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Treatment of Hemolytic Uremic Syndrome with Eculizumab

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On September 24, 2011, the Food and Drug Administration (FDA) extended the approved indications for eculizumab to include the treatment of pediatric and adult patients with atypical hemolytic uremic syndrome (aHUS). Eculizumab has been available in the United States since 2007 for the treatment of paroxysmal nocturnal hemoglobinuria. This additional indication makes eculizumab the first drug to be approved for the treatment of aHUS.¹ Recent clinical experience has also suggested that eculizumab may be of benefit in patients with shiga-toxin producing *E. coli*-induced HUS (STEC-HUS).²

Mechanism of Action

Hemolytic uremic syndrome is one of the thrombotic microangiopathies (TMA). Thrombi formation in arterioles and capillaries produce the classic triad of HUS symptoms: microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney failure. In children, HUS is often associated with a prodromal infection. The most common form, STEC-HUS, is estimated to cause more than 90% of cases. Approximately 5-10% of HUS cases are considered atypical. Unlike STEC-HUS, these cases are not typically accompanied by diarrhea and may have a recurrent course. Patients with aHUS may present at a younger age and are more likely to experience severe hypertension and develop chronic kidney failure. Current research suggests that many patients with aHUS have genetic defects resulting in faulty regulation of the alternative complement pathway.^{3,4}

Eculizumab is a monoclonal antibody that binds to the complement protein C5, inhibiting its cleavage to C5a and C5b. This prevents circulation of the pro-inflammatory C5a peptide and generation of the cytotoxic terminal complement complex C5b-9 (referred to as the membrane attack complex or MAC). In patients with HUS, eculizumab inhibits complement-mediated TMA.³⁻⁶

Pharmacokinetics

A population pharmacokinetic analysis of eculizumab in children and adults with aHUS produced results similar to those reported in adults with paroxysmal nocturnal hemoglobinuria. Based on a one compartment model, the estimated clearance is 14.6 mL/hr, with a volume of distribution of 6.14 L for an adult. The elimination half-life of eculizumab is approximately 12 days. Plasma exchange increases the clearance of eculizumab to 3,660 mL/hr and reduces the half-life to 1.3 hrs.^{5,6}

Clinical Studies

Eculizumab Use in aHUS

In 2009, Gruppo and Rother reported the first use of eculizumab in a patient with congenital aHUS.⁷ The patient, an 18-month-old boy, first developed symptoms within 8 hours of birth. He was treated during the initial presentation and three subsequent relapses with exchange transfusions, plasma infusions, and plasmapheresis. Eculizumab was initiated on day 35 of his fourth relapse, with a dose of 300 mg given intravenously weekly for 3 weeks followed by 600 mg every 2 weeks. Hematologic parameters and renal function began to improve within 2 days, and full remission was noted within 10 days. At the time of the case report, the patient had remained on therapy and in remission for 4 months.

Since that initial publication, several authors have provided additional cases supporting the utility of eculizumab in aHUS. In 2011, Lapeyraque and colleagues described the use of eculizumab in a 7-year-old girl with aHUS associated with two factor H mutations (S119L and V1197A).⁸ She was initially diagnosed at 7 months of age and managed with plasma exchange. Later recurrences were also treated with plasma infusions. Eculizumab was started in response to a severe exacerbation with hypertension and acute kidney failure. She was treated with 600 mg weekly for three doses and then 600 mg every 2 weeks. Plasma infusions

were no longer needed after beginning eculizumab. Her hypertension resolved, platelet count normalized, and renal function returned to baseline within one week. At the time of the report, she had remained on therapy and in remission for 12 months.

Tschumi and colleagues published a similar case in a 9-year-old girl with aHUS associated with heterozygous factor H mutation.⁹ After starting eculizumab at a dose of 600 mg every 2 weeks, the patient no longer required plasma exchanges. A renal biopsy performed 2 months after starting therapy demonstrated no evidence of TMA. She had remained in remission for more than 24 months at the time of the report.

Eculizumab has also been used in the management of children with aHUS who have undergone renal transplantation. It has been estimated that aHUS progresses to end-stage renal failure in 50% of patients. In patients with factor H mutation, the risk of renal allograft rejection within 2 years is as high as 80%. In 2010, Davin and colleagues described the use of eculizumab in a 17-year-old girl who had undergone three kidney transplants.¹⁰ Ten months after transplantation she developed worsening renal function and severe allergic reactions to her routine plasma infusions. Eculizumab was started at a dose of 900 mg weekly for 4 weeks followed by 1,200 mg every 2 weeks. Six months later, the authors reported that her serum creatinine had stabilized at 1.36 mg/dL and her platelet count had normalized. An additional case has been published describing a 15-year-old boy with recurrent aHUS after three kidney transplantations who was successfully treated with eculizumab 2 months post-transplant with return of renal function 3 weeks after starting therapy.¹¹

Zimmerhackl and coworkers described prophylactic use of eculizumab in a 10-year-old boy after kidney transplantation.¹² The patient had been diagnosed with aHUS at 4 years of age. Plasma exchange was done on a daily basis for the first 9 days post-transplant. On day 10, eculizumab was started at a dose of 600 mg every 2 weeks. One year later, the authors reported no evidence of active disease, no signs of graft rejection, and no need for plasma infusions. Weitz and colleagues gave prophylactic eculizumab to a 7-year-old boy with aHUS starting 3 weeks prior to transplantation.¹³ He received an initial dose of 600 mg, followed by 300 mg one week later. Maintenance therapy with 300 mg was started on week 3 and continued every 2 weeks. An additional 600 mg dose was given before and after surgery to minimize complement activation. In spite of

difficulty in maintaining complete complement blockade, there had been no need for plasmapheresis and no evidence of TMA 7 months after transplantation.

In addition to these case reports, eculizumab has been studied in larger numbers of patients as part of the FDA approval process. Eculizumab was evaluated under the FDA's priority review and accelerated approval programs, an expedited process for drugs offering a major advancement in treatment. The manufacturer submitted the results of two prospective Phase II trials and a retrospective study.⁵ In the first study, 17 adolescents and adults with aHUS were enrolled if signs of TMA persisted after at least four episodes of plasmapheresis or plasma exchange. All patients received the standard adult dosing regimen (detailed in the Availability and Dosing Recommendations section) for at least 26 weeks.

Treatment with eculizumab reduced signs of complement-mediated TMA. Mean platelet count increased from $109 \pm 32 \times 10^9/L$ at baseline to $169 \pm 72 \times 10^9/L$ at the end of one week and $210 \pm 68 \times 10^9/L$ at 26 weeks. Seventy-six percent of patients experienced normalization of hematologic indices, defined as maintenance of normal platelet counts and lactate dehydrogenase (LDH) levels for at least 4 weeks. The median duration of normalization was 37% (range 25% to 62%). Renal function also improved, with a median increase in glomerular filtration rate of $20 \text{ mL/min/1.73 m}^2$ at 26 weeks (range -1 to $98 \text{ mL/min/1.73 m}^2$). Four of the five patients who required dialysis were able to discontinue it. Only one patient progressed to requiring dialysis while receiving eculizumab.

The second prospective study enrolled 20 patients (ages 13 to 63 years) who required plasmapheresis or exchange but did not have ongoing TMA symptoms. At 26 weeks, 90% of patients experienced normalization of hematologic indices. The median duration of normalization was 38% (range 22% to 52%). Renal function also improved, with a median increase in glomerular filtration rate of $5 \text{ mL/min/1.73 m}^2$ (range -1 to $20 \text{ mL/min/1.73 m}^2$). No new patients required dialysis.⁵

Results from the 19 children (ages 2 months to 17 years) in the retrospective study were similar to those in the prospective studies. Platelet count normalized in 89% of the children, with hematologic normalization occurring in 42%. Forty-seven percent experienced an improvement in estimated glomerular filtration rate $\geq 15 \text{ mL/min/1.73 m}^2$. No new patients required dialysis while receiving eculizumab.⁵ The manufacturer continues to collect data on patients

treated with eculizumab to confirm the results of these three studies.

Eculizumab Use in STEC-HUS

In the June 30, 2011 issue of *The New England Journal of Medicine*, Lapeyraque and colleagues described the use of eculizumab in three 3-year-old patients with STEC-HUS.² The first two patients had undergone plasma exchange but progressed to central nervous system involvement and acute kidney failure requiring hemodialysis. The third patient presented with a similar course. Eculizumab was given at weekly intervals (three doses for patients 1 and 3; four doses for patient 2). All experienced improvement within 24 hours, with normalization of platelet counts and LDH values within 5 days. Dialysis was discontinued between 3 and 16 days after beginning treatment, with a full return of renal function. The authors hypothesize that the shiga toxin may have a direct activating effect on complement which is blocked by eculizumab.

At the time of publication of this case report, an outbreak of STEC-HUS was occurring in Germany that eventually affected nearly 900 children and adults.¹⁴ Physicians involved in caring for patients during the outbreak contacted Alexion Pharmaceuticals, the manufacturer of eculizumab. Working in conjunction with the German government, Alexion made the drug available on a compassionate-use basis. Many of the adult patients were treated, but because of the relative lack of experience with the drug in children, it was reserved for the most serious cases. No specific information has been made available about the efficacy of the drug in these patients, but only one child died during the outbreak. The manufacturer also has an ongoing open-label clinical trial to study the effects of eculizumab in patients with STEC-HUS who are 2 months of age or older.

Warnings and Precautions

A black box warning has been added to the prescribing information for eculizumab to call attention to reports of life-threatening and fatal meningococcal infections in patients receiving treatment. The reduction in MAC formation produced by eculizumab eliminates one of the body's defense mechanisms against *N. meningitidis*; under normal conditions, MAC binds to bacterial cell walls and increases permeability, resulting in cell death. Patients should be immunized with meningococcal vaccine at least 2 weeks prior to administering eculizumab unless the risks of delaying therapy outweigh the risk of a meningococcal infection.^{5,6}

It should be noted that the current quadrivalent meningococcal vaccines protect only against the

A, C, Y, and W-135 strains. They do not offer protection against serogroup B, which has its peak incidence in children less than 5 years of age and adolescents between 15 and 19 years of age. Use of prophylactic penicillin has been recommended in children receiving eculizumab to provide additional protection.¹⁵

Children who have not been fully immunized against *Streptococcus pneumoniae* or *Haemophilus influenzae* type b infections may be at higher risk for these infections as well and should be immunized prior to initiating eculizumab, if possible. Because of the potential for serious infections, a Risk Evaluation and Mitigation Strategy (REMS) program has been developed to educate health care providers and patients/families. Information about the REMS program can be obtained on-line at <http://www.solirisrems.com/> or by calling 1-888-SOLIRIS (1-888-765-4747).^{5,6}

Adverse Effects

The most common adverse effects reported by the 37 adults and adolescents receiving eculizumab in the two prospective aHUS studies were hypertension (in 35% of patients), headache (30%), anemia (24%), leukopenia (16%), diarrhea (32%), vomiting (22%), nausea (19%), abdominal pain (11%), upper respiratory or urinary tract infections (35% and 16%), insomnia (14%), cough or throat pain (14%), fatigue, edema, fever, vertigo, or musculoskeletal pain (11%). Fifty-four percent experienced serious adverse effects, most often hypertension or infection. Both studies used a single-arm design, so no placebo data are available for comparison. Similar results were found in the prospective aHUS study; the most common adverse effect was fever (47%), followed by diarrhea and upper respiratory tract infection (32%).^{5,6}

Availability and Dosing Recommendations

Eculizumab (Soliris[®], Alexion) is available through a restricted access program. It is supplied in 300 mg single-use vials, with a concentration of 10 mg/mL. It must be refrigerated until use and diluted to a final concentration of 5 mg/mL with 0.45% or 0.9% sodium chloride, 5% dextrose in water, or Ringer's injection. The diluted solution should be administered as an IV infusion over 35 minutes. The duration may be slowed to 2 hours for patients who experience adverse effects.^{5,6}

The recommended induction regimen for eculizumab in patients 18 years of age and older is 900 mg given once weekly for 4 weeks. The first maintenance dose of 1,200 mg is given one week after completion of the induction phase (week 5). A 1,200 mg dose is then administered

every 2 weeks. In younger patients, dosing is adjusted according to body weight. For patients between 30 and 40 kg, the induction phase consists of 600 mg given weekly for 2 doses, followed by 900 mg at week 3 and then every 2 weeks afterwards. Patients between 20 and 30 kg should receive 600 mg weekly for 2 doses, followed by 600 mg at week 3 and then every 2 weeks. Patients between 10 and 20 kg should be given 600 mg at week 1, 300 mg at week 2, and then 300 mg every 2 weeks. Infants between 5 and 10 kg should receive 300 mg at weeks 1 and 2, then 300 mg every 3 weeks. Upon discontinuation, patients should be monitored for at least 12 weeks to identify any return of symptoms.^{5,6}

Supplemental doses of eculizumab should be administered within 60 minutes after each plasmapheresis or plasma exchange, using the most recent dosage the patient has received. A supplemental dose should also be administered 60 minutes prior to each unit of fresh frozen plasma infused.^{5,6}

Summary

Eculizumab offers a new option for the management of patients with aHUS. Unlike traditional supportive therapy, eculizumab inhibits one of the proteins responsible for ongoing complement activation. Although not yet well studied, it may also be beneficial in patients with STEC-HUS. Post-marketing surveillance and additional clinical trials will provide more information on the safety and efficacy of eculizumab in HUS over the next several years.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their January meeting:

1. Ioflupane I 123 (DaTscan[™]) was added to the Formulary for imaging studies for patients with suspected Parkinsonian syndromes.
2. Tapentadol (Nucynta[®]) was added with restriction to the Pain Service and Physical Medicine and Rehabilitation for patients intolerant of other opioids.
3. One of the restrictions for pantoprazole (Protonix[®]) use, patients receiving clopidogrel who must remain on a proton pump inhibitor, was removed. Esomeprazole (Nexium[®]) was deleted from the Formulary.
4. The restriction for intravenous acetaminophen (Ofirmev[™]) was amended to specify patients unable to tolerate oral medications.
5. Use of lidocaine continuous infusions for pain management was approved.

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