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PNH Research Summary *from the*

2016 AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING

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

TECHNOLOGIES TO MONITOR BLOOD CLOTS AND PLATELETS

1252
Analysis of Platelets by Flow Cytometry in Patients with PNH

David Araten, M.D.; Daniel Boxer, M.D.; Michael A Nardi

Patients with PNH have abnormal clones, or copies, of stem cells in the bone marrow that make blood cells. The size of PNH clones can be used to predict the risk of thrombosis, or blood clots. Thrombosis is a life-threatening complication of PNH.

The easiest way to diagnose PNH is by flow cytometry analysis of red blood cells or granulocytes (a type of white blood cell). But sometimes, patients have very different proportions of PNH red cells and PNH granulocytes. When this happens, it might be useful to assess the proportion of PNH platelets in the patient's bone marrow. However, flow cytometry analysis of platelets in patients with PNH has been technically difficult.

The investigators describe a flow cytometry method that uses aspirin and filters platelets using sepharose gel. They used this technique to analyze blood samples from 49 patients with PNH and/or aplastic anemia and PNH. Of these patients, 16 had a history of thrombosis.

Key findings:

- On average, the proportions of PNH cells in the bone marrow were 24% for platelets, 86% for granulocytes, and 65% for red blood cells in patients with a history of thrombosis.
- The proportion of PNH platelets correlated closely with the proportion of PNH granulocytes.
- In two patients with almost undetectable PNH red cells but more than 90% PNH granulocytes, the proportion of PNH platelets was over 90%.

Conclusions:

- This technique might be useful for determining thrombosis risk, especially in patients with very different proportions of PNH red blood cells and granulocytes.

1271
Whole-Body Magnetic Resonance Imaging in Patients with PNH

Ferras Alashkar, M.D.; Haemi Schemuth, M.D.; Felix Nensa, M.D.; Ulrich Dührsen, M.D.; Thomas Wilfried Schlosser, M.D.; Alexander Röth, M.D.

Patients with PNH often have thromboembolic events, which means that they form blood clots that travel through the bloodstream and can block and damage organs. Early detection of these events is critical to improve the outcomes of PNH.

The investigators used whole-body magnetic resonance imaging (MRI) in 37 patients (51% female, median age 44 years) with PNH. Twenty-six of these patients were treated with eculizumab (Soliris®), including 23 who started this treatment before MRI. Eleven patients (29%) had a history of blood clots, including in the arteries of the lungs (pulmonary embolism) and in the deep veins (deep vein thrombosis).

Key findings:

- Existing thromboembolic events did not get worse in patients who had a history of these blood clots.
- Two patients treated with eculizumab who had a history of thromboembolic events developed blood clots in the legs or both kidneys, and one developed blood clots in leg bones.
- Two patients with no history of thromboembolic events had blood clots in leg bones, and a third had a previously undiagnosed blood clot blocking one kidney.

Conclusions:

- Whole-body MRI scans seem to be a feasible way to assess the system of veins and arteries in patients with PNH.
- This imaging technique makes it possible to detect previously unknown complications in the veins and arteries.

401
C3 Binding on Red Blood Cells of Patients with PNH during Eculizumab Treatment

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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 two important complement proteins, CD59 and CD55. Without these proteins, the complement system destroys red blood cells prematurely.

Eculizumab (Soliris®) is a drug that blocks complement protein attacks on blood cells and prevents premature destruction of red blood cells in people with PNH. The drug also prevents blood clots and the damage they can cause. However, almost all patients treated with eculizumab develop red blood cells bound to C3 fragments. C3 is an enzyme in the complement system. This C3 binding results in the destruction of red blood cells outside the veins and arteries that can reduce the benefits of eculizumab.

The purpose of this study was to find out why some PNH red blood cells bind to C3 and others don't. The investigators studied red blood cells from patients with PNH incubated with serum samples from patients treated with eculizumab.

Key findings:

- A fraction of the cells immediately bound to C3, and the proportion of bound cells increased from about 9% after 5 minutes to 10% after 24 hours.
- Inactivation of CD55 on normal blood cells did not result in red blood cell destruction without eculizumab or C3 binding with eculizumab.
- Normal red blood cells with inactivated CD59 underwent red blood cell destruction without eculizumab but they bound to C3 fragments with eculizumab. The same thing happened in patients with PNH treated with eculizumab.
- Inactivation of both CD55 and CD59 increased the amount of C3 binding.

Conclusions:

- The deficiency of CD59, but not CD55, plays an important role in C3 binding to PNH red cells of patients treated with eculizumab.
- These findings could lead to innovative approaches to reduce C3 binding and red blood cell destruction outside the veins and arteries of patients with PNH treated with eculizumab.

2428
ALXN1210 Treatment for Red Blood Cell Destruction in Patients with PNH: Interim Analysis

Jong-Wook Lee, M.D.; Eric Scott Bachman, M.D., Ph.D.; Rasha Aguzzi, M.S.; Jun Ho Jang, M.D., Ph.D.; Jin Seok Kim, M.D., Ph.D.; Scott T. Rottinghaus, M.D.; Lori Shafner, Ph.D.; Jeff Szer, M.B.B.S.

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 two important complement proteins, CD59 and CD55. Without these proteins, the complement system destroys red blood cells prematurely.

ALXN1210 is a biological agent that quickly and completely inhibits complement protein attacks on blood cells. This drug prevents premature destruction of red blood cells in people with PNH. ALXN1201 doesn't require as many doses as eculizumab (Soliris®).

This Phase I/II open-label study assessed the safety, tolerability, and efficacy of two different doses of intravenous ALXN1210 in 13 adults with PNH. Group 1 was treated with 400 or 600 mg of ALXN1210, followed by 900 mg every 4 weeks for a median of 6 months. Group 2 was treated with 600 or 900 mg, and then with 1,800 mg every 4 weeks for a median of 5 months.

Key findings:

- Levels of lactate dehydrogenase (LDH) dropped to the normal range in 4 patients in group 1 (67%) and 6 patients (86%) in group 2. High levels of LDH are a sign of cell damage.
- Average hemoglobin levels improved or were stable in both groups.
- 1 of 2 patients in group 1 and all 3 patients in group 2 who had red blood cell transfusions in the previous 12 months stopped needing transfusions.
- Fatigue dropped by 29% in group 1 and by 61% in group 2 at day 43. Fatigue didn't change any more in group 1 at day 169, but it improved by 76% in group 2.
- No patient had a serious side effect or had to stop the treatment because of side effects.
- The most common side effect was headache in 4 patients.

Conclusions:

- The lower monthly doses of ALXN1210 might be enough to stop abnormal blood clot formation in PNH.

2683
Combined Immunosuppressive Therapy for Aplastic Anemia and Eculizumab for Paroxysmal Nocturnal Hemoglobinuria: A UK Experience

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PNH clones are abnormal copies of abnormal stem cells in the bone marrow that have a mutation in the PIG-A gene. At least half of the patients with aplastic anemia in the United Kingdom have a PNH clone. There is little evidence to guide treatment of both aplastic anemia and PNH in the same patient.

The investigators reviewed data on 26 patients (median age 40 years) with aplastic anemia in the United Kingdom who were treated with eculizumab (a PNH treatment) and immunosuppressive therapy (for aplastic anemia) at the same time. Ten of the patients had severe aplastic anemia, and 15 had aplastic anemia that was not severe. One patient had hypoplastic MDS, a condition similar to aplastic anemia.

Key findings:

- Six of 8 patients treated with antithymocyte globulin (ATG), cyclosporine, and eculizumab responded. The 2 patients who didn't respond did go into remission after hematopoietic stem cell transplantation (HSCT).
- Eight of 14 patients treated with cyclosporin and eculizumab responded.
- Eight patients had HSCT. One patient died, but the rest went into remission.
- The 7 patients who survived HSCT stopped needing eculizumab because they no longer had PNH.
- Six patients died. One went into remission after HSCT but died 2 years later of graft-versus-host disease. The others responded only partially to treatment, didn't respond, or died during the procedure.
- In a comparison group of 14 patients treated with similar immunotherapies but not eculizumab, 4 of 9 patients treated with ATG and cyclosporin went into remission, 1 went into remission but then had a relapse, 3 had a partial response, and 1 didn't respond but did go into remission after HSCT.
- Of 5 patients in the comparison group treated with cyclosporin alone, 2 went into remission, 1 responded partially but then had a relapse, and 2 didn't respond.

Conclusions:

- Whether a patient with aplastic anemia has symptomatic PNH requiring eculizumab treatment should not influence decisions about how to treat the patient's aplastic anemia.
- Treatment with eculizumab at the same time doesn't reduce the effectiveness of immunosuppressive treatment for aplastic anemia.

1251
Phase I Study Results of APL-2 Treatment in Healthy Volunteers

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Eculizumab (Soliris®) is a drug that blocks complement protein attacks on blood cells and prevents premature destruction of red blood cells in people with PNH. The drug prevents blood clots and the damage they can cause. But almost all patients treated with eculizumab develop red blood cells bound to C3 fragments. C3 is an enzyme in the complement system.

Even with eculizumab treatment, some patients with PNH continue to need regular blood cell transfusions. In these patients, C3 continues to help form blood clots inside and outside the veins and arteries.

APL-2, a drug that inhibits C3, might prevent blood clots in people with PNH. The purpose of the two studies summarized here included assessing the safety and tolerability of APL-2 in 51 healthy adult volunteers. The two double-blind, placebo-controlled studies took place at one center in Australia. The investigators administered a single dose to 24 participants and daily doses for 28 days to 16 participants. In addition, 7 participants received a one-time placebo and 4 received daily placebo for 28 days.

Key findings:

- Participants had no major side effects.
- They also had no side effects related to the treatment that were serious enough to make them leave the study.
- The results showed no important changes in vital signs, electrocardiogram findings, or laboratory test results.
- Concentrations of APL-2 in blood were almost at steady state after daily doses for 28 days.
- Daily doses of 180 mg or 270 mg of APL-2 significantly reduced premature destruction of red blood cells as soon as 8 days after the start of treatment.
- The drug continued to have this effect through the 28-day treatment period.

Conclusions:

- The doses of APL-2 used in the study were safe, and participants tolerated them well.
- Daily administration of APL-2 seems to be better than one-time administration.