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PNH Research Summary *from the* 2015 AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING

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

DISEASE CHARACTERISTICS

3339 Features of PNH With and Without Premature Red Blood Cell Destruction

*Mustafa Nuri Yenerel, M.D.; Petra Muus, M.D., Ph.D.;
Amanda Wilson, M.P.H., Ph.D.; Jeff Szer, M.B.B.S.*

An important feature of PNH is hemolysis, or premature destruction of red blood cells. The authors compared data on 1,012 patients who did not have hemolysis and 1,565 patients who did.

Key findings:

- 69.4% of patients without hemolysis and 39.6% of those with hemolysis had had aplastic anemia.

- Patients without hemolysis had fewer major blood clots than those with hemolysis.
- Among 548 patients without hemolysis and 1,022 with hemolysis who had not been treated for PNH at enrollment, a smaller proportion of those without hemolysis died within 1 year (0.1% of those without hemolysis, 1.4% of those with hemolysis).
- All symptoms except fatigue were worse during hemolysis.

Conclusions:

- Patients with PNH had a greater risk of health problems and death after hemolysis than patients who hadn't had hemolysis.
- Ongoing monitoring of the development of hemolysis in patients with PNH is important.

DISEASE CHARACTERISTICS

3341 Difference in Features of PNH in Children and Adults

Alvaro Urbano-Ispizua, M.D., Ph.D.; Petra Muus, M.D., Ph.D.; Hubert Schrezenmeier, M.D.; Antonio Medina Almeida, M.D., Ph.D.; Amanda Wilson, M.P.H., Ph.D.; Russell E. Ware, M.D., Ph.D.

The few studies of PNH in children to date have included small numbers of patients. The authors conducted this analysis to describe PNH in children enrolled in the International PNH Registry. Another purpose was to compare the disease in children (patients younger than 18) and adults (those aged 18 or older).

The analysis included 92 children (median age at enrollment 14 years) and 2,090 adults (median age 46 years).

Key findings:

- Children had smaller clones (copies) of abnormal stem cells in bone marrow and fewer severe blood cell shortages than adults.
- Children had smaller proportions of reticulocytes (immature red blood cells) than adults.
- 77% of children and 55% of adults had had aplastic anemia or hypoplastic anemia in the past.
- Children had fewer thromboembolisms (blood clots) or major blood vessel problems than adults.
- More children than adults had abdominal pain at enrollment in the registry.

Conclusions:

- These findings may reflect the natural evolution of the disease.
- The findings could be useful for choosing how to treat PNH in children and adults.

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Protein Signatures for Accurate Diagnosis of Severe Aplastic Anemia, Hypoplastic MDS, and PNH

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Accurate diagnosis of severe aplastic anemia, PNH, and hypoplastic MDS is very challenging because these bone marrow failure syndromes have some of the same symptoms. But accurate diagnosis is important for prognosis and choosing the right treatments for each patient.

The aim of this study was to identify groups of proteins that could be used for more accurate diagnosis and prognosis of patients who have symptoms of bone marrow failure syndromes. This research team from Saudi Arabia examined proteins in blood samples from 20 patients with low blood cell counts.

Key findings:

- The expression (formation or regulation) of about 300 different species of proteins was different in samples from patients with aplastic anemia, MDS, and PNH.
- Many of these groups of proteins were involved in signaling between cells; development and function of the blood system; and trafficking of immune cells that help the body fight off viruses, bacteria, and other foreign invaders.
- Three of the proteins were expressed only in samples from patients with aplastic anemia or MDS and not in samples from those with PNH.

Conclusions:

- This study identified protein signatures that could be used to objectively classify bone marrow failure syndromes in patients.
- Once more research is done on these proteins, they could be used to improve diagnosis and to monitor treatment response and outcomes in patients with bone marrow failure syndromes

DIAGNOSIS

3264 Internet-Based Survey of Patient Experiences with PNH

Jamile M. Shammo, M.D.; Rachel L Mitchell, M.D.; Kylene Ogborn, R.N.; Ellen Salkeld, Ph.D.; Stephanie Chisolm, Ph.D.

The purpose of this study was to shed light on what happens to patients before diagnosis and the impact of PNH on quality of life. The researchers sent a Web-based survey to 1,066 patients with PNH and their families. They received responses from 163 patients aged 13–85 years.

Results:

- The most common symptoms before diagnosis were fatigue (88% of patients), weakness (73%), breathing problems (66%), red blood cells in urine (61%), headaches (59%), bruising or bleeding (58%), back pain (53%) and abdominal pain (52%).
- The average time to diagnosis was less than 2 years, but 24% of patients waited more than 5 years for an accurate diagnosis.
- 79% of patients consulted more than one physician before their PNH diagnosis, and almost 38% saw at least five physicians before diagnosis.
- 82% of patients reported researching PNH online. The websites they found most useful were those of the Aplastic Anemia and MDS International Foundation, Paroxysmal Nocturnal Hemoglobinuria Foundation, National Organization for Rare Disorders, Alexion, Mayo Clinic, and National Institutes of Health.

Conclusions:

- Raising awareness of symptoms of PNH and how to diagnose it is important in shortening the time to diagnosis and reducing the distress associated with getting an accurate diagnosis.

TREATMENT

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Evaluation of RA101495 for PNH Treatment in Animals and Human Cells

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The blood cells in people with PNH don't have the PIG-A gene. Without PIG-A, important proteins can't connect to cell surfaces and protect cells from substances in the blood called complement system. As a result, red blood cells break down too early.

Eculizumab (Soliris®) stops this process in patients with PNH. But eculizumab has limitations, including the need to be administered intravenously. Also, the drug doesn't work in patients who don't have mutations in the gene that encodes the complement system protein C5.

This study evaluated a new drug, RA101495, which can disrupt the activity of C5, in monkeys, rats, and cells from people.

Key findings:

- RA101495 stopped virtually all blood cell destruction by the complement system.
- This effect was steady and long lasting.
- The rats and monkeys tolerated doses of RA101495 that were much higher than the doses likely to be used in people.

Conclusions:

- RA101495 could offer a new way to inhibit C5 for treatment of PNH and other disorders associated with a poorly functioning complement system.

TREATMENT

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Targeted Therapy for PNH

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When the BCR-ABL gene has a mutation, it produces the abnormal BCR-ABL protein. This protein causes the bone marrow to make abnormal white blood cells. These abnormal cells crowd out healthy blood cells.

The authors report on their treatment of a Japanese woman who had PNH and chronic myeloid leukemia. They treated the woman with nilotinib (Tasigna®), which binds to the BCR-ABL gene.

Key findings:

- Almost all of the patient's granulocytes, a type of white blood cells, had mutations in the BCR-ABL gene.
- After 6 months of treatment, the number of PNH cells dropped sharply.
- After 19 months of treatment, no PNH cells could be detected in the patient.

Conclusions:

- Identifying mutations, like BCR-ABL, that drive PNH could lead to the development of targeted therapy for PNH.

OUTCOME AND RESPONSE

3340

Benefits of Eculizumab in Patients with No History of Blood Transfusions

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In patients with PNH, eculizumab (Soliris®) reduces the premature destruction of red blood cells, improves disease symptoms, and increases life expectancy.

This study assessed the benefits of eculizumab in 294 patients with PNH who had not had red blood cell transfusions in the past. The patients were enrolled in the International PNH Registry. Of the 199 patients who had not had a blood transfusion, 45 had been treated with eculizumab and 144 had not. The study also included 105 patients who had been treated with eculizumab and had had at least one blood transfusion in the previous 6 months for comparison purposes.

Key findings:

- At the start of the study, non-transfused untreated patients had the highest average hemoglobin levels and the smallest clones (copies of abnormal stem cells).
- The number of reticulocytes (immature red blood cells) was highest in the transfused, treated group.
- Non-transfused untreated patients had a smaller average change in lactate dehydrogenase over 6 months (decrease of 39 units per litre) than non-transfused treated patients (decrease of 1,319 units per litre) and transfused treated patients (decrease of 1,722 units per litre). High levels of lactate dehydrogenase, an enzyme, are a sign of cell damage.
- 74% to 84% of non-transfused treated patients had less fatigue compared to 25% or 33% of untreated patients, depending on how the researchers measured fatigue.
- The 43 non-transfused treated patients with high disease activity had greater reductions in lactate dehydrogenase levels and improvements in fatigue than the 136 untreated patients with high disease activity.

Conclusions:

- Eculizumab significantly reduced lactate dehydrogenase and improved fatigue in patients with PNH, regardless of whether they had had blood transfusions in the past, and in patients with high disease activity.

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Fatigue, Quality of Life, and Related Symptoms in Patients with MDS, Aplastic Anemia, and PNH

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Fatigue is common and very distressing in patients with MDS, aplastic anemia, and PNH. Many patients also have pain, depression, anxiety, stress, and other symptoms that reduce their quality of life (QoL).

The purpose of this study was to use surveys to measure fatigue, QoL, and related symptoms in patients with MDS, aplastic anemia, and PNH. Another goal was to determine the strategies that patients routinely use to manage these symptoms. The study included 313 patients (average age 57 years, 67% female) from the Aplastic Anemia and MDS International Foundation's patient database.

Key findings:

- Fatigue scores on a scale of 1 to 52 were 28 for aplastic anemia, 25 for MDS, and 24 for PNH. These scores indicate severe fatigue.
- QoL scores on a scale of 10 to 104, where 104 indicates better QoL, were 67 for aplastic anemia and PNH and 69 for MDS.
- Stress scores were in the normal range.
- Patients had mild pain and depression and moderate anxiety.
- To manage their fatigue, 81% of patients tried to save their energy, 75% used physical activity, and 73% took naps. Patients found these strategies helpful.

Conclusions:

- Levels of fatigue, QoL, and related symptoms are similar in patients with MDS, aplastic anemia, and PNH.
- Tailored interventions for aplastic anemia, MDS, and PNH could help patients better manage their fatigue and potentially improve their QoL.