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PNH Research Summary *from the* 2017 AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING

A Summary of Selected Scientific Abstracts for Patients with PNH and Their Caregivers

NATURAL HISTORY OF PNH

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Differences Between Asian and Non-Asian Patients with PNH

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PNH typically results in red blood cell destruction in blood vessels, failure of bone marrow to make enough healthy blood cells, and blood clots. Blood clots, bleeding, and serious infections are the most common causes of death in people with PNH.

This study assessed whether patient race affects disease outcomes. The study included data on 1,793 patients who had not been treated with eculizumab (Soliris) when they enrolled in the International PNH Registry. Of these patients, 246 were of Asian or mixed Asian race, and the other patients were white, black, or of other races.

Key findings:

- Lactate dehydrogenase (LDH) levels, a sign of red blood cell damage, were higher in Asian participants.
- Non-Asians were more likely than Asians to have had major adverse blood vessel events, such as blood clots, when they enrolled in the registry.
- Higher proportions of Asian patients had had red blood cell transfusions and taken corticosteroids than non-Asians, but smaller proportions had taken heparin or warfarin to prevent blood clots.
- 38% of non-Asians bruised easily, compared with 20% of Asians.

Conclusions:

- Genetic factors rather than lifestyle and diet seem to play a role in major adverse blood vessel events in patients with PNH.
- Registry data are useful for understanding PNH symptoms over time and possibly for identifying the best treatments based on patient race.

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Characteristics and Disease Burden of Patients Enrolled in the International PNH Registry

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The International PNH Registry is an ongoing, worldwide, observational study to evaluate the safety of eculizumab (Soliris) and characterize PNH disease burden and progression.

The purpose of this analysis was to characterize the demographics, symptoms, health status, and quality of life of patients with PNH. The study included 4,398 patients in the registry with data as of May 1, 2017. The median age of disease onset was 35 years, and 53% of the patients were female. None of the patients had been treated for PNH before enrolling in the registry.

Key findings:

- Patients had a high disease burden when they enrolled in the registry, shown by the fact that 52% had high disease activity, 19% had a history of major adverse vascular events (including blood clots), 63% had bone marrow disorders (including aplastic anemia), 61% needed red blood cell transfusions, and 42% had impaired kidney function.
- Common symptoms were fatigue (81% of patients), breathing problems (45%), hemoglobin in urine (45%), abdominal pain (35%), and impaired quality of life.
- Patients with a larger proportion of abnormal clones (copies) of stem cells in their bone marrow tended to have more severe symptoms.
- 60% of patients with a history of red blood cell transfusions and 59% of those who had undergone immunosuppressive treatment had less than 10% abnormal clones.

Conclusions:

- The disease burden of PNH is high, especially in patients with a larger proportion of abnormal PNH clones.
- However, patients with smaller proportions of abnormal clones also had major symptoms.

1175 Thrombosis in Patients with PNH but not Hemolysis

Morag Griffin, Talha Munir, Peter Hillmen, MBChB, PhD, Louise Arnold, Nicola Copeland, Kathryn Riley, Stephen John Richards, PhD, Anita Hill, MBChB (Hons), PhD

Patients with PNH have a variety of symptoms. Up to one third of patients develop thrombosis, or a blood clot in a vein or artery, over an 8- to 10-year period. Twenty percent of patients have thrombosis in several parts of the body, and some patients are first diagnosed with PNH because of thrombosis. In patients with PNH, thrombosis is an emergency because it can lead to serious complications, including death.

A research team from Leeds, UK, analyzed data on 29 patients with PNH (median age 62 years) to find out which patients with little or no hemolysis (premature destruction of red blood cells) are likely to develop thrombosis.

Key findings:

- Half the patients with at least 30% abnormal copies (clones) of white blood cells but less than 10% abnormal red cell clones in bone marrow developed thrombosis.
- The thrombosis rate in those who had at least 30% abnormal white cell clones and at least 10% red cell clones was 16%.
- None of the patients with 10% to 30% white blood cell clones and less than 10% red cell clones developed thrombosis.

Conclusions:

- In this group of patients, those with a highest risk of thrombosis had non-hemolytic PNH, a high proportion of white cell clones, and a low proportion of red cell clones.
- Although hemolysis might play a role in a patient's risk of thrombosis, white blood cells and platelets also influence thrombosis risk.

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Gene Mutations in PNH

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People with PNH have abnormal clones, or copies, of stem cells in the bone marrow that make blood cells. Because of a mutation, or change, in the *PIG-A* gene, these clones don't have proteins that would normally be attached by glycosyl phosphatidylinositol (GPI), a fat on many blood cells that anchors proteins to cell surfaces.

The purpose of this study was to find out whether mutations in genes other than *PIG-A* might play a role in PNH development. A research team from the Cleveland Clinic analyzed genetic data from 197 patients with PNH clones, or copies of abnormal bone marrow cells that lack GPI because of a *PIG-A* mutation. The analysis also included 113 patients with aplastic anemia who did not have a PNH clone.

Key findings:

- In addition to *PIG-A*, 10 of 26 patients (38%) who had aplastic anemia but no PNH clones had mutations in at least one of the genes studied. In comparison, 27 of 58 (47%) of those diagnosed with PNH had at least one of these mutations.
- 44% of those with a PNH clone had one of the mutations studied, as did 37% of those with aplastic anemia but no PNH clones.
- The most common mutations in those with aplastic anemia and PNH clones were cohesin genes (*RAD21*, *SMC3*, *STAG2*; 8% of patients), *ZRSR2* (8%), *BCOR* (4%) and *TET2* (4%).
- The most common mutations in patients with secondary PNH (those with another bone marrow disorder) were *EZH2* and *SUZ12* (9% of these patients), *ZRSR2* (9%), *BCOR* (4%), *TET2* (4%), and *LUC7L2* (4%).
- In patients with PNH, three of four mutated clones disappeared over time.
- In patients with aplastic anemia and PNH, 9 of 14 mutations developed during their disease, but 10 faded away over time.

Conclusions:

- PNH is similar to aplastic anemia in that gene mutations beyond *PIG-A* are common and include some mutations that are found in many patients with MDS.
- Many of these mutations eventually disappear, but others are long lasting and might affect the course of PNH clone development.

ECULIZUMAB TREATMENT

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Markers of Eculizumab Effectiveness

Darren J Newton, PhD, Claire E. McKinley, Alonso Ricardo, PhD, Michelle D Hoarty, PhD, Louise Arnold, Kathryn Riley, Nicola Copeland, Talha Munir, Morag Griffin, Anita Hill, MBChB (Hons), PhD, Peter Hillmen, MBChB, PhD

Eculizumab (Soliris®) is very effective for preventing red blood cell breakdown in the veins and arteries of patients with PNH. But some patients require a higher dose than the recommended 900 mg twice a week for the drug to be effective.

A research team from Leeds and Sheffield, United Kingdom, determined the concentrations of eculizumab and its target, complement protein C, during treatment. They wanted to use this information to choose the right eculizumab dose for each patient and minimize the risks of serious PNH symptoms. They collected blood samples before treatment and for up to 2 years after treatment began in 50 patients with PNH.

Key findings:

- The average C5 level in patients with PNH treated with eculizumab was a median of 403 ug/ml, which is higher than the normal range of 128 to 305 ug/ml.
- In the 7 patients who provided several blood samples, C5 levels increased over time in 5 patients and decreased in the other 2.
- The eculizumab levels in blood of 3 of 4 patients treated with the standard dose decreased over time and fell below the 100 ug/ml target.
- All patients treated with a higher dose, 1,200 mg, had an eculizumab level higher than the 100 ug/ml target.

Conclusions:

- Like other studies, this one found that C5 levels increase with eculizumab treatment.
- Eculizumab levels in blood are reasonable predictors of treatment efficacy.

ECULIZUMAB TREATMENT

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Efficacy of Eculizumab in Patients with PNH and High Disease Activity

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PNH often develops in patients who have another bone marrow failure syndrome, usually aplastic anemia. Choosing the right treatments for patients with both PNH and aplastic anemia can be challenging.

This study assessed data on 286 patients with PNH treated with eculizumab (Soliris) who had a history of aplastic anemia as well as 483 patients without aplastic anemia. All patients had high disease activity, defined as a lactate dehydrogenase level that is 1.5 times higher than normal and at least one symptom associated with PNH, such as fatigue, hemoglobin in urine, abdominal pain, breathing problems, or anemia.

Key findings:

- Eculizumab treatment was associated with substantial improvements in rates of major adverse vascular (bleeding) events and thrombotic events (blood clots in veins) as well as decreases in red blood cell transfusions needed.
- The mean lactate dehydrogenase (LDH) ratio decreased significantly in all treated patients, regardless of whether they had aplastic anemia when they started treatment.

Conclusions:

- Eculizumab treatment was associated with improvements in outcomes related to PNH, regardless of whether patients had aplastic anemia.
- Aplastic anemia doesn't seem to reduce the effectiveness of eculizumab in patients with PNH.

ECULIZUMAB TREATMENT

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Red Blood Cell Destruction in Patients with PNH Treated with Eculizumab

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The characteristic effects of PNH include red blood cell destruction (hemolysis), blood clots, and inability to make enough healthy blood cells. Lactate hydrogenase (LDH) is a protein that helps produce energy in the body. Lab tests of LDH levels are typically used as measures of hemolysis in PNH. However, LDH levels only provide information about hemolysis within blood vessels.

The purpose of this study was to find markers of hemolysis outside of blood vessels. A research team from the UK reviewed data from 141 patients (50% female) with PNH treated with eculizumab (Soliris) for at least 13 months.

Key findings:

- 72% of patients had a mean hemoglobin level below 120g/l in spite of their treatment with eculizumab
- All patients had C3, a protein that plays a role in red blood cell destruction outside the blood vessels, on their red cells.
- When the investigators assigned patients scores based on levels of C3 and bilirubin (a liver pigment formed by hemoglobin breakdown) as well as counts of reticulocytes (immature red blood cells), those with the highest scores were three times more likely to need red blood cell transfusions.

Conclusions:

- Reticulocyte counts seem to be a better indicator of red blood cell destruction outside the blood vessels than LDH.
- Reticulocyte counts correlate more strongly than LDH with higher levels of bilirubin and C3 on PNH red cells as well as a need for more red blood cell transfusions.
- This information can be used to identify patients who are more likely to need blood transfusions while during treatment with eculizumab.

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Safety of Eculizumab: Results from the International Paroxysmal Nocturnal Hemoglobinuria Registry

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The International PNH Registry is an ongoing prospective, multinational, observational study of the natural history of PNH and the long-term efficacy and safety of eculizumab (Soliris) treatment.

This study assessed the safety of eculizumab in patients in the PNH Registry. The study included data on 4,013 patients. Of these patients, 1,587 had been treated with eculizumab when they enrolled in the registry. On average, the study had 50 months of data on patients treated with eculizumab and 32 months of data on patients not treated with this drug.

Key findings:

- When they enrolled in the study, 91% of patients in the eculizumab group and 50% of the non-eculizumab group had high lactate dehydrogenase levels, a sign of red blood cell destruction.
- More patients (23%) in the eculizumab group had a history of blood clots or other serious blood vessel events than in the non-eculizumab group (9%).
- Rates of other PNH complications—such as cancer, impaired kidney or liver function, pulmonary hypertension, and death—were substantially lower in those treated with eculizumab than the untreated group.
- In patients who started eculizumab treatment after enrolling in the registry, rates of blood clots and other serious PNH complications were lower after they started treatment.

Conclusions:

- Eculizumab seems to be safe, and this study found no new signs that it's not safe.
- Rates of PNH complications were lower in those treated with eculizumab than those not treated.

NEW TREATMENTS

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ALXN1210, an Experimental PNH Treatment: Results of 2 Phase 1/2 Studies

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When a person is injured or attacked by a virus, the body's complement system recruits enzymes and other mediators to fight the invader. The abnormal red blood cells in people with PNH don't have some important complement proteins. Without these proteins, the complement system destroys red blood cells prematurely.

Two clinical trials evaluated the safety and efficacy of ALXN1210, a drug that inhibits complement protein C5. Study 103 included 13 patients with PNH treated with 900 mg or 1,800 mg of ALX1201 every 4 weeks. Study 201 included 19 patients treated with 1,000 mg ALX1201 every 4 weeks, 1,600 mg every 6 weeks, or 2,400 mg every 8 weeks. Most patients were Asian (92%) and female (54%) in Study 103. Most patients in Study 201 were Caucasian (58%) and male (77%). None of the patients had received PNH treatment before this study.

Key Findings:

- Levels of lactate dehydrogenase (LDH) quickly dropped and stayed low in 73% to 88% of patients in each group. High levels of this enzyme are a sign of red blood cell damage.
- The highest rate of LDH normalization was in the group treated with 1,800 mg of ALXN1201 every 4 weeks.
- Unlike all other treatment groups, none of the patients treated with 1,800 ALXN1201 every 4 weeks had breakthrough red blood cell destruction.
- Free hemoglobin levels dropped into the normal range in those treated with 1,800 mg ALXN1201 every 4 weeks, but levels stayed high in the other groups.
- The most common side effect related to treatment was headache, which usually got better after the patient had been on the treatment for a while.

Conclusions:

- ALXN1201 treatment had an acceptable safety level.