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Research Article

Ten Years of Clinical Experience With Eculizumab in Patients With Paroxysmal Nocturnal Hemoglobinuria

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ABSTRACT

Paroxysmal nocturnal hemoglobinuria (PNH) arises from a somatic mutation in the phosphatidylinositol glycan class A, X-linked gene, responsible for a deficiency in glycosyl phosphatidylinositol-anchored proteins. The absence of one of the glycosyl phosphatidylinositol-anchored protein complement regulatory proteins (CD59) leads to hemolysis. Clinical manifestations include chronic hemolysis, thromboembolic disease, infectious complications, chronic kidney injury, pulmonary hypertension, and smooth muscle dysfunction. Until 10 years ago, treatment was mainly supportive, with most patients suffering from significant morbidity and shortened survival compared with age-matched controls. The development of eculizumab, a humanized monoclonal antibody directed against the terminal complement protein C5, has led to dramatic improvements in survival and reduced complications. In this article, we review 10 years of clinical experience with eculizumab in PNH along with specific related situations. Extravascular hemolysis and the use of eculizumab in pregnant patients with PNH are also addressed.

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired hematopoietic stem cell disorder, diagnosed by hemolytic anemia, marrow failure, or episodes of venous thrombosis [1]. PNH arises from a somatic mutation in the phosphatidylinositol glycan class A, X-linked gene, responsible for a deficiency in glycosyl phosphatidylinositol-anchored proteins [2]. The absence of one of the glycosyl phosphatidylinositol-anchored protein complement regulatory proteins (CD59) leads to hemolysis [3]. From earlier descriptions, the clinical polymorphism of PNH has been identified by the 2 following presentations: one form, predominantly hemolytic without overt marrow failure, referred to as classic PNH [1]; and another, with marrow failure, often described as aplastic anemia PNH syndrome (AA-PNH) [4]. Before specific therapy became available, PNH resulted in the death of approximately half of affected individuals, mainly through thrombotic complications, with a particularly grim prognosis for patients presenting with classic PNH [5].

Eculizumab is a humanized monoclonal antibody that specifically binds to the human C5 complement protein and prevents its cleavage to C5a and C5b, thereby preventing formation of the membrane attack complex [6]. Eculizumab is an IgG kappa immunoglobulin with an engineered Fc portion that is a hybrid of IgG2 and IgG4 designed to have no downstream activity—eculizumab is therefore a purely "blocking" antibody that prevents cleavage and thus activation of C5. Eculizumab remains bound to the target until the complex is removed from the circulation [6]. Eculizumab revolutionized the management of PNH patients by efficiently blocking intravascular hemolysis, thereby drastically reducing transfusion requirements, leading to better quality of life, lower thrombosis occurrence, and improved overall survival. In this article, we describe the 10 years of clinical experience with eculizumab in patients with PNH, discussing pivotal prospective clinical trials along with

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real-life studies confirming the overall benefits of complement blockade in PNH, and identify new medical situations. Extravascular hemolysis and the use of eculizumab in pregnant PNH patients are also addressed.

Eculizumab in PNH: Pivotal and Real-Life Studies

Pivotal Studies

Initial studies using eculizumab to treat auto-immune disorders were unsuccessful, but demonstrated that a concentration of 35 μg/mL in the plasma was required to maintain complement inhibition, and that eculizumab was safe (only 1 case of meningococcal infection seen in over 700 patients). Moreover, no human antihuman antibodies were identified. The dosing schedule was also defined during this time, with a loading period of 600 mg/week for 4 weeks, followed by 900 mg the fifth week, and then 900 mg every 14 days (intravenous infusion) [6].

The pilot study involved 11 transfusion-dependent hemolytic PNH patients (4 or more transfusions in the 12 months before study inclusion), treated for 3 months. After the first dose, all patients immediately experienced vastly improved quality of life, no more hemoglobinuria, and a significant fall or complete resolution of transfusion requirements, clearly confirming that the terminal complement was the principal cause of intravascular hemolysis in PNH [7].

The next study was a randomized placebo-controlled trial ("TRIUMPH"). Therapy lasted 6 months, during which patients received either eculizumab or a placebo. Again, the key inclusion criteria were transfusion-dependent hemolytic patients with PNH with no overt bone marrow failure (BMF) (platelet count $> 100 \times 10^9$ G/L). Eighty-seven patients were randomized (44 patients to eculizumab and 43 to the placebo). The composite endpoints of maintenance of hemoglobin levels above their previous set-point and a highly significant reduction in transfusion requirements were met. Moreover, the secondary endpoints demonstrated eculizumab's safety and clinical benefits, along with reduced intravascular hemolysis [8].

The next study ("SHEPHERD") was an open-label non-randomized trial for hemolytic PNH patients, but eligibility was wider, with only one prior transfusion required in the previous 2 years, whereas patients with lower platelet counts ($> 30 \times 10^9$ G/L) were also accepted. Ninety-seven patients were included, with equally impressive results to both the pilot and TRIUMPH studies [9]. Overall, 195 patients were included in the 3 trials, which all demonstrated efficacy in reducing hemolysis, stopping or lowering transfusion requirements, and improving anemia and fatigue [6].

Long-Term and Registry Studies

Kelly et al. [10] reported in 2011 on 79 patients receiving eculizumab in Leeds between May 2002 and July 2010. Survival for patients receiving eculizumab was no different to age- and sex-matched normal controls, but was significantly better than 30 similar patients treated before eculizumab became available (Fig. 1A). Three patients receiving eculizumab, all aged over 50, died of causes unrelated to PNH. Forty in 61 (66%) patients receiving eculizumab for more than 12 months achieved transfusion independence. The 12-month mean transfusion requirement fell from 19.3 units before eculizumab to 5.0 units in the most recent 12 months with eculizumab ($P < .001$). Moreover, eculizumab drastically reduced PNH-related symptoms [10].

In 2016, Loschi et al. [11] reported a retrospective study by the French reference center for AA and PNH comparing 123 patients

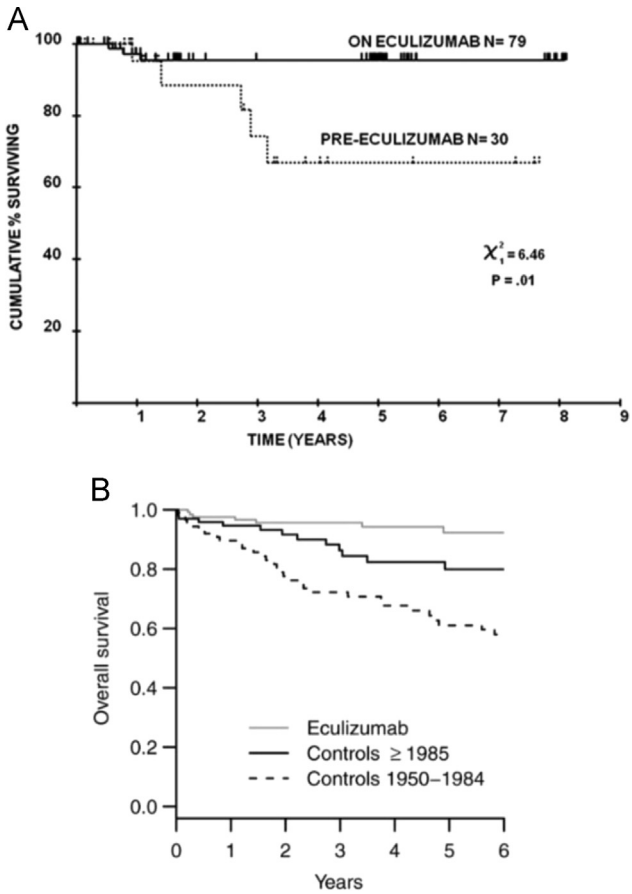

Fig. 1. (A) Overall survival of 79 patients from initiation of eculizumab treatment compared with an age- and sex-matched normal population (Kelly et al., Blood, 2011). (B) Overall survival for patients treated with eculizumab (gray line), historical controls diagnosed in 1985 or after (black line), and historical controls diagnosed before 1985 (dashed line) (Loschi et al., AJH, 2016).

recently treated with eculizumab (> 2005) and 191 historical controls (identified from the French registry [5]). Overall survival at 6 years was 92% (95% CI: 87-98) in the eculizumab cohort, versus 80% (95% CI: 70-91) in historical controls diagnosed post-1985 (hazard ratio = 0.38; 95% CI: 0.15-0.94; $P = 0.037$). For patients diagnosed in 1954-1985, overall survival was estimated to be 58% (95% CI: 48-70) (Fig. 1B). Similar rates of evolution to myelodysplastic syndrome (MDS) or acute leukemia were also seen in both patient with PNH cohorts, with or without eculizumab, showing that prolonged exposure to eculizumab was safe, at least with a median follow-up of 4.5 years [11].

Moreover, it quickly became apparent in earlier studies that eculizumab was able to play a major role in thrombosis occurrence, the major complication of PNH, confirmed by analysis combining all of the prospective trials, including the pivotal and extension studies [12]. Overall, there were 124 thrombotic events in the 195 patients before starting eculizumab, or 7.37 thromboses per 100 patient-years. Strikingly, only 3 were observed after commencing eculizumab, equating to 1.07 thromboses per 100 patient-years ($P < .0001$). In the UK retrospective study, 21 patients (27%) had a thrombosis before starting eculizumab (5.6 events per 100 patient-years) compared with 2 thromboses with eculizumab (0.8 events per 100 patient-years; $P < .001$) [10]. In the French registry study, there were also significantly fewer thrombotic events in the group of patients receiving eculizumab (4% [1-10]) compared with the historical cohort (27% [20-34]) [11].

Eculizumab has also been reported to improve renal dysfunction in PNH, with renal failure cited as at least a contributing factor