ORIGINAL ARTICLE

The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

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ABSTRACT

BACKGROUND

We tested the safety and efficacy of eculizumab, a humanized monoclonal antibody against terminal complement protein C5 that inhibits terminal complement activation, in patients with paroxysmal nocturnal hemoglobinuria (PNH).

METHODS

We conducted a double-blind, randomized, placebo-controlled, multicenter, phase 3 trial. Patients received either placebo or eculizumab intravenously; eculizumab was given at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900-mg dose and then 900 mg every other week through week 26. The two primary end points were the stabilization of hemoglobin levels and the number of units of packed red cells transfused. Biochemical indicators of intravascular hemolysis and the patients' quality of life were also assessed.

RESULTS

Eighty-seven patients underwent randomization. Stabilization of hemoglobin levels in the absence of transfusions was achieved in 49% (21 of 43) of the patients assigned to eculizumab and none (0 of 44) of those assigned to placebo (P<0.001). During the study, a median of 0 units of packed red cells was administered in the eculizumab group, as compared with 10 units in the placebo group (P<0.001). Eculizumab reduced intravascular hemolysis, as shown by the 85.8% lower median area under the curve for lactate dehydrogenase plotted against time (in days) in the eculizumab group, as compared with the placebo group (58,587 vs. 411,822 U per liter; P<0.001). Clinically significant improvements were also found in the quality of life, as measured by scores on the Functional Assessment of Chronic Illness Therapy-Fatigue instrument (P<0.001) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. Of the 87 patients, 4 in the eculizumab group and 9 in the placebo group had serious adverse events, none of which were considered to be treatment-related; all these patients recovered without sequelae.

CONCLUSIONS

Eculizumab is an effective therapy for PNH. (ClinicalTrials.gov number, NCT00122330.)

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Paroxysmal nocturnal hemoglobinuria (PNH), an uncommon form of hemolytic anemia, results from the clonal expansion of hematopoietic stem cells that have somatic mutations in the X-linked gene *PIG-A*.[1,2] *PIG-A* mutations cause an early block in the synthesis of glycosylphosphatidylinositol (GPI) anchors, which tether many proteins to the cell surface. Consequently, the blood cells in patients with PNH have a partial deficiency (type II) or a complete deficiency (type III) of GPI-linked proteins.

Intravascular hemolysis is a prominent feature of PNH and is the consequence of the absence of the GPI-linked complement regulatory protein CD59.[3,4] CD59 blocks the formation of the terminal complement complex (also called the membrane-attack complex) on the cell surface, thereby preventing erythrocyte lysis and in vitro platelet activation.[5-8] Excessive or persistent intravascular hemolysis in patients with PNH causes anemia, hemoglobinuria, and complications related to the presence of plasma free hemoglobin, including thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension.[9-12] Indeed, the symptoms in PNH are often disproportionate to the degree of anemia. Many patients with this disease are dependent on transfusions. Currently, there is no therapy that effectively reduces intravascular hemolysis or improves the symptoms in patients with PNH.

Eculizumab (Soliris, Alexion Pharmaceuticals) is a humanized monoclonal antibody directed against the terminal complement protein C5.[13] In a preliminary, 12-week, open-label clinical study involving 11 patients with PNH, eculizumab reduced intravascular hemolysis and the patients' transfusion requirements.[14] However, this two-center, uncontrolled study did not have a control group or predefined criteria for the administration of a transfusion, such as a predefined hemoglobin level at which transfusions were administered or a prespecified number of units of packed red cells for a given hemoglobin level.

We report the results of the phase 3 Transfusion Reduction Efficacy and Safety Clinical Investigation, a Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (TRIUMPH) study, which investigated whether eculizumab stabilized hemoglobin levels and reduced transfusion requirements in 87 transfusion-dependent patients with PNH during 6 months of treatment. Intravascular hemolysis and the quality of life were also assessed.

METHODS

PATIENTS

The trial consisted of a 2-week screening period, an observation period of up to 3 months, and a 26-week treatment period. Patients 18 years of age or older who had received at least four transfusions during the previous 12 months were eligible. A PNH type III erythrocyte proportion of 10% or more, platelet counts of at least 100,000 per cubic millimeter, and lactate dehydrogenase levels that were at least 1.5 times the upper limit of the normal range were also required. Concomitant administration of erythropoietin, immunosuppressive drugs, corticosteroids, coumarins, low-molecular-weight heparins, iron supplements, and folic acid were permitted, provided that the doses were constant before and throughout the study. Because persons who have a genetic deficiency of terminal complement proteins have an increased risk of neisserial infections, all patients were vaccinated against *Neisseria meningitidis* with the use of locally approved vaccines. The protocol was approved by the institutional review board at each center, and all patients gave written informed consent.

Patients receiving transfusions who had a mean hemoglobin level greater than 10.5 g per deciliter before transfusion during the 12 months before entry into the study or who had received another investigational drug within 30 days before the first visit were excluded. Patients who had a complement deficiency, an active bacterial infection, or a history of meningococcal disease and those who had undergone bone marrow transplantation were also excluded.

An individualized transfusion algorithm was calculated for each patient on the basis of the history of transfusions during the previous 12 months; the written algorithm documented the number of units of packed red cells to be transfused for given hemoglobin values and served as a prospectively determined guide for transfusion during the observation and treatment periods. Before randomization, eligible patients were observed for up to 13 weeks. Patients who did not require a transfusion during the observation period were considered ineligible. A transfusion administered to a patient who had a hemoglobin

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level of 9 g per deciliter or less with symptoms or 7 g per deciliter or less with or without symptoms qualified the patient for the study (qualifying transfusion) and established the hemoglobin set point. This set point was required for the primary efficacy variable and was individualized for each patient.

STUDY DESIGN

Randomization was performed centrally in a 1:1 ratio without blocking and with stratification according to the number of units of packed red cells transfused during the past year; patients were assigned, by means of an interactive voice–response system, to receive either placebo or eculizumab within 10 days after the administration of the qualifying transfusion. Patients received infusions of 600 mg of eculizumab or placebo every week (±2 days) for 4 weeks, followed 1 week (±2 days) later by 900 mg of eculizumab or placebo, and then by a maintenance dose of 900 mg of eculizumab or placebo every 2 weeks (±2 days) through week 26.

CLINICAL EFFICACY

The two primary end points were the stabilization of hemoglobin levels, defined as a hemoglobin value that was maintained above the level at which the qualifying transfusion was administered, in the absence of transfusions during the 26-week treatment period, and the number of units of packed red cells transfused during that period. The trigger for the administration of transfusions during the study remained unchanged: patients received transfusions when they had symptoms resulting from anemia and their hemoglobin levels reached the individualized, predetermined set point. Prespecified secondary end points included transfusion independence; hemolysis, as measured by the lactate dehydrogenase value for the area under the curve from baseline to 26 weeks; and changes in the level of fatigue, as assessed from baseline to 26 weeks with the use of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument (scores can range from 0 to 52, with higher scores indicating improvement in fatigue).[15] Prespecified exploratory analyses included assessment of the quality of life with the use of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (scores can range from 0 to 100, with higher scores on the global health status and functioning scales and lower scores on the symptom scales and single-item measures indicating improvement)[16]; changes in lactate dehydrogenase levels from baseline through week 26; and the presence of thrombosis. Other prespecified measurements included the pharmacokinetics, pharmacodynamics, and immunogenicity of eculizumab. The time to the first transfusion during the treatment period and the proportion of PNH type III blood cells were assessed.

SAFETY

Adverse events related to study infusions and vital signs (assessed at each of the 17 study visits during treatment), the results of biochemical analyses and blood counts (assessed at 9 visits), and findings on electrocardiograms (assessed at 3 visits) were documented. Adverse events were coded with the use of preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) (www.msso.org/MSSOWeb/index.htm) and tabulated as incidence rates in the two study groups.

STATISTICAL ANALYSIS

The planned sample size of 75 patients provided the study with a statistical power of 82%, at an alpha level of 0.05, to detect an increase of 35 percentage points (i.e., a change from 20% to 55%) in the rate of the stabilization of hemoglobin levels and a reduction in the median number of units of packed red cells transfused from 6 to 2 (±2). For the two primary end points, the analyses were performed according to the intention-to-treat principle with the use of data on all 87 patients who underwent randomization; stabilization of hemoglobin levels was analyzed with the use of Fisher's exact test, and the total number of units of packed red cells transfused was analyzed with the use of the Wilcoxon rank-sum test. To assess the effect of treatment on whether or not transfusions were required, Fisher's exact test was used. The log-rank test was used to compare the time to the first transfusion in the two groups. The area under the curve for lactate dehydrogenase was compared between the two groups with the use of the Wilcoxon rank-sum test.

Fatigue was assessed according to the scoring guidelines for the FACIT-Fatigue instrument.[17] The assessment of the quality of life was based on the EORTC QLQ-C30 scores and was conducted as described previously.[18] Changes in scores

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on the FACIT-Fatigue instrument and the EORTC QLQ-C30 instrument from baseline through week 26 were analyzed with the use of a mixed model, with baseline scores as the covariate, treatment and time as fixed effects, and the patient identifier as a random effect. Changes in the levels of lactate dehydrogenase, PNH type III erythrocytes, and hemoglobin from baseline through week 26 were analyzed with the use of the same mixed model. All reported P values are two-sided and were not adjusted for multiple analyses. The incidence rates of adverse events were compared with the use of Fisher's exact test. No interim analyses were performed, and blinding regarding the results was maintained until the end of the study.

The authors and the sponsor were jointly responsible for the trial design and the development of the protocol. Data were collected by an electronic case-report form with the use of InForm software (version 4.0, Phase Forward) and were analyzed by the sponsor. The decision to publish the trial data and final decisions on the content of the manuscript rested with Dr. Hillmen in consultation with the other authors. The manuscript was prepared by Dr. Hillmen, with substantial review and comments by the other authors. All authors had access to the primary data and take responsibility for the veracity and completeness of the data reported.

Table 1. Baseline Characteristics of the Patients.

Characteristic	Placebo Group (N=44)	Eculizumab Group (N=43)
Sex — no.		
Male	15	20
Female	29	23
Age — yr		
Median	35	41
Range	18–78	20–85
Duration of PNH — yr		
Median	9.2	4.3
Range	0.5–38.5	0.9–29.8
Reticulocyte counts — per mm^3		
Median	204,400	206,600
Range	45,400–556,200	40,200–570,400
History of aplastic anemia — no. (%)	12 (27)	6 (14)
History of myelodysplastic syndrome — no. (%)	0	2 (5)
History of thrombosis — no. (%)	8 (18)	9 (21)
Total no. of thrombotic events	11	16
Use of erythropoietin — no. (%)	0	3 (7)
Use of cyclosporine — no. (%)	1 (2)	1 (2)
Use of anticoagulant agents (coumarins or heparins) — no. (%)	11 (25)	21 (49)
Use of corticosteroids or androgenic steroids — no. (%)	12 (27)	12 (28)

RESULTS

PATIENTS' CHARACTERISTICS

Of a total of 115 patients with PNH who underwent screening, 87 (35 men and 52 women) at 34 sites in the United States, Canada, Europe, and Australia who received a qualifying transfusion, met the inclusion criteria and did not meet any of the exclusion criteria were randomly assigned to eculizumab (43 patients) or placebo (44 patients) between October 2004 and June 2005. At each of 16 sites one patient underwent randomization, at each of 6 sites two patients underwent randomization, and at each of 12 sites 3 or more patients underwent randomization. There were no significant differences in the baseline characteristics of the patients in the two groups (Table 1).

Of 87 patients who underwent randomization, 85 completed the trial (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). Two patients in the eculizumab group did not complete the trial, one because traveling to the study center was inconvenient and the other because of pregnancy; these patients were included in the analyses. Ten patients in the placebo group discontinued infusions because of a perceived lack of efficacy but remained in the study for monitoring, as prespecified in the protocol, and were included in the analyses.

PHARMACOKINETICS AND PHARMACODYNAMICS

In 42 of 43 patients in the eculizumab group, a 900-mg dose of eculizumab every 2 weeks (±2 days) completely blocked serum hemolytic activity, as assessed by a presensitized erythrocyte hemolytic assay,[14] throughout the study period. In one patient, therapeutic trough levels of eculizumab were not maintained.

EFFECT ON HEMOLYSIS

The effect of eculizumab on chronic intravascular hemolysis was demonstrated by an immediate

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(1 week) and sustained decrease in lactate dehydrogenase levels (Fig. 1A). In the eculizumab group, the mean (±SE) lactate dehydrogenase level decreased from 2199.7±157.7 U per liter at baseline to 327.3±67.6 U per liter at 26 weeks, whereas in the placebo group the levels remained elevated, with values of 2258.0±154.8 U per liter at baseline and 2418.9±140.3 U per liter at 26

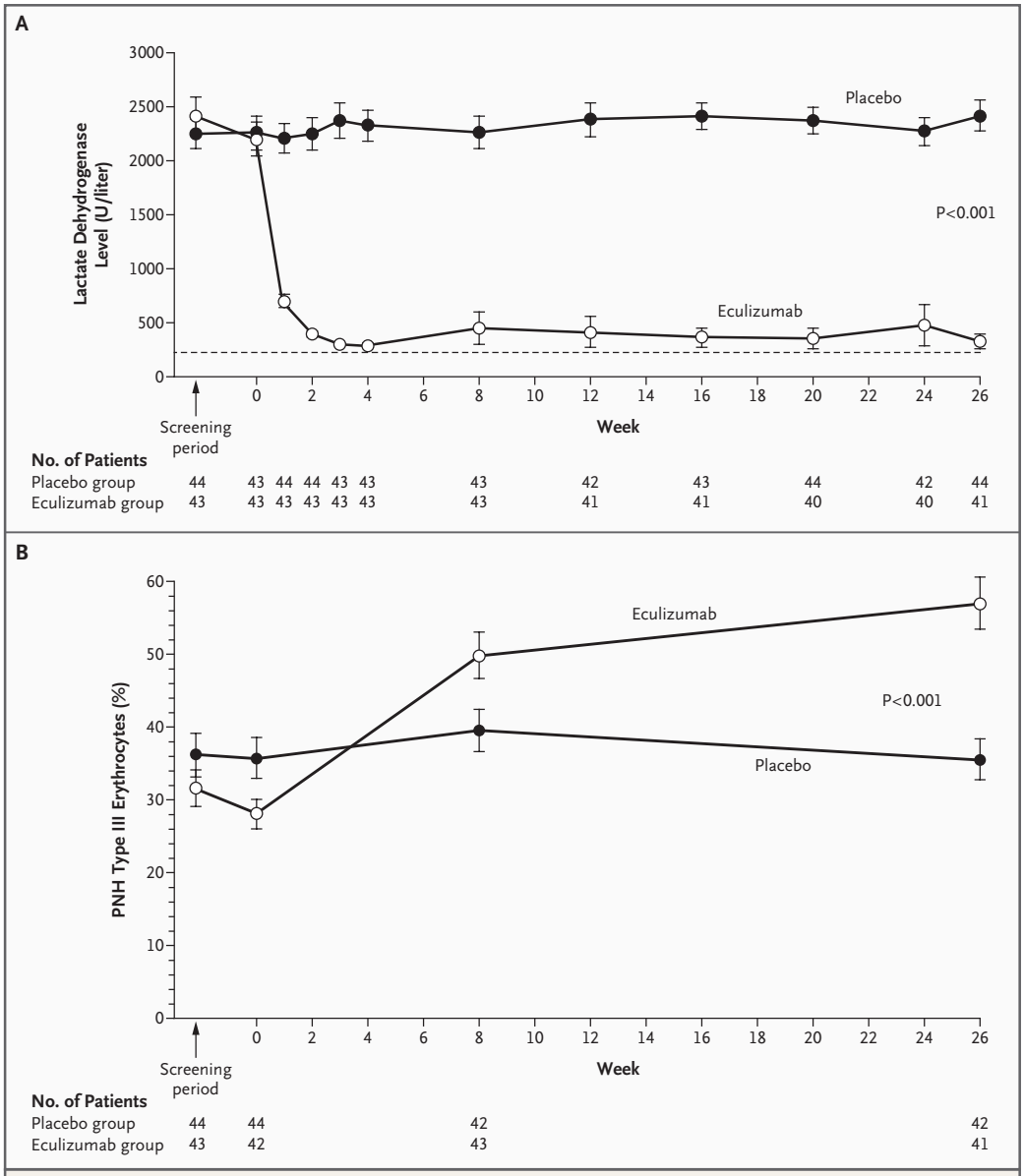

Figure 1. Levels of Lactate Dehydrogenase and PNH Type III Erythrocytes during Treatment with Eculizumab.
Panel A shows the degree of intravascular hemolysis according to the mean levels of lactate dehydrogenase from baseline (week 0) to week 26 in the two study groups. The dashed line indicates the upper limit of the normal range for lactate dehydrogenase (normal range, 103 to 223 U per liter). In the eculizumab group the mean level of lactate dehydrogenase was reduced to just above the upper limit of the normal range at week 26; of 41 patients in this group who completed the study, 15 had levels within the normal range. In the placebo group, all patients had levels at least five times above the upper limit of normal at week 26. Panel B shows the mean proportion of PNH type III erythrocytes in patients in the two groups. Screening occurred up to 3 months before week 0. P values are from a mixed analysis-of-covariance model from baseline through week 26. I bars indicate the standard error.

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weeks (P<0.001). The median value of the areas under the curve for lactate dehydrogenase plotted against time (in days) was 85.8% lower in the eculizumab group than in the placebo group (58,587 vs. 411,822 U per liter; P<0.001). A second biochemical measure of hemolysis, the serum level of aspartate aminotransferase, also showed significant improvement with eculizumab, as compared with placebo (data not shown).

The reduction in intravascular hemolysis in the eculizumab group resulted in an increase in PNH type III erythrocytes (Fig. 1B) from a mean of 28.1±2.0% at baseline to 56.9±3.6% at week 26. The proportion of PNH type III erythrocytes in patients in the placebo group remained constant (35.7±2.8% before treatment and 35.5±2.8% at 26 weeks, P<0.001 for the comparison with the eculizumab group and the placebo group). The proportion of PNH type III granulocytes and monocytes did not change significantly between the two groups (data not shown).

CLINICAL EFFICACY

Primary End Points

The two primary efficacy end points were the stabilization of hemoglobin levels and the number of units of packed red cells transfused. At the end of the treatment period, 49% of patients in the eculizumab group (21 of 43) had levels of hemoglobin that remained above the prespecified set point (median, 7.7 g per deciliter for both groups) in the absence of transfusions, whereas stabilization of hemoglobin levels did not occur in any patient in the placebo group (P<0.001) (Table 2). By week 26, the median number of units of packed red cells transfused per patient was 0 in the eculizumab group and 10 in the placebo group (P<0.001), whereas the mean number of units of packed red cells transfused was 3.0±0.7 and 11.0±0.8, respectively. In the 6-month period before the study, the median number of units of packed red cells transfused per patient was 9.0 in the eculizumab cohort and 8.5 in the placebo cohort, and the mean number of units of packed red cells transfused was 9.6±0.6 and 9.7±0.7, respectively. The mean hemoglobin levels changed from 10.0±0.2 g per deciliter and 9.7±0.2 g per deciliter in the eculizumab group and the placebo group, respectively, at baseline to 10.1±0.2 g per deciliter and 8.9±0.2 g per deciliter, respectively, at week 26 (P<0.001, by mixed-model analysis).

The median time to the first transfusion was significantly longer in eculizumab-treated patients than in patients who received placebo (P<0.001) (Fig. 2). Transfusion independence was achieved in 51% of patients in the eculizumab group (22 of 43) and 0% of those in the placebo group (0 of 44, P<0.001). By week 26, the total number of units of packed red cells transfused was 131 in the eculizumab group and 482 in the placebo group (Table 2). By contrast, during the 6 months before the study, the total number of units transfused was 413 in the eculizumab group and 417 in the placebo group.

Table 2. Stabilization of Hemoglobin Levels and the Number of Units of Packed Red Cells Transfused during Treatment.*

Primary End Point	Before Treatment†		During Treatment		P Value
	Placebo Group	Eculizumab Group	Placebo Group	Eculizumab Group	
Patients with stabilized hemoglobin levels (%)	NA	NA	0	49	<0.001‡
Packed red cells transfused (units/patient)					
Median	8.5	9.0	10	0	<0.001§
Interquartile range	7–12.5	6–12	6–16	0–6	
Mean	9.7±0.7	9.6±0.6	11.0±0.8	3.0±0.7	
Total	417	413	482	131	

* Plus–minus values are means ±SE. NA denotes not applicable.
† Transfusion data obtained during 12 months before treatment were normalized to a value equivalent to the value for a 6-month period.
‡ The P value is for the comparison between groups during treatment, calculated with the use of a two-tailed Fisher's exact test.
§ The P value is for the comparison between groups during treatment, calculated with the use of the Wilcoxon rank-sum test.

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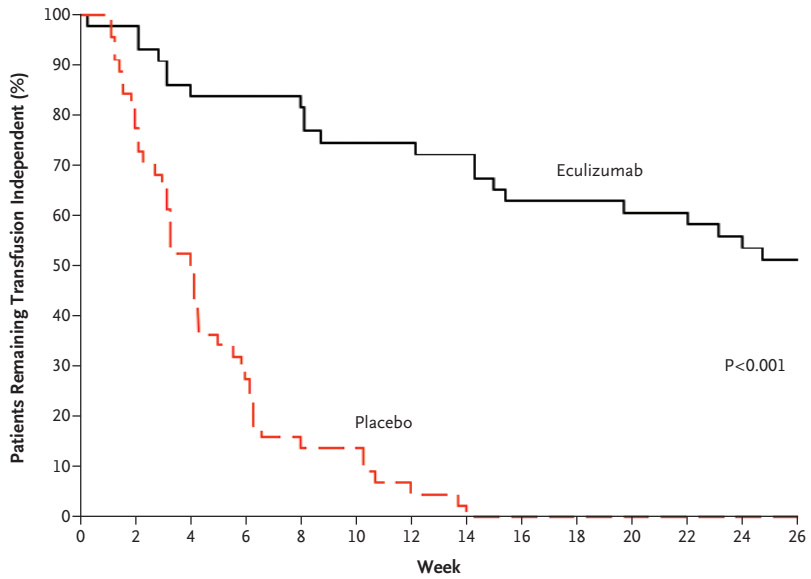

No. at Risk

Placebo group	44	44	36	30	23	13	7	6	3	1	0	0	0	0	0
Eculizumab group	43	41	41	39	37	36	36	32	32	31	27	27	26	26	24	22

Figure 2. Kaplan–Meier Curves for the Time to the First Transfusion during Treatment.
The P value for the comparison of times to the first transfusion between the two groups was calculated by the log-rank test.

Quality of Life

Assessments of the quality of life were performed with the use of two instruments, the FACIT-Fatigue instrument and the EORTC QLQ-C30 instrument. Patients in the eculizumab group had a mean increase (improvement) in scores on the FACIT-Fatigue instrument of 6.4±1.2 points from baseline to week 26, whereas in the placebo group the mean score decreased by 4.0±1.7 points during this period, for a total difference between the two groups of 10.4 points (Fig. 3). A mixed-model analysis of covariance was performed that showed a significant difference between the two groups (P<0.001).

With respect to the EORTC QLQ-C30 instrument, the eculizumab group had significant improvements in scores on the scale for global health status, on all five scales for functioning, on two of three symptom scales, and on three of six single-item measures, as compared with the placebo group (P≤0.01 for each scale and measure) (Table 3).

SAFETY

No patients died during the study. Serious adverse events were reported in 13 patients: 4 in the eculizumab group and 9 in the placebo group (Table 4). No serious adverse events were considered to be treatment-related; all these patients recovered without sequelae. The most common adverse events reported in the eculizumab group were headache, nasopharyngitis, back pain, and nausea. Headache and back pain occurred more frequently in the eculizumab group than in the placebo group. The number of headaches that occurred was similar in the two groups after the first 2 weeks of therapy. There were no significant differences in the incidence rates between the two groups for any reported adverse event. A single thrombosis occurred in a patient in the placebo group.

One patient in each of the two groups had detectable levels of antibodies against eculizumab. The levels were low, were detected at a single visit, and in the patient receiving eculizumab, the antibodies did not affect complement inhibition.

DISCUSSION

Patients with PNH have chronic intravascular hemolysis with acute exacerbations. Anemia and the

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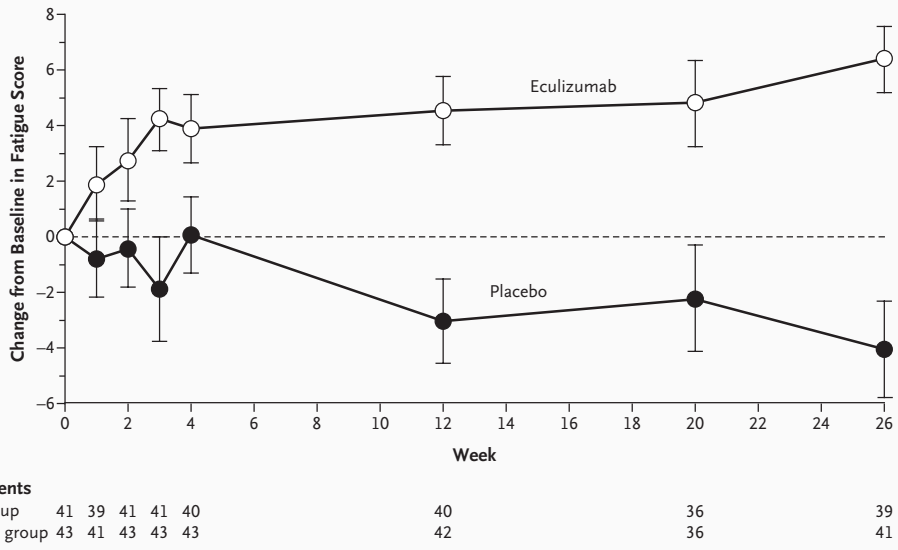

Figure 3. Change in Fatigue Scores from Baseline to Week 26.

Week 0 (baseline) represents the end of the observation period, within 10 days after the patient's receipt of the qualifying blood transfusion. Fatigue scores are therefore higher (indicating less fatigue) at week 0 than at the initial screening visits (data not shown). Values for the change from baseline (dashed line) represent means. A positive change from baseline indicates an improvement in fatigue and a negative change from baseline indicates a worsening in fatigue. I bars indicate the standard error.

need for transfusions to sustain hemoglobin levels occur frequently, as does deterioration of the patient's quality of life. In this study, in approximately half the patients treated with eculizumab, the end points of stabilization of hemoglobin levels and transfusion independence were reached, whereas none of the patients in the placebo group reached either of these end points. The median time to the first transfusion was 4 weeks in the placebo group and more than 6 months in the eculizumab group. The overall rate of transfusion was reduced by 73% in the eculizumab group. Even among patients receiving eculizumab in whom transfusion independence was not reached, the number of units of packed red cells transfused was reduced by 44%, as compared with patients in the placebo group (data not shown).

Intravascular hemolysis is central to the occurrence of serious coexisting conditions in patients with PNH and contributes to the risk of death among these patients.[9,12] Lactate dehydrogenase, a biochemical marker of hemolysis, was immediately reduced from approximately 10 times the upper limit of the normal range to normal levels or to just above normal levels in all patients in the eculizumab group. Residual low-level hemolysis in some patients despite terminal-complement blockade may be caused by an inherent decrease in the survival of PNH type III erythrocytes[19] or may be due to the fact that these cells are opsonized with C3b, which mediates extravascular clearance through the reticuloendothelial system.

Before treatment with eculizumab, the hemoglobin levels were maintained by transfusion. Therefore, the stabilization of hemoglobin levels with a concomitant cessation of or reduction in the number of transfusions indicates an increase in endogenous erythrocyte mass. The reduction in hemolysis with eculizumab results in a new steady-state hemoglobin level, as determined by a balance of the underlying bone marrow dysfunction, the increased half-life of PNH erythrocytes because of eculizumab therapy, and the new level of transfusions (if any) required.

For most patients with PNH, the quality of life is impaired, and the impairment has been attributed not only to anemia but also to excessive in-

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Table 3. Change in the Quality of Life during Treatment.*

Scale	Mean Change in Score from Baseline to Week 26†		Absolute Difference	P Value‡
	Placebo Group	Eculizumab Group		
Global health status scale	−8.5	10.9	19.4	<0.001
Functioning scales				
Role	−6.9	17.9	24.8	<0.001
Social	2.0	16.7	14.7	0.003
Cognitive	−6.1	7.9	14.0	0.002
Physical	−3.5	9.4	12.9	<0.001
Emotional	−3.7	7.5	11.2	0.008
Symptom scales				
Fatigue	10.0	−16.9	26.9	<0.001
Pain	5.3	−12.3	17.6	0.002
Nausea and vomiting	2.8	−0.4	3.2	0.06
Single-item measures				
Dyspnea	8.9	−7.9	16.8	<0.001
Loss of appetite	3.3	−10.3	13.6	<0.001
Insomnia	4.9	−7.9	12.8	0.01
Financial difficulties	0.0	−10.3	10.3	0.19
Constipation	0.0	−6.3	6.3	0.20
Diarrhea	5.7	4.8	0.9	0.15

* The quality of life was assessed with the EORTC QLQ-C30 instrument.
† A positive value for a score on the scales for global health status and functioning indicates improvement, whereas a negative value for a score on the symptom scales and for a score on the single-item measures indicates improvement.
‡ P values are from a mixed model, with baseline scores as the covariate, treatment and time as fixed effects, and the patient identifier as a random effect.

travascular hemolysis and the scavenging of nitric oxide by cell-free hemoglobin.[9-11] In this study, the reduction in intravascular hemolysis with eculizumab, as compared with placebo, was associated with a significant improvement in fatigue, as assessed by scores on the FACIT-Fatigue instrument. Eculizumab increased the baseline score for fatigue by 6.4 points. A change of three or more points in scores on this instrument represents a clinically important difference.[20] Improvement with eculizumab in the fatigue component of the EORTC QLQ-C30 instrument provides additional evidence for the benefit shown by scores on the FACIT-Fatigue instrument. These improvements with eculizumab occurred without complete resolution of the anemia, providing further evidence of the contribution of hemolysis, in contrast to anemia, to the diminishing quality of life of patients with PNH. Clinical assessment of additional symptoms related to the quality of life of such patients, including abdominal pain, dysphagia, and erectile dysfunction, have also been reported to improve during eculizumab therapy.[21]

There were no deaths during the study, and only a single thrombotic event occurred in a patient in the placebo group. There were four serious adverse events in the eculizumab group and nine in the placebo group; all these patients recovered. The issue of possible protection against the risk of thrombosis through terminal complement inhibition with eculizumab is being evaluated in ongoing clinical studies of PNH. All 85 patients who completed the study elected to receive eculizumab in an open-label extension study.

The results of this randomized, double-blind, controlled study show that terminal complement inhibition with eculizumab reduces intravascular

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Table 4. Adverse Events.*

Adverse Event	Placebo Group (N=44)	Eculizumab Group (N=43)
	no. (%)	
Total no. of serious adverse events	9 (20)	4 (9)
Exacerbation of PNH	3 (7)	1 (2)
Renal colic	0	1 (2)
Lumbar- or sacral-disk prolapse	0	1 (2)
α-Hemolytic streptococcal bacteremia	0	1 (2)
Central-line and urinary tract infections	1 (2)	0
Upper respiratory tract infection	1 (2)	0
Probable viral infection	1 (2)	0
Neutropenia	1 (2)	0
Cellulitis, folliculitis, and neutropenia	1 (2)	0
Anemia and pyrexia	1 (2)	0
Most frequent adverse events†		
Headache‡	12 (27)	19 (44)
Nasopharyngitis	8 (18)	10 (23)
Upper respiratory tract infection	10 (23)	6 (14)
Back pain	4 (9)	8 (19)
Nausea	5 (11)	7 (16)
Cough	4 (9)	5 (12)
Diarrhea	5 (11)	4 (9)
Arthralgia	5 (11)	3 (7)
Abdominal pain	5 (11)	2 (5)
Dizziness	5 (11)	2 (5)
Vomiting	5 (11)	2 (5)
Fatigue	1 (2)	5 (12)
Viral infection	5 (11)	1 (2)

* Adverse events were coded with the use of preferred terms from the MedDRA.
† The event occurred in at least 10% of patients in either group.
‡ After the first 2 weeks of treatment, 10 patients (23%) receiving placebo and 9 patients (21%) receiving eculizumab had headache.

hemolysis, reduces or eliminates the need for transfusion, and improves anemia, fatigue, and the quality of life in patients with PNH. The data provide support for the central role of intravascular hemolysis in the pathogenesis of the disease and indicate that eculizumab is an effective treatment in patients with PNH.

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APPENDIX

In addition to the authors, the following investigators and institutions participated in the TRIUMPH study: **Australia** — Princess Alexandra Hospital, Woolloongabba: A. Mills; Queen Elizabeth Hospital, Woodville South: J. Norman; Royal Melbourne Hospital, Parkville; Royal Perth Hospital, Perth, WA: R. Herrmann; **Belgium** — St. Luc University Hospital, UCL, Brussels: E. Van Den Neste; **Canada** — University of Alberta, Cross Cancer Institute, Edmonton, AB.: L. Larratt, A. Turner, M.A. Hamilton; **Germany** — Universitätsklinikum Essen, Essen: U. Dührsen; Medizinische Hochschule Hanover, Hanover: A. Ganser; Universitätsklinik Greifswald, Greifswald: M. Montemurro; Institut für Klinische Transfusionsmedizin and Immungenetik, University Hospital Ulm, Ulm; Saarland University Medical School, Hamburg; **France** — Hospital de l'Hotel-Dieu, Paris: B. Rio; Hospital St. Louis and INSERM, Paris; **Ireland** — St. James Hospital, Dublin; **Italy** — Ospedale San Martino, Genoa: A. Bacigalupo; Azienda-Ospedaliera Universitaria Careggi, Florence: E. Antonioli, G. Gianfaldoni, F. Mannelli, A. Bosi; Ospedale San Bortolo, Vicenza: F. Rodeghiero; Federico II University, Naples: B. Rotoli, F. Alfinito; Ospedale Maggiore di Milano, Milan: A. Zanella, C. Boschetti; Istituto Toscana Tumori, Florence; **the Netherlands** — Radboud University Medical Center, Nijmegen; **Sweden** — Lund University Hospital, Lund: P.-G. Nillson; Umea University Hospital, Umea: A. Wahlin; Stockholm South Hospital, Stockholm: J. Samuelsson, L.G. Lundberg, P. Andersson; **United Kingdom** — St. George's Hospital, London; Leeds General Infirmary, Leeds; Belfast City Hospital, Belfast: M.F. McMullin; **United States** — Washington University School of Medicine, St. Louis: M. Bessler, L. Andritsos, M. Blinder, S. Devine; Johns Hopkins University Medical Center, Baltimore; Memorial Sloan-Kettering Cancer Center, New York: H. Castro-Malaspina, D. Araten; Stanford University Medical Center, Stanford, CA: S. Coutre; Duke University Medical Center, Durham, NC: C. de Castro III; Cleveland Clinic Florida, Weston, FL: E. Stone; University of Pennsylvania, Philadelphia: B. Konkle; Massachusetts General Hospital, Boston: D. Kuter; Cleveland Clinic Foundation, Cleveland: A. Lichtin; New York University Clinical Cancer Center, New York: T. Moskovits, B.G. Raphael, E. Amorosi, K.B. Hymes, P. Cook; City of Hope National Medical Center, Duarte, CA; Indiana University Cancer Center, Indianapolis: R. Nelson; University of California at Los Angeles, Los Angeles: R. Paquette; Hartford Hospital, Hartford, CT: R. Siegel; National Heart, Lung, and Blood Institute, Bethesda, MD: B. Savani.

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