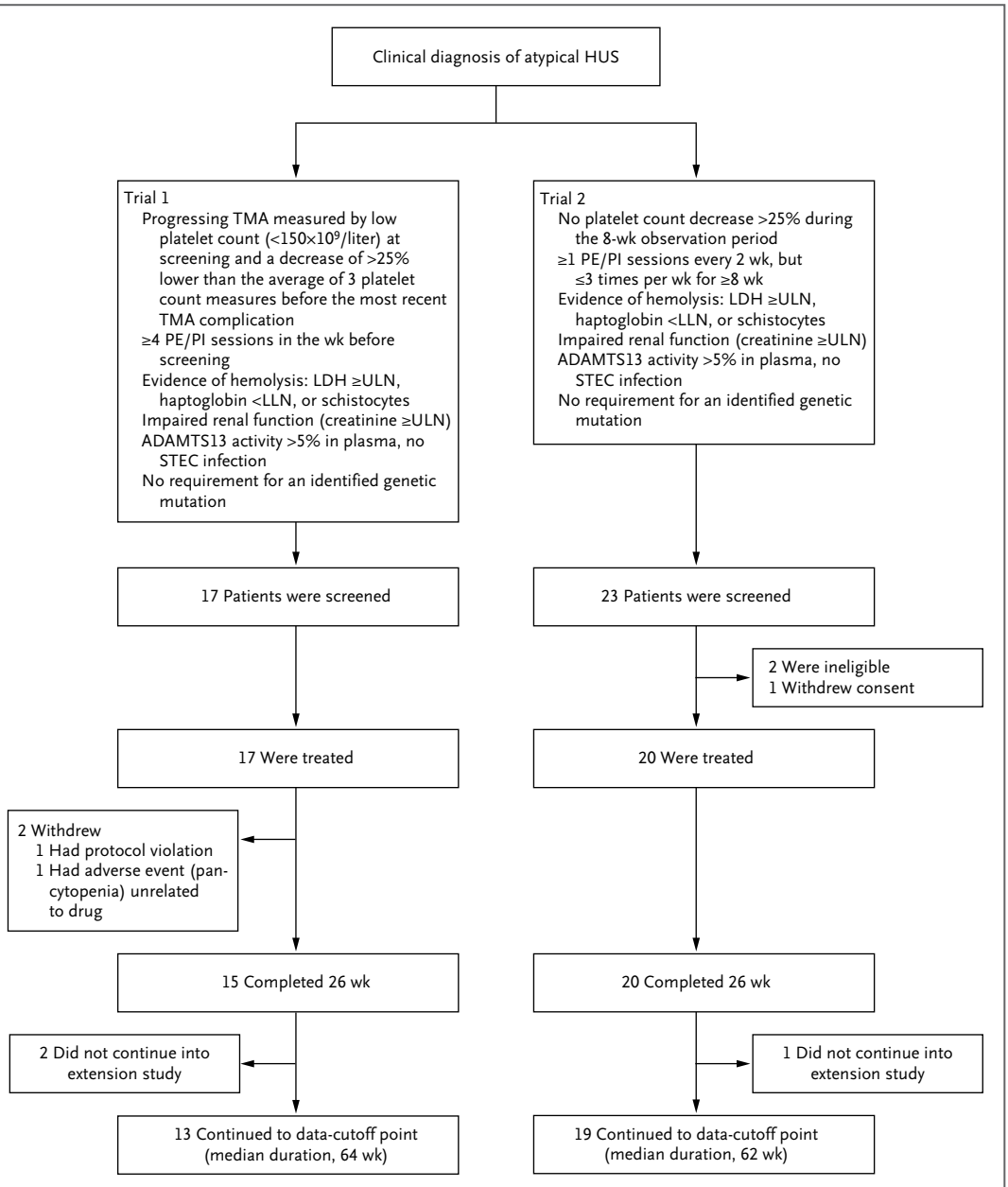

Figure 1. Screening, Treatment, and Follow-up.

ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) was measured at a central laboratory. HUS denotes hemolytic–uremic syndrome, LDH lactate dehydrogenase, LLN lower limit of the normal range, PE/PI plasma exchange or infusion, STEC Shiga toxin–producing *Escherichia coli*, TMA thrombotic microangiopathy, and ULN upper limit of the normal range.

1 to 6 hours after their most recent plasma exchange or infusion session. Eculizumab was administered intravenously at a dose of 900 mg per week for 4 weeks, a dose of 1200 mg 1 week later, and a maintenance dose of 1200 mg every 2 weeks. Patients who received plasma exchange or infusion during the eculizumab treatment period received a supplemental dose of 600 mg before plasma infusion or within 1 hour after the completion of each plasma exchange. All patients received meningococcal vaccination at least 14 days before the initiation of

eculizumab treatment or they received prophylactic antibiotic therapy until 2 weeks after vaccination.

END POINTS

Each trial had two primary end points: inhibition of complement-mediated thrombotic microangiopathy, as indicated by a change in the platelet count (in trial 1) or thrombotic microangiopathy event–free status for at least 12 weeks (no decrease in the platelet count of >25%, no plasma exchange or infusion, and no initiation of dialysis) (in trial 2), and normalization of hematologic values (a normal platelet count and lactate dehydrogenase level, sustained for at least two consecutive measurements over a period of at least 4 weeks) (in both trials) (see Section 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org, for definitions of end points and assessments). Thrombotic microangiopathy event–free status was a secondary end point in trial 1. Secondary end points for both trials included measures of renal function, changes in health-related quality of life (as measured by means of the EuroQoL Group 5-Dimension Self-Report Questionnaire [EQ-5D]) (Section 7 in the Supplementary Appendix),[32] pharmacokinetics and pharmacodynamics, and safety and tolerability.[33] Three-piece linear modeling was used to analyze changes in the platelet count and estimated glomerular filtration rate (GFR) during three periods: before eculizumab treatment (slope 1), during the first 28 days of treatment (slope 2), and from day 29 to the data-cutoff point (slope 3). End points were analyzed through the 26-week treatment period and the long-term extension period up to the data-cutoff point (March 2011) and were assessed in patients with or without identified genetic mutations or complement factor H autoantibodies.

STUDY OVERSIGHT

The studies were designed by all the authors in conjunction with the sponsor (Alexion Pharmaceuticals). Data were collected by the sponsor in association with Parexel International (an independent clinical research organization) and were analyzed by the sponsor and Pharsight, which performed statistical analyses. The authors, the sponsor, and Pharsight vouch for the completeness and accuracy of the data and analyses and for the fidelity of this report to the study protocols, available at NEJM.org. An independent data and safety monitoring committee reviewed the safety data. The decision to submit the manuscript for publication was made by all the authors and the sponsor, which retains the data. All the authors had access to all analyses, wrote the first draft of the manuscript, and approved the final manuscript. Alexion Pharmaceuticals and Infusion Communications provided medical-writing support.

The studies and informed-consent process were approved by the institutional review board at each center or by an independent ethics committee and were conducted in accordance with the Declaration of Helsinki. All patients, their parents or guardians, or both provided written informed consent.

STATISTICAL ANALYSIS

All primary analyses were performed in the intention-to-treat population. Means (±SE), medians and ranges, least-squares means, and 95% confidence intervals were determined for all continuous variables. All 26-week results presented here are from models based on only the first 26 weeks of data.

RESULTS

PATIENTS

Thirty-seven patients with atypical hemolytic–uremic syndrome were enrolled in the trials (Fig. 1). For the 17 patients (16 adults and 1 adolescent) with progressive thrombotic microangiopathy who were enrolled in trial 1, the median interval between diagnosis of atypical hemolytic–uremic syndrome and screening was 9.7 months (Table 1). All patients had substantial renal damage (100% had an estimated GFR of <60 ml per minute per 1.73 m^2 of body-surface area for a median of 17 days). All but 1 patient (who could not undergo plasma exchange or infusion because of side effects) received plasma exchange or infusion within 1 week before initiation of treatment with eculizumab (Section 2 in the Supplementary Appendix). For the 20 patients (15 adults and 5 adolescents) enrolled in trial 2, the interval between diagnosis and screening was longer (median, 48.3 months), and most of the patients had chronic renal insufficiency (90% had an estimated GFR of <60 ml per minute per 1.73 m^2 for a median of 299 days) and were re-

ceiving long-term plasma exchange or infusion (median duration of treatment, 10.1 months) (Table 1).

In trial 1, patients were treated with eculizumab for 26 weeks (Fig. 1). Thirteen patients (76%) continued to receive eculizumab during the extension period. At the data-cutoff point, the median duration of eculizumab treatment was 64 weeks (range, 2 to 90). In trial 2, patients were also treated with eculizumab for 26 weeks, with 19 patients (95%) continuing to receive eculizumab during the extension period. At the data-cutoff point, the median duration of treatment with eculizumab was 62 weeks (range, 26 to 74). A total of 24% of patients in trial 1 and 35% of patients in trial 2 had no identified complement gene mutation or complement factor H autoantibodies (Table 1).

PRIMARY END POINTS

In trial 1, eculizumab treatment was associated with a significant absolute increase in the platelet count from baseline to week 26 (mean, 73×10^9 per liter; 95% confidence interval [CI], 40×10^9 per liter to 105×10^9 per liter; P<0.001) (Table 2, and Fig. 2A) and to week 64 (91×10^9 per liter; 95% CI, 67×10^9 per liter to 116×10^9 per liter; P<0.001) (Table 2). The platelet count was significantly increased by day 7 (P=0.03) (Fig. 2A). Fifty-three percent of the patients with an abnormal platelet count at baseline had a normal platelet count ($\geq150\times10^9$ per liter) by day 7, and 87% had platelet counts that remained normal at both weeks 26 and 64. All 13 patients with a low platelet count at baseline who were treated for 26 weeks had normalization of the platelet count by week 26, and in all 13 patients who entered the extension period, platelet counts remained normal through the median treatment duration of 64 weeks (Table 2, and Section 6 in the Supplementary Appendix).

In trial 2, a total of 16 of 20 patients (80%) met the primary end point by week 26; this proportion increased to 85% through the median treatment duration of 62 weeks. Four patients did not meet the end point at 26 weeks because of a transient decrease in the platelet count of more than 25% from baseline, although all four maintained normal platelet counts. With initiation of eculizumab, plasma exchange or infusion was discontinued in all patients, and no new dialysis was required.

Normalization of hematologic values (the platelet count and lactate dehydrogenase levels) occurred in 88% of patients in trial 1 and in 90% of patients in trial 2 (Table 2). In both trials, positive results were seen for all end points in patients with or without identified genetic mutations or complement factor H autoantibodies (Section 3 in the Supplementary Appendix).

SECONDARY END POINTS

Thrombotic Microangiopathic Outcomes

In trial 1, a total of 15 of the 17 patients (88%) had thrombotic microangiopathy event–free status through week 26, as did 13 patients who were treated for 64 weeks (Table 2). A total of 15 patients (88%) did not receive plasma exchange or infusion for the entire duration of the study. One patient received five sessions of plasma exchange or infusion without an interruption in eculizumab treatment, and 1 received plasma exchange or infusion after discontinuation of eculizumab and withdrawal from the study because of a protocol violation.

Renal Outcomes

After discontinuation of plasma exchange or infusion and initiation of eculizumab treatment, there were continuous, time-dependent increases in the estimated GFR from baseline to week 26 (mean increase in trial 1, 32 ml per minute per 1.73 m^2; 95% CI, 14 to 49; P=0.001; mean increase in trial 2, 6 ml per minute per 1.73 m^2; 95% CI, 3 to 9; P<0.001). This improvement was maintained at week 60 (mean increase in trial 1, 32 ml per minute per 1.73 m^2; 95% CI, 16 to 47; P<0.001; mean increase in trial 2, 9 ml per minute per 1.73 m^2; 95% CI, 4 to 14; P=0.003) (Fig. 2B and 2C). In both trials, improvement in the estimated GFR was accompanied by a decrease in proteinuria in patients with baseline proteinuria of grade 1+ or higher (P<0.001 in trial 1 and P=0.03 in trial 2 at 1 year) (Table 1). In addition, in trial 1, dialysis was discontinued in four of five patients (80%) who had required dialysis at the time of initiation of eculizumab, and these patients remained dialysis-free throughout eculizumab treatment. In both trials, earlier initiation of eculizumab (i.e., a shorter interval between the current clinical manifestation of atypical hemolytic–uremic syndrome and enrollment) was associated with a significantly greater improvement in the estimated GFR throughout the treatment period (P=0.007 in trial 1 and P<0.001 in

trial 2) (Sections 4, 5, and 6 in the Supplementary Appendix).

The three-piece linear models showed that the change in the estimated GFR before eculizumab treatment (slope 1) did not differ significantly from zero in either trial. From the initia-

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

Variable	Trial 1 (N=17)	Trial 2 (N=20)
Age — yr		
Median	28	28
Range	17–68	13–63
Female sex — no. (%)	12 (71)	12 (60)
White race — no.†	15	17
Time from diagnosis of atypical HUS to screening — mo		
Median	9.7	48.3
Range	0.3–235.9	0.7–285.8
Time from current clinical presentation of atypical HUS to screening — mo		
Median	0.8	8.6
Range	0.2–3.7	1.2–45.0
First clinical manifestation of atypical HUS — no. (%)	7 (41)	5 (25)
History of kidney transplantation — no. (%)	7 (41)	8 (40)
Dialysis before the first dose of eculizumab — no. (%)	6 (35)‡	2 (10)§
Sessions of plasma exchange or infusion during current clinical presentation — no./patient		
Median	17	62
Range	2–35¶	20–230
Duration of plasma exchange or infusion treatment — mo		
Median	0.7	10.1
Range	0.1–3.2	2.4–47.0
No identified genetic mutation or autoantibody — no. (%)‖	4 (24)	6 (30)
Identified genetic mutation, autoantibody, or both — no. (%)	13 (76)	14 (70)
Single	9 (53)	8 (40)
Multiple	4 (24)	6 (30)
Platelet count		
Median — $\times 10^{-9}$/liter	118	218
Range — $\times 10^{-9}$/liter	62–161	105–421
<150×10^{9}/liter — no. (%)	15 (88)**	3 (15)
Hemoglobin — g/liter		
Median	87	108
Range	67–126	79–131
Lactate dehydrogenase		
Median — U/liter	269	200
Range — U/liter	134–634	151–391
>Upper limit of normal range — no. (%)	10 (59)	4 (20)
Serum creatinine — μmol/liter		
Median	256	234
Range	124–787	106–893

Table 1. (Continued.)

Variable	Trial 1 (N=17)	Trial 2 (N=20)
Estimated GFR		
Median — ml/min/1.73 m²	19	28
Range — ml/min/1.73 m²	5–59	6–72
≥60 ml/min/1.73 m² — no. (%)	0††	2 (10)‡‡
45–59 ml/min/1.73 m² — no. (%)	1 (6)	2 (10)
30–44 ml/min/1.73 m² — no. (%)	4 (24)	6 (30)
15–29 ml/min/1.73 m² — no. (%)	5 (29)	6 (30)
<15 ml/min/1.73 m² or receiving dialysis — no. (%)	7 (41)	4 (20)
Proteinuria grade ≥1+ — no. (%)§§	15 (88)	11 (55)
Urinary protein:creatinine¶¶	4.3±0.32	0.9±0.26
Medication — no. (%)		
ESAs	10 (59)	16 (80)
ACE inhibitors or ARBs	6 (35)	18 (90)

* Plus–minus values are means ±SE. ACE denotes angiotensin-converting enzyme, ARB angiotensin II–receptor blocker, ESA erythropoiesis-stimulating agent, GFR glomerular filtration rate, and HUS hemolytic–uremic syndrome.
† Race was self-reported.
‡ One of the six patients who had been receiving dialysis within 8 weeks before eculizumab treatment discontinued dialysis 5 weeks before the first dose of eculizumab. The duration of dialysis before the initiation of eculizumab treatment ranged from 6 to 26 days.
§ The duration of dialysis before the initiation of eculizumab treatment was 119 days in one patient and 1128 days in the other.
¶ One patient had no plasma exchange or infusion sessions during the 7 days before the initiation of eculizumab treatment and did not meet the inclusion criterion of a minimum of four sessions of plasma exchange or infusion before screening because this patient had an allergic reaction and discontinued plasma exchange or infusion after two sessions. (See Section 2 in the Supplementary Appendix for additional information.)
‖ One patient in trial 2 who had an isolated complement factor H–related 3/1 deletion (a risk factor for atypical hemolytic–uremic syndrome) was included under "no identified genetic mutation" in this analysis.
** Two patients with baseline median platelet counts of 150×10^9/liter or higher were eligible for inclusion, since their average platelet count during screening was lower than 150×10^9/liter.
†† The median duration of an estimated GFR of less than 60 ml per minute per 1.73 m² in all patients was 17 days (range, 5 to 105).
‡‡ The median duration of an estimated GFR of less than 60 ml per minute per 1.73 m² in 18 patients was 299 days (range, 91 to 553). Of the two patients with an estimated GFR between 60 and 89 ml per minute per 1.73 m² at baseline, one patient had an estimated GFR of less than 60 ml per minute per 1.73 m² for 118 days and an estimated GFR of 60 to 90 ml per minute per 1.73 m² for 556 days, and the other patient had an estimated GFR of less than 60 ml per minute per 1.73 m² for 42 days and an estimated GFR of 60 to 89 ml per minute per 1.73 m² for 329 days.
§§ Proteinuria was reported according to grade (negative, traces, 1+, 2+, etc.) or as urinary protein with a normal range of 0 to 12 mg per deciliter.
¶¶ Protein was measured in grams per liter, and creatinine was measured in millimoles per liter.

tion of eculizumab treatment through day 28 (slope 2), there was a rapid and significant increase in the estimated GFR in both trials ($P<0.001$ in trial 1 and $P=0.001$ in trial 2). The slope of change in the estimated GFR from day 0 to 28 was significantly greater than the slope of change during the pretreatment period (slope 2 vs. slope 1: $P<0.001$ in trial 1 and $P=0.007$ in trial 2). In trial 1, the improvements in the estimated GFR from day 0 to 28 were maintained from day 29 through the data-cutoff point (slope 3), with no further increase, whereas in trial 2, the estimated GFR continued to improve after day 28 ($P=0.03$) (Fig. S3 and S4 in the Supplementary Appendix).

Health-Related Quality of Life Outcomes

Eculizumab was associated with a significant improvement in health-related quality of life. The EQ-5D scores range from 0 to 1, with higher scores

indicating a better quality of life. In trial 1, the mean increase in the EQ-5D score at week 26 was 0.32 (95% CI, 0.24 to 0.39; P<0.001) (Section 6 and Fig. S5 in the Supplementary Appendix), and in trial 2, the mean increase was 0.10 (95% CI, 0.05 to 0.15; P<0.001) (Table 2, and Section 6 and Fig. S6 in the Supplementary Appendix). The clinically meaningful threshold[34] of 0.06 was exceeded in 87% of

Table 2. Primary and Secondary End Points.*

End Point	Trial 1		Trial 2	
	Week 26†	Median Treatment Duration 64 Weeks†‡	Week 26	Median Treatment Duration 62 Weeks‡
Efficacy				
Change in platelet count from baseline — $\times 10^{-9}$/liter				
Mean	73	91	5	
95% CI	40 to 105	67 to 116§	−17 to 28	NA
P value for comparison with 0	<0.001	<0.001	NS	NA
Normalization of platelet count — no./total no. (%)				
All patients	14/17 (82)	15/17 (88)	NA	NA
Patients with baseline count of $<150\times10^9$/liter	13/15 (87)	13/15 (87)	NA	NA
Thrombotic microangiopathy event–free status — no./total no. (%)	15/17 (88)	15/17 (88)	16/20 (80)	17/20 (85)
Normalization of hematologic values — no./total no. (%)	13/17 (76)	15/17 (88)	18/20 (90)	18/20 (90)
Thrombotic microangiopathy				
Intervention rate — no. of events (plasma exchange or infusion, dialysis, or both)/patient/day				
Before eculizumab treatment				
Median	0.88	0.88	0.23	0.23
Range	0.04 to 1.59	0.04 to 1.59	0.05 to 1.09	0.05 to 1.09
During eculizumab treatment				
Median	0	0	0	0
Range	0 to 0.31	0 to 0.31	0 to 0	0 to 0
P value for comparison with pretreatment values	<0.001	<0.001	<0.001	<0.001
Complete thrombotic microangiopathic response — no./total no. (%)	11/17 (65)	13/17 (76)	5/20 (25)	7/20 (35)
Increase in hemoglobin of >20 g/liter — no./total no. (%)	11/17 (65)	13/17 (76)¶	9/20 (45)	10/20 (50)¶
Lactate dehydrogenase ≤upper limit of normal range — no./total no. (%)	14/17 (82)	15/17 (88)	19/20 (95)	19/20 (95)
Renal function				
Decrease in serum creatinine level of ≥25% — no./total no. (%)	11/17 (65)	13/17 (76)	3/20 (15)	7/20 (35)
Increase in estimated GFR of ≥15 ml/min/1.73 m^2 — no./total no. (%)	8/17 (47)	9/17 (53)	1/20 (5)	3/20 (15)
Improvement in CKD of at least 1 stage — no./total no. (%)	10/17 (59)	11/17 (65)	7/20 (35)	9/20 (45)
Decrease in proteinuria by ≥1 grade in patients with proteinuria grade ≥1 at baseline — no./total no.	12/15	9/11**††	6/11	7/9**‡‡
Decrease in urinary protein:creatinine‖	1.05±0.94	0.64±0.62	0.47±0.39	0.44±0.47
P value for comparison with baseline	0.01	0.03	0.04	0.004

Table 2. (Continued.)

End Point	Trial 1		Trial 2	
	Week 26†	Median Treatment Duration 64 Weeks†‡	Week 26	Median Treatment Duration 62 Weeks‡
Health-related quality of life				
Change in EQ-5D score§§				
Mean	0.32	0.30	0.10	0.13
95% CI	0.24 to 0.39	0.25 to 0.35	0.05 to 0.15	0.08 to 0.18¶¶
P value for comparison with baseline	<0.001	<0.001	<0.001	<0.001
Achievement of clinically meaningful threshold of 0.06 — no./total no. (%)	12/15 (80)‖‖	13/15 (87)‖‖	8/11 (73)***	8/11 (73)***

* Plus–minus values are means ±SE. P values were calculated with the use of a repeated-measures analysis for continuous data and a Wilcoxon signed-rank test for categorical variables. CI denotes confidence interval, CKD chronic kidney disease, EQ-5D EuroQoL Group 5-Dimension Self-Report Questionnaire, NA not applicable, and NS not significant.
† One patient discontinued eculizumab after one dose because of an exclusion criterion (the patient received a diagnosis of systemic lupus erythematosus) and another patient discontinued eculizumab after 6 weeks (four doses) because of an adverse event deemed to be unrelated to eculizumab.
‡ Statistical assessments for patients who continued treatment into the extension period of the study and measurements during that time were not prespecified (ClinicalTrials.gov).
§ Data were from week 60.
¶ Of the patients who were receiving ESAs at baseline, seven (70%) in trial 1 and nine (56%) in trial 2 discontinued, decreased, or maintained ESA use during eculizumab treatment.
‖ This outcome, which was based on data at 52 weeks, was not specified as a secondary end point.
** This result is based on the number of patients who had proteinuria of grade 1 or higher at baseline and at 52 weeks.
†† At week 52, of the patients who had a decrease in proteinuria, one was not receiving ACE inhibitors or ARBs, four had a decrease in proteinuria before treatment with ACE inhibitors or ARBs was initiated, and four had a decrease after such treatment was initiated.
‡‡ At week 52, of the patients who had a decrease in proteinuria, four had no change in dose or number of ACE inhibitors or ARBs, two began treatment with ACE inhibitors or ARBs, and one discontinued ACE inhibitors or ARBs.
§§ The EQ-5D scores range from 0 to 1, with higher scores indicating a better quality of life.
¶¶ Data were calculated with the use of an index scored according to the time-tradeoff value set for the United States.
‖‖ Data could be evaluated for 15 patients.
***Data could be evaluated for 11 patients.

patients in trial 1 and in 73% of patients in trial 2 throughout the treatment period (Table 2 and Section 7 in the Supplementary Appendix).

PHARMACOKINETICS AND PHARMACODYNAMICS

In both trials, eculizumab significantly reduced complement activity within 1 hour after initiation of treatment, and all patients had complete inhibition of complement activity, which was maintained through week 26 (P<0.001) (Fig. 2D). The specified dosing schedule was sufficient to achieve and maintain the minimum serum concentration of eculizumab required to block terminal complement activation (Section 8 in the Supplementary Appendix).

SAFETY

Adverse events are listed in Table 3 and Section 9 in the Supplementary Appendix. There were no cases of meningococcal infection or infection-related serious adverse events. All patients were alive at the time of data cutoff. In trial 1, all patients had at least one serious adverse event; four events were reported as being possibly related to eculizumab, one of which was considered severe (hypertension in a patient with a history of this disorder). In trial 2, a total of 10 patients (50%) had serious adverse events, of whom 2 patients had a total of three serious adverse events that were possibly or probably drug-related (peritonitis, influenza, and vein disorder). One patient had one drug-related serious adverse event and the other patient had two such events. All serious adverse events possibly or probably related to eculizumab resolved without interruption of treatment. No new adverse events were reported after the first 26 weeks of treatment. Adverse events were similar among patient subgroups, in-

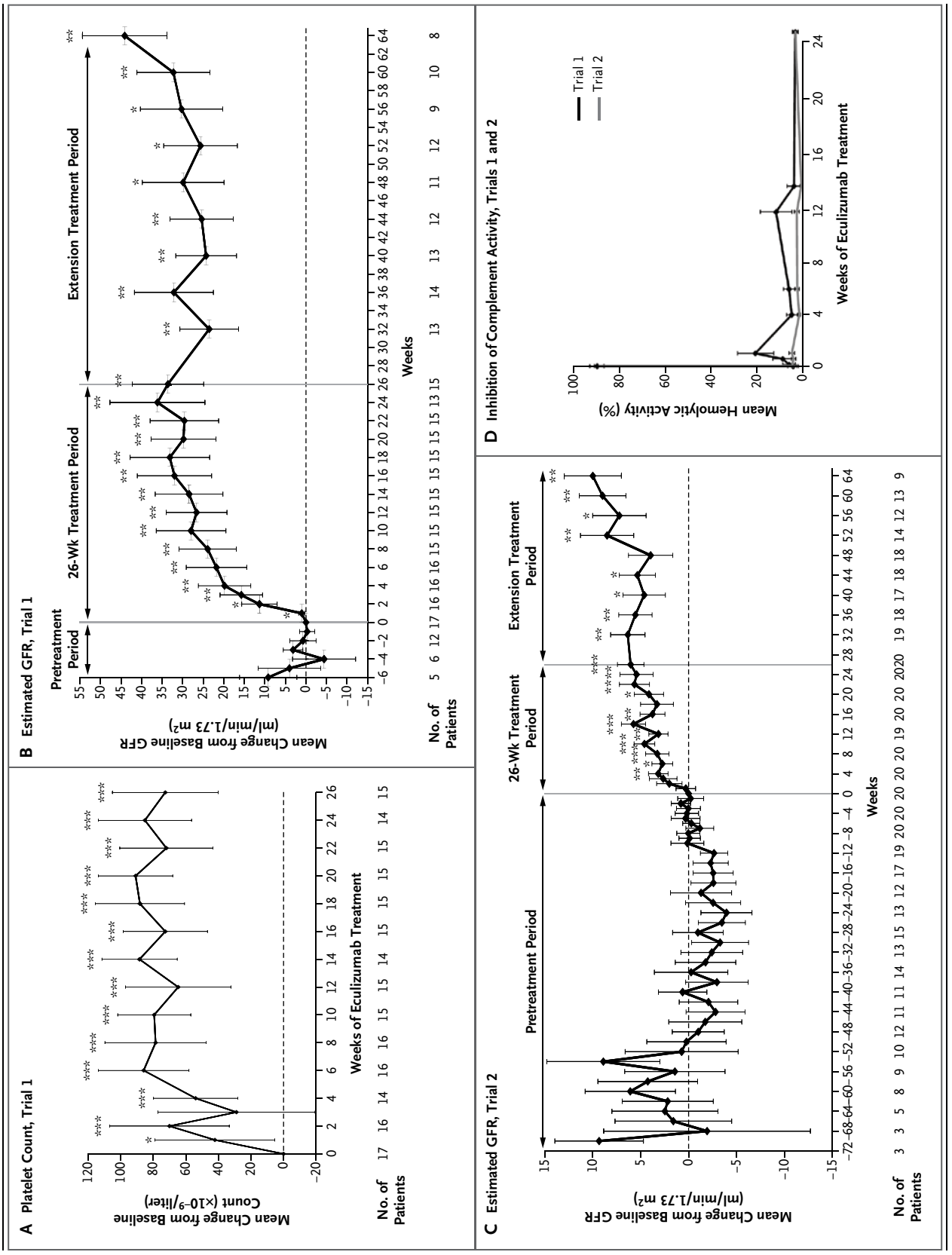

Figure 2 (facing page). End Points.

Panel A shows the change in the platelet count (the primary end point) in trial 1. Least-squares mean changes are shown. I bars indicate 95% confidence intervals. Panels B and C show the change from baseline in the estimated glomerular filtration rate (GFR) (the secondary end point) in trials 1 and 2, respectively. In Panel B, the mean (±SE) estimated GFR on day 0 was 22.8±3.8 ml per minute per 1.73 m^2 of body-surface area. In Panel C, the mean (±SE) estimated GFR on day 0 was 30.8±4.2. Baseline data were obtained from 20 patients, and data are for 20 patients at each time point unless otherwise stated. Mean estimated GFR levels on day 0 were 30.8 (±4.24) ml per minute per 1.73 m^2. Data are shown to 64 weeks; there was no 62-week time point. One patient with end-stage renal disease who was receiving long-term dialysis commenced and continued eculizumab treatment before, during, and after kidney transplantation on day 217. This patient's renal data were censored on day 217 and during continued eculizumab treatment. Panel D shows the inhibition of complement activity (the secondary end point) in trials 1 and 2. Mean hemolytic activity was based on a validated pharmacodynamic assay that quantified the complement activity in serum by measuring the degree of hemolysis; the measure of hemolysis is the amount of hemoglobin release as determined by means of spectrophotometer. Inhibition of complement activity is indicated by 20% or lower hemolysis. P<0.001 through week 26. In trial 1 on day 7, complete complement blockade was not maintained in 4 patients. I bars indicate standard errors. In Panels A, B, and C, one asterisk denotes P<0.05, two asterisks P<0.01, and three asterisks P<0.001.

cluding the 15 patients who had undergone kidney transplantation and were receiving concomitant immunosuppressive therapy.

DISCUSSION

In both prospective, open-label, phase 2 trials — one involving patients with atypical hemolytic–uremic syndrome and clinical evidence of progressive thrombotic microangiopathy (trial 1) and the other involving patients with a long duration of the syndrome, chronic kidney damage, and prolonged plasma exchange or infusion (trial 2) — eculizumab therapy was associated with significant inhibition of complement-mediated thrombotic microangiopathy as measured by a change in the platelet count (trial 1) and an absence of thrombotic microangiopathic events (trial 2). Plasma exchange or infusion was discontinued in 88% of patients in trial 1 and in 100% of patients in trial 2. Eculizumab therapy was associated with large and sustained improvements in renal function, and four of five patients who were receiving dialysis at the beginning of the study no longer required it (trial 1). These results showed that treatment with a terminal complement inhibitor improved renal function across patient subgroups, including those with long-standing, substantial kidney damage who had undergone plasma exchange or infusion.

Earlier intervention with eculizumab (i.e., a shorter interval between the current clinical manifestation of atypical hemolytic–uremic syndrome and initiation of treatment) was associated with significantly greater improvement in the estimated GFR in both trials. These findings suggest that starting eculizumab treatment earlier may lead to improved clinical outcomes and reversal of organ damage. Eculizumab was also associated with significant improvements in health-related quality of life.

Historically, the risk of ESRD or death has been similar among patients with and those without identified complement mutations or complement factor H autoantibodies.[8] In the present trials, the response to eculizumab therapy was also similar, irrespective of status with respect to these two factors,[8] although the studies were not powered to evaluate differences according to mutation status. This finding lends support to the recommendation that treatment with eculizumab in patients with atypical hemolytic–uremic syndrome be considered without requiring results of complement mutation testing.[24]

Treatment with eculizumab during a period of 62 to 64 weeks was not associated with major adverse events in these studies. The safety profile of eculizumab reported here, for patients with atypical hemolytic–uremic syndrome, was generally consistent with that in a study involving patients with paroxysmal nocturnal hemoglobinuria who received treatment for up to 8 years.[28] Infection-related serious adverse events were not observed in our trials. Rates of adverse events remained steady or declined between the initial 26-week period and the extension period. No new adverse events emerged after the initial 26-week study period. Adverse events were similar among patient subgroups, including patients who had undergone kidney transplantation and were receiving concomitant immunosuppressive therapy. No deaths were reported in either trial. Follow-up of patients is ongoing.

Deviations from approved eculizumab dosing

Table 3. Serious Adverse Events Considered Possibly, Probably, or Definitely Associated with Eculizumab as Identified by the Investigator (throughout the Median Treatment Duration of 64 Weeks in Trial 1 and 62 Weeks in Trial 2).

Variable	Trial 1 (N=17)	Trial 2 (N=20)
	no. of patients (%)	
Patients with at least one related serious adverse event		
Overall	4 (24)	2 (10)
To wk 26	2 (12)	2 (10)
Wk 26 to data-cutoff point	2 (12)	1 (5)
Serious adverse events		
Accelerated hypertension	2 (12); moderate severity	
Hypertension	1 (6); severe	
Influenza		1 (5); severe
Peritonitis		1 (5); severe
Venous sclerosis at infusion site		1 (5); severe
Asymptomatic bacteriuria	1 (6); mild	

are associated with a risk of clinical complications, including rapid progression to ESRD.[14,34,35] Such approaches include limiting eculizumab treatment to a single dose, early discontinuation followed by reinitiation of treatment, and administration of doses at intervals longer than those recommended in the eculizumab prescribing information.[24,30] Five of 18 patients who missed eculizumab doses in our two prospective trials or a retrospective study had severe subsequent complications of thrombotic microangiopathy.[29,30] These findings highlight the likelihood of ongoing thrombotic microangiopathy in patients with atypical hemolytic–uremic syndrome and underscore the importance of continued monitoring of patients and sustained treatment.[24,30]

Previous studies have suggested that eculizumab is effective in treating atypical hemolytic–uremic syndrome.[20-24,34,35] To confirm an eculizumab treatment effect in these open-label, single-group trials, pretreatment data were used as within-patient controls. In both trials, the rate of intervention for thrombotic microangiopathy was significantly lower during the period of eculizumab treatment than during the period before treatment. The data highlight the inadequate efficacy of management with plasma exchange or infusion and confirm the clinically relevant treatment effect of eculizumab on thrombotic microangiopathy and organ outcomes. The results of eculizumab therapy appear to represent a substantial advancement in the treatment of patients who have this severe and life-threatening systemic disease.

These two clinical studies suggest that long-term eculizumab treatment is effective in patients with atypical hemolytic–uremic syndrome, with earlier intervention associated with a greater clinical benefit. The data indicate that terminal complement inhibition with eculizumab inhibits complement-mediated thrombotic microangiopathy, decreases the need for thrombotic microangiopathy–related intervention, significantly improves the platelet count and renal function across patient groups, and is associated with substantial kidney recovery and improved clinical outcomes in patients with atypical hemolytic–uremic syndrome.

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APPENDIX

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