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Eculizumab in Paroxysmal Nocturnal Haemoglobinuria

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Abstract

Eculizumab is a monoclonal antibody that binds with high affinity to the complement protein C5, preventing terminal complement-mediated intravascular haemolysis in patients with paroxysmal nocturnal haemoglobinuria (PNH). In three well designed clinical trials in patients with PNH, eculizumab blocked serum haemolytic activity and decreased transfusion rates. Pooled data from the three clinical trials demonstrated that eculizumab treatment decreased the overall thromboembolism rate in patients with PNH. Eculizumab carries a black box warning for the potential increased risk of meningococcal infections and requires patients to receive the meningococcal vaccine at least 2 weeks before starting treatment. Eculizumab is the first drug to be approved by the US FDA for the treatment of PNH and is a novel treatment that offers a new option for patients with PNH.

The clinical syndrome of paroxysmal nocturnal haemoglobinuria (PNH) was first described in 1882 as haemoglobinuria after sleep.[1,2] More than 100 years later, we now know that PNH is not paroxysmal or related to sleep, but is an acquired stem cell disorder that leads to chronic haemolysis.[3,4] PNH is acquired through a haematopoietic stem cell mutation of the phosphatidylinositol glycan complementation class A gene, which is located on the X-chromosome.[5,6] An entire class of cell surface proteins, normally present on stem cells and their progeny, are lost as a result of this mutation.[3] This class of cell surface proteins is known as glycosylphosphatidylinositol (GPI)-anchored proteins and includes CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis).[3,5] Loss of CD55 and CD59 from the surface of erythrocytes in affected individuals results in haemolysis due to an inability to restrict the activation of the alternative pathway of complement[5] (see figure 1).

PNH erythrocytes are defined as either type I, II or III based on their sensitivity to complement-mediated lysis. Type I have normal expression of GPI-anchored proteins CD55 and CD59, type II are partially deficient and type III are completely deficient, making type III erythrocytes the most sensitive to complement-mediated lysis.[5]

Clinically, patients with PNH experience haemolysis with periods of acute exacerbations, cytopenia and thrombosis.[2] Common symptoms related to this haemolysis are haemoglobinuria, dysphagia, abdominal pain, erectile dysfunction and fatigue.[6] In a group of 80 patients who were followed-up for 30 years, it was found that 80% of patients had thrombocytopenia and 55% had neutropenia at the time of their diagnosis. It is also worth noting that 39% of patients had one or more epi-

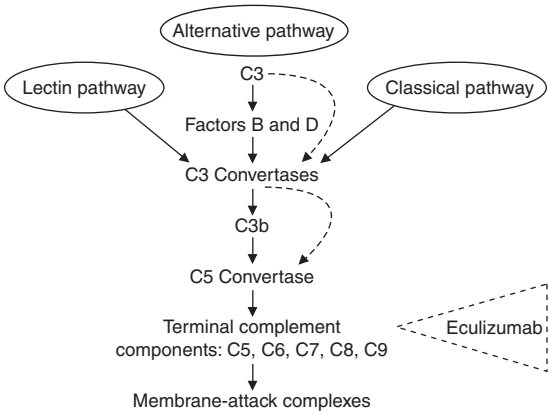

Fig. 1. Complement activation. Each of the three pathways is initiated by a specific recognition event. The alternative pathway, which is important in paroxysmal nocturnal haemoglobinuria (PNH) is always 'on' at a low level. Patients with PNH are deficient in CD55 and CD59, which are important regulators of the alternative pathway. CD55 competes with factor B and CD59 prevents formation of membrane attack complexes on autologous cells. All three pathways meet at the step of C3 activation. Eculizumab is a monoclonal antibody that prevents the formation of membrane-attack complexes by binding to the terminal complement component[3,5,7] (reproduced from Brodsky,[3] with permission).

sodes of venous thrombosis during the course of their illness.[8]

Traditionally, the options for drug treatment of PNH are limited. Corticosteroids, androgens, and iron and folate supplementation have been used. These treatments are limited by inconsistent response rates as well as unfavourable toxicity profiles.[9]

Eculizumab (Soliris™)[1] is the first drug to be approved specifically for the treatment of PNH. It received approval on 16 March 2007 from the US FDA. Since it is estimated that 1 in 1 million people are diagnosed with PNH, eculizumab is considered an orphan drug by the FDA. This gives Alexion Pharmaceuticals, Inc. a 7-year period of exclusive marketing.[10] Eculizumab has also been licenced by the European Medicines Agency for use in the EU since 20 June 2007.

Literature was obtained from MEDLINE (1966 to April 2008) and International Pharmaceutical Abstracts (1971 to April 2008) using the search terms eculizumab and Soliris™, and also from Alexion Pharmaceuticals, Inc.

1. Pharmacology of Eculizumab

1.1 Pharmacodynamics

Eculizumab is a monoclonal antibody that binds with high affinity to the complement protein C5, which ultimately prevents the assembly of the membrane attack complexes[3,11,12] (see figure 1).

Inhibition of the complement cascade at the level of C5 conserves the patient's ability to generate early components of complement, particularly C3b. These early components of complement are necessary for the opsonization of micro-organisms and clearance of immune complexes.[12]

Terminal complement-mediated intravascular haemolysis is inhibited in patients with PNH treated with eculizumab.[11]

1.2 Pharmacokinetics

Pharmacokinetic data was obtained from 40 PNH patients receiving the FDA-approved dosage regimen (see section 5).[11] A standard one-compartment model was used to determine the population pharmacokinetics in patients receiving multiple doses of eculizumab. At week 26, the mean observed peak serum concentration was 194 ± 76 μg/mL and the mean observed trough concentration was 97 ± 60 μg/mL.[11]

Studies have demonstrated that maintaining peak and trough levels of eculizumab >35 μg/mL is necessary in order to block serum haemolytic activity.[11,13,14]

The clearance of eculizumab for a 70 kg patient with PNH using the model described has been reported to be 22 mL/h with a volume of distribution of 7.7 L. The half-life was reported as 272 ± 82 hours (mean ± standard deviation).[11]

To date, no studies have been conducted to evaluate the pharmacokinetics in patients with renal or hepatic impairment, or in paediatric or geriatric patients.[11]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

2. Clinical Trials with Eculizumab

In a 12-week, open-label pilot study, the safety, pharmacokinetics, pharmacodynamics and immunogenicity of eculizumab were assessed in 11 patients.[13] Male and female subjects were eligible if they (i) were at least 18 years of age; (ii) had been diagnosed with PNH at least 6 months prior to study initiation; (iii) had a detectable GPI-deficient clone; (iv) had received at least four erythrocyte transfusions in the previous year; and (v) had negative throat cultures for *Neisseria meningitidis* and *N. gonorrhoeae*. All subjects were vaccinated against *N. meningitidis*. Patients received eculizumab on the following dosage schedule: 600 mg weekly for 4 weeks, then 900 mg 1 week later, and then 900 mg every 2 weeks until week 12.[13]

The study included six male and five female patients with a mean age of 48 years. The median duration of PNH in the 11 subjects was 8.6 years. In terms of safety, all patients completed the 12 weeks of the study with no deaths or thrombotic events. All patients reported at least one adverse event. Two serious adverse events occurred. The first was a patient hospitalized for a viral chest infection. The second was a patient who experienced nausea, vomiting and headache after the first infusion of eculizumab. The patient tolerated subsequent infusions well.[13]

Eculizumab serum concentrations remained above 35 μg/mL from 1 hour after the first infusion until the end of the 600 mg weekly infusions. Serum haemolytic activity was blocked for the entire 12 weeks in ten patients, while one patient experienced a low trough eculizumab concentration in week 12 with consequent serum haemolytic activity. Antibodies against eculizumab were not detected in any patient. Lactate dehydrogenase (LDH) levels dropped from a mean of 3111 ± 398 IU/L before initiation of the study to 594 ± 32 IU/L during the study ($p = 0.002$). Type III erythrocytes, which are highly sensitive to complement-mediated lysis, increased during the study from a mean of 36.7 ± 5.9% to 59.2 ± 8.0% at the end of the study ($p = 0.005$). There were no significant changes in PNH type III neutrophils, monocytes or platelets.[13] The mean number of transfusions per month decreased from 2.1 before initiation of the study to 0.6 at 12 weeks ($p = 0.003$). Haemoglobin did not increase significantly. Haemoglobinuria paroxysms, monitored by the patients by recording urine colour, decreased from 2.9 days per patient per month to 0.12 days ($p < 0.001$).[13] Quality of life (QOL) was significantly improved by eculizumab in the domains of global health status, physical functioning, emotional functioning, cognitive functioning, fatigue, dyspnoea and insomnia.[13]

A 12-month open-label extension of this study has been conducted. The subjects received 900 mg every 2 weeks. Two of the 11 patients received the dose every 12 days to maintain adequate complement inhibition.[14] The decreased LDH levels found during the initial 12-week study remained decreased for the extension study (3111 ± 398 IU/L before initiation of the study to 594 ± 32 IU/L after 12 weeks to 622 ± 41 IU/L after 12 months). Levels of haptoglobin, haemoglobin, bilirubin, reticulocytes and platelets did not change significantly.[14] PNH type III erythrocytes increased from 36.7 ± 5.9% before study initiation to 59.2 ± 8.0% after 12 weeks to 58.4 ± 8.5% after 12 months. PNH type II erythrocytes increased from 5.3 ± 1.4% at baseline to 13.2 ± 2.4% after 12 months ($p = 0.013$).[14] The number of haemoglobinuria paroxysms decreased from 3.0 per patient per month prior to study initiation to 0.1 after 12 weeks to 0.2 after 12 months ($p < 0.001$). Mean transfusion rates decreased from 2.1 units per patient per month prior to initiation of the study to 0.6 units after 12 weeks to 0.5 units after 12 months.[14]

During this 12-month study, no deaths or thrombotic events occurred. All patients reported at least one adverse event. One serious adverse event occurred in which a patient experienced neutropenia with extravascular haemolysis, possibly related to a viral syndrome.[14]

The TRIUMPH (Transfusion Reduction Efficacy and Safety Clinical Investigation Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria) study was a randomized, double-blind, placebo-controlled trial.[15] Patients aged 18 years and older were eligi-

ble if they fulfilled the following inclusion criteria: (i) had received at least four transfusions in the preceding year; (ii) had at least 10% PNH type III erythrocytes; (iii) had a platelet count of at least 100 000/mm^3; and (iv) had LDH levels ≥1.5 × the upper limit of normal. All patients received vaccinations against *N. meningitidis*. Patients were excluded if they (i) had a haemoglobin level >10.5 g/dL before transfusion in the preceding 12 months; (ii) had a complement deficiency; (iii) had a history of meningococcal disease; (iv) had received a bone marrow transplant; or (v) did not require a blood transfusion in the pre-study observation period.[15]

During the observation period, subjects were given a transfusion if they had a haemoglobin level of ≤9 g/dL with symptoms, or ≤7 g/dL without symptoms. The level of haemoglobin at the time of transfusion set the haemoglobin setpoint for the patient during the study. Patients received intravenous eculizumab 600 mg or placebo every week for 4 weeks, intravenous eculizumab 900 mg or placebo the following week, and then intravenous eculizumab 900 mg or placebo every 2 weeks until week 26.[15]

A total of 43 patients were randomly assigned to receive eculizumab and 44 were assigned to placebo. In 42 of 43 eculizumab patients, serum haemolytic activity was completely blocked by the 900 mg every 2 weeks dose.[15] LDH levels decreased from 2199.7 ± 157.7 IU/L at baseline to 327.3 ± 67.6 IU/L at 26 weeks in the eculizumab group. In the placebo group, LDH increased from 2258.0 ± 154.8 IU/L at baseline to 2418.9 IU/L ± 140.3 IU/L at 26 weeks ($p < 0.001$ for eculizumab vs placebo at 26 weeks). Type III erythrocytes increased from 28.1 ± 2.0% at baseline to 56.9 ± 3.6% at 26 weeks in the eculizumab group. In the placebo group, type III erythrocytes remained the same (35.7 ± 2.8% at baseline to 35.5 ± 2.8% at 26 weeks; $p < 0.001$ for eculizumab vs placebo at 26 weeks).[15] At the end of 26 weeks, 49% of subjects in the eculizumab group maintained haemoglobin levels above their setpoints set during the observation period without transfusions. In contrast, no subject in the placebo group achieved this goal ($p < 0.001$). The mean number of units for transfusions at the end of 26 weeks was 3.0 ± 0.7 in the eculizumab group versus 11.0 ± 0.8 in the placebo group. A total of 51% of patients in the eculizumab group were transfusion-free, compared with no patients in the placebo group ($p < 0.001$).[15] QOL, as measured by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, was significantly improved by eculizumab treatment compared with placebo.[15]

The results of a second phase III study (SHEPHERD [Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria]) have been recently published.[16] This open-label, non-placebo-controlled study examined the long-term efficacy and safety of eculizumab in PNH patients. Patients were eligible if they were (i) aged 18 years or older; (ii) had at least one transfusion in the previous 2 years; (iii) had at least 10% PNH type III erythrocytes; (iv) had a platelet count of at least 30 000/mm^3; and (v) had LDH levels ≥1.5 × the upper limit of normal. All patients received vaccinations against *N. meningitidis*. A total of 97 patients were included in the study and given eculizumab 600 mg weekly for 4 weeks, then 900 mg 1 week later, and then 900 mg every 2 weeks until week 52.[16] A total of 96 patients completed the study. The median patient age was 41 years and the median duration of PNH was 4.9 years.[16]

At 52 weeks, LDH levels were reduced from a median of 2051 IU/L at baseline to 269 IU/L ($p < 0.001$). Transfusion units decreased from a median of 8.0 units/patient pre-treatment (range 0–66 units) to a median of 0.0 units during the 1-year study ($p < 0.001$). A total of 51% of patients did not require any transfusions during the study.[16] With the dose regimen of 900 mg every 2 weeks, 89 of 97 patients had complete inhibition of serum haemolytic activity. During the last 1 or 2 days of the administration interval, the remaining eight patients had a return of haemolysis. Of these patients, six had their administration interval reduced to 12 days, which resulted in a reduction in haemol-

ysis.[16] Significant reductions in patient fatigue (measured by the FACIT-Fatigue instrument) were also observed within 1 week of the start of treatment with eculizumab and were independent of the baseline LDH level or platelet count. As in TRIUMPH, the EORTC QLQ-C30 was also significantly improved by eculizumab treatment.[16]

2.1 Thrombosis

To determine the effect of eculizumab therapy on rates of thrombosis, a major cause of morbidity and mortality in PNH patients, data were pooled from the three studies described in the previous section.[13-17]

Eculizumab treatment decreased the overall thromboembolism rate from 7.37 events/100 patient-years before eculizumab therapy to 1.07 events/100 patient-years with eculizumab treatment ($p < 0.001$), a relative reduction of 85%.[13,15-17]

In patients receiving antithrombotics, the pre-eculizumab rate of thrombosis was 10.61 events/100 patient-years, compared with 0.62 events/100 patient-years with eculizumab ($p < 0.001$). When examining patients receiving anticoagulants only (excluding patients receiving antiplatelet agents), the rates were 11.54 events/100 patient-years prior to eculizumab versus 0.72 events/100 patient-years after eculizumab ($p < 0.001$).[17]

2.2 Tolerability

The tolerability profile of eculizumab was established in the two phase III trials conducted.[15,16] In TRIUMPH, serious adverse events occurred in 4 of 43 subjects in the eculizumab group and 9 of 44 in the placebo group; none were deemed to be related to treatment. Headache, nasopharyngitis, back pain and nausea were the most common adverse events in the eculizumab group, with headache and back pain occurring more often in the eculizumab group than the placebo group. One thrombotic event occurred in the placebo group and none in the eculizumab group. No deaths occurred in either group. One subject in the eculizumab group had detectable antibodies against eculizumab, although this did not affect complement inhibition. One subject in the placebo group also had detectable antibodies against eculizumab.[15]

In SHEPHERD, the most common adverse reactions were headache, nasopharyngitis and upper respiratory tract infections. The majority (76.1%) were considered to be unrelated to the study medication. Two subjects were judged to have experienced adverse events definitely related to study treatment (dysgeusia and haematoma). No serious adverse events were related to the study drug. Most infections were mild to moderate in intensity and 91% were unrelated to the study drug.[16]

The prescribing information for eculizumab contains a black box warning for the potential increased risk of meningococcal infections.[11] Patients must be vaccinated with a meningococcal vaccine at least 2 weeks before starting eculizumab treatment, preferably with a quadrivalent conjugated vaccine. Patients must be observed for signs of meningococcal infections and treated promptly. Discontinuation of eculizumab treatment may be warranted. In clinical trials, two patients receiving eculizumab who had been vaccinated, developed meningitis.[11]

Antibody formation was detected in three patients receiving eculizumab in clinical trials; however, this did not affect the efficacy of the drug.[11] Patients should be monitored for at least 8 weeks after discontinuation of eculizumab to monitor for serious haemolysis because treatment increases the number of PNH erythrocytes.[11]

3. Dosage and Administration

The FDA-approved dosage regimen for eculizumab is as follows: 600 mg intravenously once weekly for 4 weeks, then 900 mg intravenously 1 week after that, then 900 mg intravenously every 2 weeks. It is recommended that eculizumab be administered on the correct day of the above schedule, or within 2 days. Eculizumab is available as 300 mg single-use vials at a concentration of 10 mg/mL. The required amount of eculizumab solution must be diluted to 5 mg/mL using 0.9% sodium chloride, 0.45% sodium chloride, 5% dextrose in water or Ringer's injection, and infused intravenously over 35 minutes. The infusion rate may be

slowed if an adverse reaction occurs, but total infusion time should not exceed 2 hours.[11]

4. Conclusion

Eculizumab is the first drug to be approved (also approved by the European Medicines Agency) for the treatment of PNH. In well designed clinical trials, eculizumab was effective in controlling serum haemolytic activity. In addition, fatigue and QOL measurements improved in all trials; however, improvement of other symptoms of PNH, such as dysphagia, abdominal pain and erectile dysfunction, were not measured. The effect of eculizumab on life expectancy has not been studied.[6,13-16] Although there have been no trials designed to specifically evaluate rates of thrombosis, research indicates that eculizumab does decrease the rate of thromboembolism.[17] This drug does carry a black box warning for the potential increased risk of meningococcal infections and requires patients to receive the meningococcal vaccine at least 2 weeks before starting treatment.[11] Despite the concern for infection, eculizumab is a novel treatment that offers a new option for patients with PNH.

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