Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival
Journal Club 6-26-20XX
Amber Schilling, PharmD

BACKGROUND	
• Background	• Paroxysmal nocturnal hemoglobinuria (PNH) is a rare type of hemolytic anemia that is caused by intravascular RBC destruction by complement. It usually (but not always) manifests itself as dark-colored urine passed in the morning from the accumulation of hemoglobin-laden urine in the bladder over the course of the night. • PNH is caused by an acquired defect (somatic / non-inherited / non-genetic) that results in clonal expansion of hematopoietic stem cells with a mutation in one of the genes responsible for biosynthesis of glycophosphatidylinositol (GPI). GPI is a glycolipid needed on the surface of RBCs to anchor CD55 and CD59 – proteins that serve a regulatory / inhibitory role in the complement cascade and serve to protect the cells from complement attack. Without CD55 and CD59, a hemolytic anemia ensues. The disorder affects RBCs, WBCs, and platelets. • Although the hemolysis in PNH is chronic and often requires blood transfusions on a regular basis, it is also paroxysmal in nature because it is punctuated by exacerbations where symptoms become more severe. • The Hb released during the hemolysis binds with circulating nitric oxide (NO), rendering it unable to function as a smooth muscle relaxant. Reduced nitric oxide can result in some of the other symptoms of the disease: dysphagia, abdominal pain, pulmonary HTN, and erectile dysfunction. • Other notable symptoms of PNH include thrombosis and renal impairment. • The median age at diagnosis is the early 30s. The median survival is 10-15 years from the time of diagnosis, with thromboembolism accounting for 40% of PNH deaths. Warfarin has routinely been used as prophylaxis in these patients. • Historically, the only curative treatment has been an allogenic bone marrow transplant. • Eculizumab is a humanized monoclonal antibody that binds to and inhibits C5, thus preventing the final stages of the complement cascade and potentially protecting RBCs in PNH patients from hemolysis.
STUDY OVERVIEW	
• Title/Citation	• Kelly RJ, Hill A, et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. Blood 2011; 117(25): 6786-6792.
• Funding	• National Health Service, either via central commissioning in England or local funding in Wales or Scotland
• Study Dates	• May 2002 – July 2010 • 7 years prior to eculizumab's availability (retrospectively used as the control group for comparison) ➢ Q: Approved / licensed by FDA in March 2007 and European Medicines Agency in June 2007, but this study began in 2002; so what does "7 years prior" mean?
• Objectives	• To gain additional data regarding eculizumab's ability to: ➢ improve survival in patients with paroxysmal nocturnal hemaglobinuria (PNH) ➢ provide a sustained improvement of symptoms in patients with PNH
METHODS	
• Inclusion Criteria	• Diagnosis of PNH, as established or confirmed using multicolor flow cytometery of the patient's erythrocytes and granulocytes • Meeting of the nationally-commissioned (England?) indications for treatment with eculizumab: ➢ Transfusion-dependent hemolysis (4 or more transfusions in 12 months) ➢ A significant PNH-related complication (i.e., thrombosis or renal failure), regardless of transfusion history • Control groups: ➢ Age- and sex-matched survival averages from the 2001 UK census data ➢ 30 PNH patients treated at Leeds Hospital prior to eculizumab availability (between 1997-2004) who fulfilled the criteria for treatment with eculizumab (see above) ➢ The PNH patients themselves – pre and post-eculizumab treatment
• Exclusion Criteria	---
• Interventions	• Treatment with eculizumab, according to the following dosing schedule: ➢ 600-mg IV infusion (>30 mins) once a week, for 4 doses ➢ 900-mg IV infusion for 5th dose ➢ 900-mg dose given every 14 days (+/- 2 days) indefinitely, unless the patient experienced "break-through" symptoms (red or black urine, abdominal discomfort, increased LDH levels immediately prior to scheduled dose) ➢ If "break-through" symptoms, then higher doses (1200 or 1500 mg) given q14 days • Vaccination with tetravalent meningococcal vaccine (Serogroups A, C, W, and Y) due to complement being important in fending off infection with *Neisseria meningitidis*. ➢ Antibiotic prophylaxis was included in addition to vacccine, beginning in January 2010, to also cover Serogroup B

	○ Penicillin V, 500 mg, BID –OR– ○ Erythromycin 500 mg, BID (for PCN-allergic)
• Major Outcomes	• Outcomes (it doesn't specify which are primary and which are secondary): ➢ survival rates ➢ transfusion requirements ➢ thrombotic events ➢ platelet counts • Pts assessed at start of treatment w/ eculizumab for the following: ➢ Presenting features of their PNH (hemoglobinuria, abdominal pain, dysphagia, thrombosis, anemia) ➢ LDH levels ➢ Neutrophil, platelet, and reticulocyte count ➢ PNH clone sizes • Pts assessed q12 weeks during treatment w/ eculizumab for the following: ➢ multicolor flow cytometry of erythrocytes and granulocytes ➢ occurrence of thrombosis ➢ blood transfusions needed ➢ LDH levels ➢ Cause and date of death, if applicable
• Statistical Analysis	• Survival rates: ➢ Kaplan-Meier method used to generate survival curves ➢ Log-rank test used to evaluate statistical significance between groups ➢ Patient survival on eculizumab compared with age- and sex-matched averages from 2001 UK census data ➢ Time-dependent Cox regression model used to compare treated and untreated patients with PNH • Transfusion requirements: ➢ Wilcoxon signed rank-sum test used to compare patients' transfusion requirements in the 12 months prior to receiving eculizumab versus past 12 months of treatment ➢ If patients had not reached transfusion independence by taking eculizumab, they were further analyzed using a paired t test to determine if the difference in number of transfusions they were requiring before and since treatment was statistically significant • Thrombotic event rates: ➢ Wilcoxon signed rank-sum test used to compare occurrence of thrombosis before and after starting eculizumab treatment ➢ Means calculated as number of thrombotic events per year • Platelet counts: ➢ Paired t test used to compare platelet counts at start of eculizumab treatment with those after 12 months of treatment
RESULTS	
• Enrollment	• A total of 79 patients with PNH were treated with eculizumab at Leeds Teaching Hospitals during the study period. • 4 of the 79 patients did not meet the inclusion criteria, but were included as exceptions because of "profound symptoms"
• Study Results	• Avg duration of treatment of eculizumab was 39 months (3.3 years) • 2 patients stopped eculizumab treatment before the end of the study date (1 due to spontaneous remission of PNH and 1 due to predominant aplastic anemia). • 74 pts received a maintenance dose of 900 mg q14 days; 4 pts received a maintenance dose of 1200 mg q 14 days; 1 received a maintenance dose of 1500 mg q 14 days. • 3 pts died while on eculizumab, all from causes unrelated to their PNH (i.e., metastatic colon cancer, pneumonia, CHF) • Survival rates: ➢ Survival rates of those treated showed no significant difference compared to age- and sex-matched averages from UK population census (p=0.46) ➢ Survival rates of those treated were significantly better than the 30 patients managed before eculizumab became available (p=0.03, hazard ratio=0.21). ○ 5-yr survival rate of untreated PNH pts = 66.8% (CI=95%) ○ 5-yr survival rate of treated PNH pts = 95.5% (CI=95%) ➢ No deaths in the 45 patients beginning eculizumab under the age of 50yo. • Transfusion requirements: ➢ Transfusion requirements were compared for 12 months before eculizumab with most recent 12 months on therapy ○ Mean number of units of blood transfused fell from 19.3 units to 5.0 units (a 74% drop, p<0.001)

	➢ 61/75 patients were transfusion-dependent prior to beginning therapy ○ 40/61 became transfusion independent after receiving eculizumab (66%) ○ The remaining 21 experienced a significant reduction in the # of transfusions needed (p=0.028). Mean number of units needed dropped from 24.6 units to 14.6 units. • Thrombotic event rates: ➢ Rate of thrombotic events before eculizumab was **5.6** events/100 patient-years versus **0.8** events/100 patient-years while on eculizumab (p<0.001) ➢ 46/79 pts were receiving anticoagulation treatment at time of starting eculizumab; warfarin was able to be stopped in 21 of those pts after receiving eculizumab. However, patients who had a previous history of thrombotic events were NOT stopped on their anticoagulation regimens. ➢ Anticoagulation in pts on eculizumab has been stopped for a mean duration of 10.8 months since publication of the article, with no thrombotic events occurring as a result of the d/c. ➢ 2 pts had a thrombotic event while on eculizumab. The first had a stroke before starting eculizumab; the second was on hemodialysis for end-stage renal failure • Platelet counts: ➢ No overall difference observed in platelet counts before and after treatment
AUTHORS' CONCLUSIONS	
• Eculizumab improves survival and major symptoms of PNH. Survival was improved to such an extent as to mirror survival rates within the general population. • There may be an even greater improvement in patients who are treated with eculizumab for a period of 12 months or longer (done in this study), as opposed to the 6-month treatment period utilized in other clinical trials. • Eculizumab did not appear to effect occurrence of myelodysplasia (MDS) or acute myeloid leukemia (rare developments of PNH patients).	
IMPRESSION	
• This study produced very promising results, but the sample size was limited due to the rarity of the disease state, affecting only about 1 to 5 in 1 million. Thus, the true test of eculizumab's safety and efficacy will be when it gets out into the broader population and given time to affect a larger subset of patients.	