COVER STORY

Eculizumab's triumph over PNH

The first-of-its-kind drug has provided patients with PNH their first viable treatment option.

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The FDA approval of the orphan drug eculizumab in March 2007 marked a distinct change in how physicians were able to treat patients with paroxysmal nocturnal hemoglobinuria.

The results of several clinical trials have found that eculizumab (Soliris, Alexion) not only prevented the breakdown of red blood cells but also virtually eliminated many of the quality-of-life symptoms associated with PNH, **Wendell Rosse, MD**, told HemOnc Today.

"I have been with patients with PNH for more than 50 years now," Rosse said. "It has been fascinating to observe how by scientific method we have come to understand much of the disease and the causes of the disease. Now, we finally have a rational treatment based on that understanding."

HemOnc Today spoke with Rosse, professor emeritus at Duke University and Red Cells & Hemoglobinopathies Section Editor of the HemOnc Today Editorial Board, and several other experts in the field about how eculizumab has changed PNH and the questions that are still unanswered.

"Eculizumab has dramatically changed PNH," **Peter Hillmen, MD**, a consultant hematologist at the Leeds Teaching Hospitals NHS Trust in England, told HemOnc Today. "PNH is often diagnosed when people are in their 20s and 30s.

The symptoms of the disease — severe lethargy, abdominal pain, difficulty swallowing, hypertension and erectile problems for men — can persist for years.

"Until eculizumab arrived there was no specific treatment for PNH apart from transfusion and occasionally bone marrow transplant," he said.

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Bone marrow transplantation—which is the only thing that can cure the disease— has a 15% to 20% mortality rate, even with an identical donor, Rosse said. "It is not a very satisfactory alternative, although sometimes it is necessary," he said. "Beyond that, the only thing we had was symptomatic treatment. The hemolysis could be treated, but not very well, by high-dose prednisone, which could not be maintained on a daily dose." Iron replacement, transfusion, folic acid replacement and general medical care were all used to treat the symptoms of the disease, according to Rosse.

Robert A. Brodsky, MD, is Director, Division of Hematology, and Clara Lucas Lynn Chair in Medicine, The Johns Hopkins University.

Photo by Frederick Dubs

DISCUSS IN OUR FORUM

How do you think eculizumab has changed PNH?

"We had very little to offer patients," **Robert A. Brodsky, MD**, director of the division of hematology and Clara Lucas Lynn Chair in Medicine at The John Hopkins University, said in an interview. "I recently had a patient with PNH present in absolute crisis. Several years ago the only thing we would have had to offer him was narcotics and maybe fluids. Now that eculizumab is approved, all I have to do is call down to the pharmacy and tell them that we need to start the patient on this drug."

Prior to the drug's approval, patients with PNH had to cope with sometimes debilitating symptoms such as anemia, fatigue, thrombosis, hemoglobinuria, dyspnea, dysphagia, erectile dysfunction, hypertension and kidney problems for 10 to 15 years, with very few treatment options.

Patients with PNH whose symptoms are related to intravascular hemolysis will derive the most benefit from eculizumab, according to **Charles Parker, MD**, of the University of Utah School of Medicine, Salt Lake City. "This group of patients have a relatively large PNH clone and as a result of that have a great deal of intravascular hemolysis," he said. "Those patients, in addition to having anemia, will also have a variety of constitutional symptoms that greatly impact their quality of life."

By eliminating the intravascular hemolysis, eculizumab also ameliorates many of the symptoms of PNH.

"It relieves the symptoms of the disease in a way that many patients have not experienced since their diagnosis," Rosse said. "The esophageal spasm is gone, the abdominal pain is gone, the erectile dysfunction is gone, the hypertension is reduced and the kidney function is improved. … It makes a major difference in the way patients can live with the disease."

Testing an orphan drug

Charles Parker

The FDA approval of eculizumab was based on the results of clinical trials that examined the efficacy of eculizumab in treating transfusion dependence in patients with PNH.

"Although the leading cause of death in PNH is thrombosis, not everyone clots, so thrombosis could not be the primary endpoint of these trials," Brodsky said. "In addition, the median survival of the disease is long, 10 or 15 years, so survival could not be an endpoint. Therefore, the researchers examined hemolysis measured through transfusion avoidance as the primary endpoint."

An open-label pilot study was conducted from May to December 2002 in 11 transfusion-dependent patients with PNH. Patients received weekly IV infusions of 600 mg eculizumab for four weeks, followed by a 900-mg dose, and then 900 mg eculizumab every two weeks until week 12. The results of the study indicated a decrease in intravascular hemolysis, a decrease in transfusion requirements and an improved quality of life for patients receiving eculizumab.

To test the drug under more rigorous standards, researchers from several institutions in the United States and Europe started the TRIUMPH trial. In this phase-3, double blind, randomized study, 87 patients were randomly assigned to either placebo or the pilot-study regimen of IV eculizumab for 24 weeks. Placebo was chosen instead of standard care because no method of treatment was considered an industry standard.

"The patients that went into TRIUMPH were a very restricted PNH group," Brodsky said. "They were patients who had to have a normal platelet count of over 100,000, and had to be fairly heavily red–cell-transfused dependent." Brodsky estimated that only about 10% to 20% of the patients with PNH that he sees would fit these eligibility criteria.

Results of the TRIUMPH study were published in 2006 in The New England Journal of Medicine. Forty-nine percent of the patients in the eculizumab group achieved stabilization of hemoglobin levels in the absence of transfusion, compared with none in the placebo group ($P<.001$). Eculizumab reduced intravascular hemolysis compared with placebo and there were improvements in quality of life ($P<.001$) and fatigue scores ($P<.001$) in the eculizumab group compared with the placebo group.

"TRIUMPH showed a dramatic effect on reduction in intravascular hemolysis," Parker said. "It was the definitive study on the efficacy of eculizumab."

Wendell Rosse **Peter Hillmen**

Next, researchers began the SHEPHERD trial. This study was also phase-3 but was open label instead of randomized. It also relaxed its inclusion criteria to include patients with minimal transfusion requirements and lower platelet counts.

"The SHEPHERD study was a much larger, real-world population of PNH patients," Brodsky said. "This population probably captured more than 70% to 80% of patients with the disease. About 70% of patients on SHEPHERD would not have been eligible for TRIUMPH."

In this study, 97 patients were assigned to the pilot-study regimen of eculizumab for 52 weeks. Results showed an 87% reduction in hemolysis ($P<.001$). Treatment with eculizumab also resulted in an improvement in anemia and fatigue scores and a reduction in transfusion dependence.

"Both trials generated very compelling data for the use of the drug in patients with PNH whose clinical symptoms are related to intravascular hemolysis," Parker said.

Finally, all of the patients enrolled in these three studies were rolled over into an open-label extension study to examine the effect of eculizumab on thrombosis. "The major cause of morbidity and death in PNH is the tendency toward thrombosis," Rosse said. "This is because of abnormalities in the platelets. The activation of complement brings about the excessive thrombosis, particularly in the veins of the abdomen and liver."

Extension study

In the extension study, the researchers compared thromboembolism rate while on eculizumab with the pretreatment rate of thromboembolism in the same patients. At study end, the thromboembolism rate was 1.07 events per 100 patients years on eculizumab compared with 7.37 events per 100 patient years prior to treatment ($P<.001$). When the researchers compared an equal number of years before and during treatment, thromboembolism events were still reduced from 39 events prior to treatment to only three events on treatment ($P<.001$).

"It is very clear. There was a significant reduction in the number of thromboses in patients on eculizumab compared to patients not on the drug," Hillmen said.

However, the results of this trial still leave some room for questions, according to Brodsky. "Only about 40% to 50% of patients with PNH develop thrombosis, or it may take a patient four to five years from diagnosis before they have their first clot," he said. "In a perfect world you would want to do a randomized trial to examine thrombosis, but the disease is so rare that it would be too expensive and take too long to do a study like that." Despite that, Brodsky said that the drug greatly reduces, if not eliminates, the risk of thrombosis.

Despite the overwhelmingly positive results of the clinical trials leading to eculizumab's approval, treatment with the drug does have some drawbacks.

TRIUMPH

Transfusion Reduction Efficacy and Safety Clinical Investigation, a Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

Investigated whether eculizumab stabilized hemoglobin levels and reduced transfusion requirements in transfusion-dependent patients with PNH.

Indication:	PNH
Design:	phase-3, randomized, double blind, placebo-controlled
Centers:	34
Countries:	United States, Canada, Europe, Australia
Patients:	87

RESULTS: 87 patients were randomly assigned to either placebo or IV eculizumab. 49% of patients in the eculizumab group achieved stabilization of hemoglobin levels in the absence of transfusion compared with none in the placebo group ($P<.001$). Eculizumab reduced intravascular hemolysis compared with placebo (58,587 U per liter vs. 411,822 U per liter; $P<.001$) and there were improvements in quality of life ($P<.001$) and fatigue scores ($P<.001$) in the eculizumab group compared to the placebo group.

N Engl J Med. 2008;355:1233-1243.

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SHEPHERD

Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria

Designed to examine the safety and efficacy of eculizumab in a broader population of patients with PNH.

Indication:	PNH
Design:	phase-3, open-label, non–placebo-controlled
Centers:	33
Countries:	United States, Canada, Europe, Australia
Patients:	96

RESULTS: All patients were assigned to eculizumab at 600 mg every 7 days for 4 weeks, then 900 mg 7 days later, then 900 mg every 14 days for a total of 52 weeks. Patients treated with eculizumab had an 87% reduction in hemolysis ($P<.001$). The number of transfusions was also reduced 52% in patients assigned eculizumab from a mean of 12.3 to 5.9 units of packed red cells per patient. 51% of patients achieved transfusion independence during the study period.

Blood. 2008;111:1840-1847.

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Pitfalls of PNH

"One of the major pitfalls of this drug is that it is intravenous," Brodsky said. Patients being treated with eculizumab have to get IV infusions of the drug every two weeks, potentially for the rest of their lives.

"If they stop, within a month they will have their disease back again," Brodsky said. "The IV infusion is given over 30 minutes and there is little in the way of side effects, but you still have to go to an infusion center and by the time you check in and get the IV started and the medicine comes up from the pharmacy you basically lose half a day every two weeks."

However, for patients with severe PNH, this inconvenience may be considered minor, according to Hillmen. "Prior to eculizumab, patients had to be transfused maybe once every week or two or once every few months," he said. "One of the problems with PNH is that one day you can feel reasonably OK and the next day you cannot get out of bed. It's a very difficult disease to manage, so being treated by infusion every two weeks is trivial to those patients that are badly affected."

Another drawback to the treatment is that it is extremely expensive, Rosse said. "The estimated cost is about $380,000 per year per patient." Multiply that number over 20 or 30 years and it adds up.

"The disease is so rare that the insurers are not too bothered by it," Brodsky said. "But it is still a very expensive medication." The cost limits access to treatment in developing countries.

Finally, because eculizumab is an antibody against the C5 component of complement, patients with PNH treated with the drug are at an increased risk for *Neisseria* infections, particularly *Neisseria* meningitides, Rosse said.

"Everyone is vaccinated before they start the drug," Brodsky said. "The risk of *Neisseria* meningitides on this drug is about 0.5% per year. But if you have a 20-year-old woman on it, and she will be on it for the rest of her life, over the next 60 years she probably has a 30% chance of coming down with *Neisseria* meningitides."

FAST FACTS

Issues at Hand

1 Prior to the approval of eculizumab, patients diagnosed with paroxysmal nocturnal hemoglobinuria had few treatment options available to them and often had to deal with severe symptoms such as lethargy, erectile dysfunction and thrombosis for 10 to 15 years.

2 Eculizumab was approved in March 2007 based on the results of the TRIUMPH trial, which indicated that eculizumab helped patients achieve stabilization of hemoglobin levels, reduced intravascular hemolysis and improved quality of life.

3 Although eculizumab dramatically improves symptoms of PNH, it does not cure the disease. Physicians who are prescribing eculizumab to patients with PNH should still be aware of a patient's risk for *Neisseria* meningitides, thrombosis and extravascular hemolysis.

Questions unanswered

In addition to considering the possible pitfalls of prescribing eculizumab, there are other questions that physicians should consider when prescribing the drug.

"Eculizumab is not right for everyone with PNH and does require judgment on the part of the prescribing physician to identify the appropriate patient for treatment," Parker said.

"In patients with small PNH clones who don't have much hemoylsis, their main clinical problems are related to bone marrow failure. This is typically seen in the setting of some other bone marrow failure syndrome, particularly aplastic anemia and the refractory anemia variant of myelodysplasia," Parker said. "In those cases the focus of treatment is really on the bone marrow failure component of the disease."

In addition, a patient with a small proportion of abnormal cells probably does not need the medicine because their symptoms are not incapacitating, Rosse said.

The role of anticoagulants once a patient is started on eculizumab is also unclear, Parker added. Many patients with PNH are assigned an anticoagulant to prevent either first or recurrent thrombosis. However, according to Parker, there are little data to address whether or not to continue an anticoagulant in combination with eculizumab.

"In my opinion, anyone who has had a prior thromboembolic complication should remain on anticoagulation," Parker said. "You could probably make a better case for discontinuing anticoagulation in a patient who has never had a thromboembolic

complication once they start eculizumab, but again that issue has not been addressed by appropriate clinical studies."

Physicians should also be aware that patients with PNH are at risk for both intravascular and extravascular hemolysis, according to Parker. "In patients who are treated with eculizumab, the intravascular hemolytic process is ameliorated almost completely by the drug, but there is another part of hemolysis ,called extravascular hemolysis, that is not blocked by eculizumab."

These patients will typically still require some transfusion and possibly other modification of their treatment to maintain an adequate hemoglobin level, according to Parker. "It is important for physicians to be aware that there are a high percentage of patients that do continue to have ongoing hemolysis, although it is almost exclusively extravascular. As we use the drug more, we are seeing more of these patients.

"One thing that is important to understand is that eculizumab does not treat the underlying clonal proliferative disease in PNH. It only treats the hemolysis by blocking complement. Ultimately, the issue is that the drug is really just treating the symptoms rather than the underlying disease. We still need to understand the pathophysiology better so that we can eventually develop an approach to cure the disease, as opposed to just ameliorating the symptoms," Parker said. – *by Leah Lawrence*

POINT / COUNTER

Should patients remain on an anticoagulant after being assigned to eculizumab?

For more information:

- Brodsky RA, Young NS, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008;111:1840-1847.
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- Hillmen P, Hall C, Marsh JCW, et al. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2004;350:552-559.

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