HIGHLIGHTS FROM THE

2011 American Society of Hematology Annual Meeting

A Summary of Abstracts for Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) and their Caregivers

Aplastic Anemia & MDS
INTERNATIONAL FOUNDATION

The Aplastic Anemia & MDS International Foundation (AA&MDSIF) is an independent non-profit organization. Our mission is to support patients, families, and caregivers coping with:

- Aplastic anemia
- MDS (myelodysplastic syndromes)
- PNH (paroxysmal nocturnal hemoglobinuria)
- Related bone marrow failure diseases

This booklet offers summaries of abstracts presented at the 53rd Annual Meeting of the American Society of Hematology (ASH) in December 2011. It provides some of the most up-to-date information about new research into the biology and treatment of paroxysmal nocturnal hemoglobinuria (PNH). Although the information in this booklet has undergone a thorough, independent medical review to insure its accuracy, this information is not intended to be a substitute for the advice of your doctor. You should always seek medical advice from a qualified physician.

For more information, call us at (800) 747-2820, or visit us online at www.AAMDS.org.

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Aplastic Anemia & MDS
INTERNATIONAL FOUNDATION

PATIENT EDUCATION COUNCIL APPROVED

This publication is made possible through an unrestricted education grant from Alexion Pharmaceuticals.

Dear Patient or Caregiver,

The purpose of this booklet is to provide you with the most up-to-date information about new research into the biology and treatment of paroxysmal nocturnal hemoglobinuria (PNH), as presented at the 53nd Annual Meeting of the American Society of Hematology (ASH) in December 2011.

The ASH Annual Meeting is the world's largest professional gathering of hematologists and hematological oncologists—i.e., doctors who care for patients with blood disorders or blood and bone marrow cancers. This conference is where many major findings in the field of blood and marrow disorders are first announced to attendees, the larger medical and scientific community, and the media. New information that researchers hope is important enough to be presented at this meeting is submitted a few months ahead of the conference in the form of an "abstract"— i.e., a brief summary of the study and its results—and authors of the most interesting and noteworthy abstracts are asked by ASH to present their research in more detail, either in the format of a tacked-up printed poster or an oral (podium) presentation.

We selected the ASH abstracts in this summary because we feel they are the most relevant and important for people living with PNH to know about. By reviewing the information presented in the booklet, we hope you will:

- Learn how ongoing research on PNH may affect the diagnosis, treatment, and prognosis of patients in the near term as well as the more distant future
- Understand how researchers are approaching the most promising areas of PNH therapy
- Learn about the importance of clinical trials in identifying novel therapies for PNH
- Know the most important issues about PNH which you may want or need to understand and to ask your health care providers about as part of your ongoing treatment.

Please note that the research results discussed at the ASH Annual Meeting sometimes involve experimental drugs that are not approved for general use by the Food and Drug Administration (FDA) or investigation of potential new uses of previously approved treatments. By providing summaries of the research presented, we do not intend to recommend or endorse any particular medication or treatment approach. Our goal is simply to inform you about current news and trends in healthcare related to PNH.

If you are interested in participating in research studies such as those discussed in this booklet, we encourage you to speak to with your doctor about clinical trials or to visit www.clinicaltrials.gov. As always, please contact AA&MDSIF if you have questions about these summaries or any aspect of managing your disease.

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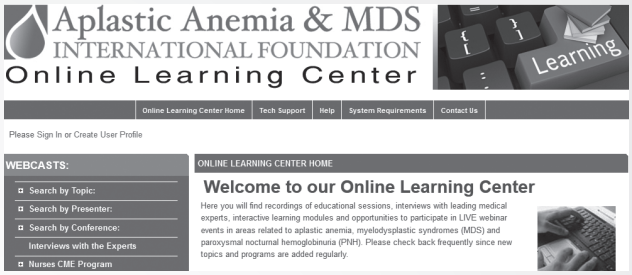
The abstracts summarized in this booklet may be viewed on the American Society of Hematology Web site at http://ash.confex.com/ash/2011/webprogram/keywordindexm.html. You may type in the abstract number or title in the search box. Any conflicts of interest or other relevant disclosures by the study authors are noted in each abstract.

Research Update on PNH Diagnosis and Treatment Now Available on the Online Learning Center (OLC): www.AAMDS.org/Learn



In early 2012, AA&MDSIF produced webinars on the latest diagnosis and treatment research as reported at the 53rd Annual Meeting of the American Society of Hematology (ASH). These webinars are now posted on the Online Learning Center and are available for on-demand viewing.

To view this and other archived webinars, visit our Online Learning Center at www.AAMDS.org/learn and choose Archived Webinars.

The Online Learning Center (OLC) is your comprehensive information source on all aspects of bone marrow failure diseases. Created expressly for patients and their families, caregivers and advocates, all OLC content is free and available to anyone with access to a computer and a high-speed Internet connection. In addition to archived webinars, here is what else you will find on the OLC:

- Live webinars conducted by the nation's leading experts
- Innovative interactive learning modules
- Interviews with experts on aplastic anemia, MDS and PNH
- Webcasts of pre-recorded presentations

More than 80 programs are now available, and more are being added all the time. Here are just a few:

- Beating Fatigue
- PNH: Long-Term and Post-Treatment Issues
- Complementary and Alternative Therapies: Myths, Realities and Opportunities
- Fundamentals of Hematology and Bone Marrow Failure Diseases
- Growth Factors: Examining the Risks and Benefits
- Thrombosis in PNH: Debates in Prevention and Treatment

Read what one patient had to say about the AA&MDSIF Online Learning Center:

The live and archived webinars, interviews with experts, and interactive learning modules are an invaluable source of information about bone marrow failure diseases such as mine. Whenever I have questions, the Aplastic Anemia & MDS International Foundation is always my "go to" source for answers. Thank you so very much for the knowledge and support you provide.

-Charles (PNH patient)

AA&MDSIF Online Learning Center: www.AAMDS.org/Learn

Don't have Internet access? Go to your public library or local community center, or ask a friend or family member to help you the next time you visit.

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PNH Research and Clinical Development

PNH data presented at the annual ASH conferences this year includes research exploring the how PNH develops and evolves. These research efforts will continue to help our understanding of the evolution of the PNH clone within the bone marrow—which may one day lead to new treatments or a cure for PNH.

731 An in Vitro Model of the Bone Marrow in Paroxysmal Nocturnal Hemoglobinuria Showing a Direct Effect of T-Cells within the Bone Marrow Allowing Clonal Expansion

Richard J. Kelly, M.B.Ch.B., FRCPath, Stephen John Richards, Ph.D., FRCPath, Matthew Cullen, M.Sc., Louise M Arnold, R.N., B.Sc., hons., Gemma L Brooksbank, R.N., B.Sc., hons., Anita Hill, M.B.Ch.B., Ph.D., Reuben Tooze, Ph.D., Gina M Doody, Ph.D., and Peter Hillmen, M.B.Ch.B., Ph.D.

Paroxysmal nocturnal hemoglobinuria (PNH) begins with abnormal copies, or clones, of bone marrow stem cells, followed by growth of these abnormal clones and eventually, symptoms.

To better understand the expansion of abnormal clones in PNH, a group of researchers in Leeds, United Kingdom, developed a model of PNH bone marrow using stromal cells. Stromal cells support the bone marrow's blood cell-forming activity. This model provides an environment that can maintain PNH stem cells for up to 8 weeks. Unlike in other models, these stem cells can make the progenitor cells that form the abnormal clones. The investigators used this technique to evaluate different types of bone marrow cells from 11 patients with PNH (median age 47 years) and 10 healthy people (median age 42 years).

Key Findings:

- When the investigators used patient mononuclear cells (a type of white blood cell with one nucleus) in their model, the cell culture grew poorly and stopped growing after only about 2 weeks.
- When the investigators used CD34 selected cells in their model, the bone marrow cells continued to grow for up to 8 weeks.
- When the researchers removed T cells, a type of white blood cell that helps the body's immune response, from patients' mononuclear cells, the cells from patients with PNH survived as long as the cells from healthy patients.
- The proportion of normal progenitor cells increased with both the CD34 cells and those mononuclear cells whose T cells had been removed.

Conclusions:

This research shows that PNH stem cells are not better at multiplying than normal hematopoietic (blood-forming) stem cells. T cells and CD34 cells play an important role in how the bone marrow forms normal blood cells and in the development of PNH.

This model could be used to identify how the bone marrow loses its ability to make healthy blood cells in PNH and aplastic anemia. This information is important for developing effective treatments.

732 A Novel View of Paroxysmal Nocturnal Hemoglobinuria (PNH) Pathogenesis: Do Pathologic PNH Hematopoietic Stem/Progenitor Cells (HSPCs) Displace Normal HSPCs from Their Niches in Bone Marrow Because They Are More Motile Due to Defective Adhesion and Enhanced Migratory Properties?

Janina Ratajczak, M.D., Ph.D., Rui Liu, Ph.D., Nagendra Natarajan, M.D., M.P.H., Jaroslaw P. Maciejewski, M.D., Ph.D., Vivek R. Sharma, M.D., FRCPA, and Mariusz Z Ratajczak, M.D., Ph.D., D.Sc.

Hematopoietic stem/progenitor cells (HSPCs) form blood cells in the bone marrow. Patients with paroxysmal nocturnal hemoglobinuria (PNH) have a mutation, or change, in the *phosphatidylinositol glycan* (PIG)-A gene. The goal of this study was to explore the mobilization of HSPCs by the bone marrow of patients with PNH. The authors isolated mononuclear cells (a type of white blood cell with one nucleus) from the blood of 6 patients with PNH. They then compared the PNH cells to the cells from healthy volunteers.

Key Findings:

- Stromal derived factor-1 (SDF-1) is a protein that activates certain white blood cells. PNH cells that responded to (SDF-1) have 20 times more migrating cells that form red blood cells and white blood cells than cells from healthy volunteers.
- Sphingosine-1-phospate (S1P) is a fat that controls the movement of HSPCs from the bone marrow into the peripheral blood. The progenitor cells from PNH patients that form red blood cells did not stick as well as progenitor cells from healthy volunteers to fibroblasts (cells that form connective tissue) or fibronectin (type of protein) in the with of SDF-1 and S1P.

Conclusions:

Because patients with PNH do not have the PIG-A protein, HSPCs are more mobile in people with PNH than healthy people. Over time, HSPCs in people with PNH might crowd out normal HSPCs from the bone marrow. The abnormal HSPCs that stay in the bone marrow contribute to the formation of abnormal blood cells.

Until this year, not a lot has been studied about the effects of PNH in children. Presentations at ASH 2011 described children experiencing the burden of disease as similar to adults, Likewise, children treated with eculizumab showed a rapid and sustained reduction in LDH levels, and that treatment was well tolerated. Results from these studies are the beginning of a better understanding of PNH and treatment outcomes in children with PNH.

2102 Clinical Characteristics of Classic Paroxysmal Nocturnal Hemoglobinuria (PNH) in Pediatric Patients: A Comparison with Classic PNH in Adults. An International PNH Registry Study

Alvaro Urbano-Ispizua, M.D., Hubert Schrezenmeier, M.D., Petra Muus, M.D., Ph.D., Jaroslaw P Maciejewski, M.D., Ph.D.,, Gérard Socié, Jeffrey Szer, M.B.B.S., FRACP, Robert A. Brodsky, M.D., Monica Bessler, M.D., Ph.D.,, Wendell F Rosse, M.D., Yuzuru Kanakura, Gus Khursigara, Ph.D., Camille L Bedrosian, M.D., and Peter Hillmen, M.B.Ch.B., Ph.D.

The goal of this study was to look at the differences between children and adults with paroxysmal nocturnal hemoglobinuria (PNH). Limited information is available on PNH in children. This international group of authors' report is the largest study of PNH in children and the first study to compare PNH in children and adults. The authors looked at information from 497 patients with PNH at 204 sites in 21 countries on 5 continents. Of these patients, 49 were first diagnosed when they were younger than 18 years.

Key Findings:

- Blood cell counts, lactate dehydrogenase (LDH) level (a measure of red blood cell destruction), and number of blood transfusions were similar in adults and children.
- Adults and children had similar bone marrow disorders, kidney impairment, pain in the abdomen, headaches, and shortness of breath.
- Fewer children (57%) had fatigue compared to adults (77%).
- The rates of thromboembolism, or clots in blood vessels, were much lower in children than in adults. But both children and adults with PNH had a much higher risk of thromboembolism than the general population.
- Two percent of children and 12% of adults developed thrombophlebitis (inflammation in a vein) or deep vein thrombosis (blood clot in a deep-lying vein, usually in the leg).
- Patients who were older than 18 when their disease began or who had kidney disease had a higher risk of thromboembolism.

Conclusions:

PNH has similar effects on the blood of children and adults. Fatigue is less frequent in kids. Thromboembolisms are less common in children than adults with PNH, but children with PNH are still at risk for thromboembolism.

1034 Efficacy and Safety of Eculizumab in Children and Adolescents with Paroxysmal Nocturnal Hemoglobinuria

Ulrike M. Reiss, M.D., Jeffrey Schwartz, M.D., Kathleen M. Sakamoto, M.D., Ph.D., Geetha Puthenveetil, Masayo Ogawa, M.D., FAAP, and Russell E. Ware, M.D., Ph.D.

Eculizumab (Soliris) is a drug that reduces hemolysis, or the breakdown of red blood cells, in persons with PNH. People with PNH who undergo eculizumab treatment need fewer blood transfusions. Eculizumab can also improve quality of life and prevent some of the most serious symptoms of PNH, including blood clots, high blood pressure in the lung arteries, and chronic kidney problems.

The evidence on the use of eculizumab (Soliris) to treat PNH in children is limited, partly because PNH is rare in children. The aim of this study was to evaluate the use of eculizumab to treat children and adolescents with PNH. This 12-week study included 4 girls and 3 boys aged 11–17 years. One of the patients also had aplastic anemia at the time of study enrollment.

Key Findings:

- The average LDH level, which is a measure of red blood cell destruction, dropped from 1,020 U/L at the beginning of the study to 256 U/L at 12 weeks.
- The most common side effects of the treatment were mild-to-moderate headaches, fever, and nasal congestion.
- The safety and side effects of eculizumab in this study were similar to those in adults with PNH.

Conclusions:

Like adults, children and teens with PNH tolerate short-term treatment with eculizumab well, and this treatment reduces red blood cell destruction.

Hemolysis (the destruction of red blood cells) happens constantly in PNH due to uncontrolled complement activation (part of the body's immune system). It is the main cause of the serious, life-threatening health problems associated with PNH. Some researchers are looking at whether some of the symptoms of PNH are predictors of some of life-threatening consequences of PNH.

3166 Uncontrolled Complement Activation and the Resulting Chronic Hemolysis as Measured by LDH Serum Level at Diagnosis as Predictor of Thrombotic Complications and Mortality in a Large Cohort of Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Jong Wook Lee, M.D., Ph.D., Jun Ho Jang, M.D., Ph.D., Jin Seok Kim, Sung-Soo Yoon, M.D., Ph.D., Je-Hwan Lee, M.D., Ph.D., Yeo-Kyeoung Kim, M.D., Ph.D., Deog-Yeon Jo, M.D., Ph.D., Jooseop Chung, M.D., Ph.D., and Sang Kyun Sohn

Thromboembolisms, or clots in blood vessels, are responsible for 46% of deaths in patients with PNH in South Korea. The blood cells of patients with PNH lack certain proteins on their surface, which makes these cells more vulnerable to destruction by complement proteins. These complement proteins help white blood cells fight infection.

The goal of this study was to find out whether measuring complement activation can predict risk of thromboembolism and death in patients with PNH. The authors analyzed data on 224 patients from a South Korean registry. They measured complement activation based on patients' LDH levels, which are signs of red blood cell destruction.

Key Findings:

- Patients whose LDH level at diagnosis was at least 1.5 times as high as normal LDH levels were almost five times as likely to die as healthy people of the same age and sex.
- Life expectancy in patients whose LDH level at diagnosis was less than 1.5 times normal levels were similar to those in the general population.
- Ninety-six percent of patients whose LDH level was at least 1.5 times higher than normal at diagnosis developed a thromboembolism.

Conclusions and Recommendations:

Uncontrolled complement activation, measured by LDH levels that are at least 1.5 times higher than normal at diagnosis, is a strong predictor of complications and death in patients with PNH.

Hematopoietic stem cell transplant (HSCT) can potentially cure PNH. This procedure involves the infusion of healthy blood-forming (hematopoietic) stem cells from a healthy donor. The donor's stem cells (known as a graft) enter the bone marrow and take residence, where they form healthy blood cells. The transplant is allogeneic when the cells come from a donor who is not the patient.

Doctors use drugs, such as chemotherapy, to weaken the patient's immune system before the transplant and to eliminate the patient's bone marrow cells. This procedure, known as conditioning, prevents the patient's immune system from attacking the transplanted bone marrow cells and allows the patient's bone marrow to make healthy blood cells. "Reduced intensity" conditioning refers to giving less chemotherapy to achieve this, and hopefully have less toxicity.

2047 Hematopoietic Cell Transplantation after Reduced Intensity Conditioning for Severe Paroxysmal Nocturnal Hemoglobinuria

Rafic Farah, Georg Franke, M.D., Tara B. Gregory, M.D., Mark W. Brunvand, M.D., Thoralf Lange, Rainer Storb, M.D., and Robert P. Witherspoon

The authors studied conditioning for HSCT with a combination of the drug fludarabine (Fludara) and total body irradiation. The study included 19 patients with PNH who were treated at nine different centers. Five of the patients were male, and median patient age was 34 years. Patients were treated with 30 mg/m2 of fludarabine each day for 3 days, starting 4 days before HSCT. They also were also treated with total body irradiation, mycophenolate mofetil (Cellcept), and cyclosporine or tacrolimus (Prograf) on the day of their transplant.

The authors were able to evaluate graft-versus-host disease (GVHD) in 18 patients. In GVHD, the donated stem cells (the graft) in the patient treat the patient's body (the host) as foreign, causing an immune system response.

Key Findings:

- Ten years after their HSCT, 15 patients (79%) were still alive and none had any signs of relapse.
- Fifteen patients developed neutropenia, a shortage of neutrophils (a type of white blood cell) after HSCT. Neutrophil levels recovered within a median of 16 days in patients whose donated cells engrafted, or began to grow and reproduce.
- Engraftment was successful in 17 patients (90%).
- Eight patients developed graft-versus-host disease (GVHD) within 100 days of their HSCT. Fourteen patients developed GVHD after the first 100 days.

Conclusions:

Patients tolerated conditioning with fludarabine and total body irradiation well. This conditioning treatment led to a high rate of successful engraftment. The conditioning treatment's graft-versus-host effect seems to be big enough to wipe out abnormal copies, or clones, of bone marrow stem cells as desired.

2403 Allogeneic Hematopoietic Stem Cell Transplantation in Paroxysmal Nocturnal Hemoglobinuria: A Transplant Versus No Transplant Matched Comparison Study on Behalf of the Severe Aplastic Anemia Working Party (SAA WP) of the European Group for Blood and Marrow Transplantation (EBMT) Group and the French Society of Hematology (SFH)

Régis Peffault de Latour M.D., Ph.D,, Hubert Schrezenmeier, Andrea Bacigalupo, M.D., Didier Blaise, M.D., Carmino Antonio De Souza, Stephane Vigouroux, M.D., Roelof Willemze, Louis Terriou, André Tichelli, Mohamad Mohty, Sophie De Guibert, Judith C. W. Marsh, M.B., M.D., Jakob Passweg, Jean-Yves Mary, and Gerard Socie,

Identifying which patients with paroxysmal nocturnal hemoglobinuria (PNH) might benefit from hematopoietic stem cell transplant (HSCT) is challenging. The authors analyzed data on 211 patients with PNH from the European Group for Blood and Marrow Transplantation Group registry who underwent HSCT between 1978 and 2008 and 401 patients with PNH from the French Society of Hematology who did not have an HSCT.

Key Finding:

- Sixty-eight percent of transplanted patients and 83% of non-transplanted patients survived for at least 5 years. Patients who underwent HSCT were less likely to survive if the reason for their HSCT was a thromboembolism, also known as blood clots.
- When the authors compared 24 matched pairs of transplanted and non-transplanted patients who had a thromboembolism, they found that non-transplanted patients tended to survive longer.

Conclusions:

HSCT might not be a good treatment option for patients with PNH who develop thromboembolism. The researchers suggest that ecluizumab should be considered as an alternative to HSCT for thromboembolism.

The Aplastic Anemia & MDS International Foundation (AA&MDSIF) is here to help.
We provide the following services:

- Personalized support from patient educators
- Free educational materials on many topics related to PNH
- Online Learning Center
- Patient and family conferences
- Peer Support Network
- Print and electronic newsletters with important information and updates
- Clinical trials information

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