3472

Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (PNH): A Report of All 153 Patients Treated in the United Kingdom 10-Year Experience

Anita Hill, MBChB, PhD,[1] Richard J. Kelly, MBChB,[1] Austin G. Kulasekararaj, MBBS, MD,[2] Shreyans A. Gandhi, MBBS, MD,[2] Lindsay D. Mitchell, MBChB,[3] Modupe Elebute, MBChB, MD,[2] Stephen John Richards, PhD,[1] Matthew Cullen, MSc,[1] Louise M. Arnold, RN, BSc,[1] Joanna Large, RN, BSc,[2] Alexandra Wood, RN, BSc,[1] Gemma L. Brooksbank, RN, BSc,[1] Tracy Downing,[1] Claire McKinley, BSc,[1] Dena Cohen, BSc, MSc,[4] Walter M. Gregory, PhD,[4] Judith C. W. Marsh, MD, PhD,[2] Ghulam J. Mufti, MD,[2] Peter Hillmen, MBChB, PhD[1]

[1]Department of Haematology, St. James's University Hospital, Leeds, UK; [2]Department of Haematological Medicine, King's College Hospital, London, UK; [3]Department of Haematology, Monklands Hospital, UK; [4]Clinical Trials Research Unit, University of Leeds, Leeds, UK

PNH National Service

INTRODUCTION

- Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem-cell disorder arising on the background of bone marrow failure.
- PNH can result in hemolytic anemia, thromboembolism (TE), pulmonary hypertension (PHT) and chronic kidney disease (CKD) through uncontrolled complement activation.
- Despite transfusion and anticoagulation, approximately half of PNH patients die as a result of their PNH within 10 years.
- The terminal complement inhibitor eculizumab has previously been shown to rapidly and significantly reduce intravascular hemolysis, leading to a reduction in TE and PHT and improvements in CKD, quality of life and survival.
  - Long-term eculizumab therapy has been well tolerated by PNH patients.

OBJECTIVE

- Describe the long-term safety, efficacy and outcomes in all patients with PNH from the UK who received eculizumab treatment from May 2002 to April 2012.

METHODS

- The UK has a nationally commissioned PNH service, led by the Leeds and King's centers.
- All UK PNH patients were assessed for long-term safety and efficacy.
- PNH patients were treated with eculizumab if they had:
  - Transfusion-dependent hemolysis *or*
  - Any of the following (independent of transfusions):
    - TE *or*
    - CKD *or*
    - PHT *or*
    - Pregnancy *or*
    - Lactate dehydrogenase (LDH) >1.5 times the upper limit of normal (ULN) with anemia and symptoms such as fatigue, dysphagia, dyspnea, or abdominal pain due to PNH

RESULTS

Baseline Demographics

- Between May 2002 and April 2012, 153 patients were treated with eculizumab for PNH in the UK.

Table 1. Patient Characteristics at Study Baseline

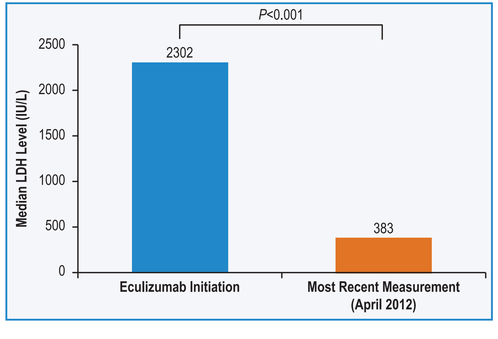
Characteristic	N=153
Female, n (%)	77 (50.3)
Median age at diagnosis, years (range)	34 (12–80)
Median age at commencement of eculizumab, years (range)	42 (14–84)
Concomitant immunosuppression, n (%)	25 (16.3)
Concomitant anticoagulation, n (%)	93 (60.8)
LDH level, IU/L (range)	2302 (151–10300)[a]

[a]Normal <430 IU/L. IU=international units.

Effect of Eculizumab on Intravascular Hemolysis

- Between the initiation of eculizumab therapy and April 2012, intravascular hemolysis, as assessed by levels of LDH, was reduced by 83.4% (*P*<0.001; Figure 1).

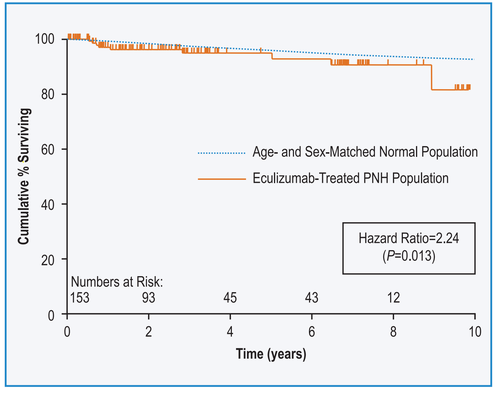
Figure 1. Long-term Eculizumab Reduced Intravascular Hemolysis



Survival with Long-term Eculizumab Treatment

- The survival of UK PNH patients on eculizumab was compared with age- and sex-matched controls (Figure 2).
- Survival of PNH patients after 10 years of eculizumab treatment was slightly inferior to controls, and causes of death were either unrelated to hematologic conditions or related to the underlying bone marrow failure and not due to hemolysis or TE associated with the underlying PNH.
  - No causes of death were related to PNH.
- UK PNH patients on eculizumab had improved survival as compared with historical controls in previously published accounts.

Figure 2. Kaplan-Meier Survival Plot for UK PNH Patients on Eculizumab Compared with Age- and Sex-Matched Controls

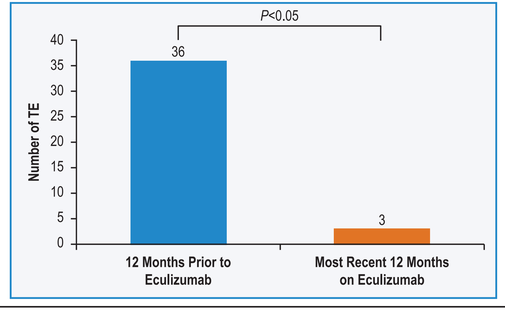


- As of April 2012, 9 PNH patients on eculizumab (5.9%) have died.
  - 3 patients (2.0%) have died because of progression of their underlying bone marrow failure to myelodysplastic syndrome/acute myelogenous leukemia.
  - 1 patient (0.7%) has died of veno-occlusive disease immediately after bone marrow transplant.
  - 5 patient deaths (3.3%) were not directly related to PNH.

Reduction in TEs with Sustained Eculizumab Therapy

- 22 patients (14.4%) reported 36 TEs in the 12 months prior to eculizumab therapy (Figure 3).

Figure 3. Reduction in TE with Long-term Eculizumab Therapy



- In the most recent 12 months on therapy, TEs were significantly reduced, to 3 events in 3 patients (2.0%; *P*<0.05; Figure 3).
  - 1 patient developed a Budd-Chiari TE during complement blockade breakthrough caused by an infection.
  - 1 patient suffered from a cerebrovascular accident during reversal of warfarin overanticoagulation.
  - 1 patient developed transient ischemic attack/lacunar infarct, which was thought to be due to diabetic small vessel disease.
- None of the 22 patients who had a TE in the 12 months prior to starting eculizumab experienced any further TEs once on eculizumab therapy.

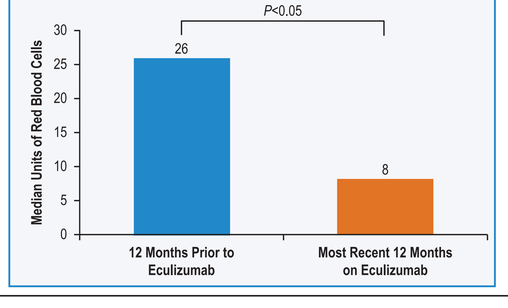
Effect of Discontinuing Anticoagulation in PNH Patients on Eculizumab Therapy

- 15 of 65 patients (23.1%) who were receiving anticoagulation therapy prior to the initiation of eculizumab experienced TEs, and together these 15 patients reported 28 TEs.
- Primary prophylaxis with warfarin was discontinued in 43 of 50 patients (86.0%) on anticoagulation therapy.
- Secondary prophylaxis was discontinued in 4 of 50 patients (8.0%) due to the risk of bleeding from varices and/or thrombocytopenia.
  - No thrombotic sequelae have been reported in these patients since discontinuation of anticoagulation.

Reduction of Transfusion Requirements with Long-term Eculizumab Therapy

- 10 patients were transfusion-free before receiving eculizumab.
- 117 patients were transfused in the 12 months before receiving eculizumab and were on therapy for the most recent 12 months.
  - Of these 117 patients, 77 (65.8%) became transfusion independent.
- Among those patients still requiring transfusions (n=40), there was a significant reduction in the number of units transfused, from a median of 26 units 12 months before therapy to 8 units in the most recent 12 months on therapy (*P*<0.05; Figure 4).

Figure 4. Reduction in Transfusion Requirements with Long-term Eculizumab Therapy for Patients Who Remained Transfusion Dependent (n=40)



Safety of Long-term Eculizumab

- In the 153 patients treated throughout the 10-year period (137 patients on drug at year 10), 3 cases of meningococcal septicemia were reported (0.6 cases per 100 patient-years on therapy).
  - All cases were managed promptly and effectively, and all patients remain on eculizumab therapy and are doing well.
- 137 patients were still on treatment as of April 2012.
  - 7 of the surviving 144 patients discontinued eculizumab therapy.
    - 1 patient discontinued due to predominant aplastic anemia.
    - 2 patients had spontaneous remissions of PNH clone during eculizumab treatment.
    - 3 patients were treated for the indication of pregnancy alone (with 1 patient subsequently restarting therapy).
    - 1 patient underwent successful transplant for very severe aplastic anemia.

CONCLUSIONS

- The UK PNH service now has more than 10 years of experience managing PNH with eculizumab.
- The results from this UK PNH patient cohort demonstrate that the significant clinical benefits and long-term safety of eculizumab were sustained over 10 years of treatment.
- Long-term eculizumab treatment led to:
  - Significant improvement in survival,
  - A significant reduction in the incidence of TE,
  - Safe discontinuation of primary anticoagulation,
  - Persistent and significant improvement in symptoms and quality of life, with no evidence of intolerance or refractoriness,
  - Transfusion independence in the majority of patients and significant reductions in the number of units transfused for those still requiring transfusions.
- These results confirm the long-term safety and efficacy of continuous eculizumab treatment and demonstrate the impact of eculizumab on quality of life, reduction in PNH-related morbidities and improved survival for PNH patients.

DISCLOSURES

Drs. Hill and Kelly have been consultants for and have received honoraria from Alexion Pharmaceuticals. Dr. Gandhi has received research funding from Alexion Pharmaceuticals. Drs. Mitchell, Arnold and Marsh have received honoraria from Alexion Pharmaceuticals. Dr. Elebute has been a consultant for and has received honoraria and research funding from Alexion Pharmaceuticals. Dr. Hillmen has been a consultant for, has received honoraria from and has served on an advisory committee for Alexion Pharmaceuticals.

Presented at the 54th Annual Meeting of the American Society of Hematology
December 8–11, 2012, Atlanta, Georgia, USA