# Paroxysmal nocturnal hemoglobinuria

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# PNH

- PNH is an acquired disease
- It is caused by a mutation in blood stem cells, the precursors of our blood cells in the bone marrow
- This mutation causes destruction of red blood cells and increases the risk of blood clots
- About 16 in 1000 people are affected by PNH

# PNH

- About 20 to 35% of patients with PNH die within 6 years of diagnosis without appropriate therapy
- With new therapy life expectancy is the same as the general population
- Not everybody diagnosed with PNH requires immediate treatment

# PNH

- Symptoms of PNH are due to the destruction of the red blood cells by complement, which is part of our immune system

- Complement also causes other problems that complicate patients with PNH

# Symptoms of PNH

- Fatigue
- Anemia
- Problems swallowing food or water
- Abdominal pain
- Erectile dysfunction
- Chest pain
- Shortness of breath
- Blood clots in veins or arteries
- Stroke
- Bone marrow failure or low blood counts
- Brown urine

# PNH

- Causes of death without the appropriate treatment is usually due to blood clots in Europe and the US, and to renal failure in Asia

# PNH and other bone marrow conditions

- PNH can be present with other conditions in the bone marrow, such as aplastic anemia (an empty bone marrow), MDS (myelodysplastic syndrome), or rarely other conditions
- It can also present with low blood counts or iron deficiency due to iron loss in the urine after RBCs are destroyed

# Aplastic anemia and PNH

- In some studies, 26% up to 57% of patients with aplastic anemia have PNH. These patients respond to aplastic anemia therapy better than the ones without PNH

# Complement

- It is a system of more than 30 proteins in the blood that is part of our immune system
- These proteins help fight microbes and clear them from the blood. They also cause an inflammatory response and can make holes in cells to destroy them

# Complement cascade

- The complement cascade involves a series of reactions and changes in proteins in order to create products that take care of microbes
- It starts with a protein called C3, that eventually gives rise to C5 and later to C5a and C5b.

# Complement cascade

- C5a causes inflammation and changes in WBC and cells lining the blood vessels
- C5b-9 causes inflammation and cell destruction
- The general population can control complement to keep it safe, but not PNH patients. They lack some proteins that protect the red blood cells from complement

# Types of PNH

- Severe bone marrow failure with very little PNH
- Bone marrow failure with severe PNH (destruction of red blood cells present)
- Relatively normal bone marrow and severe PNH with RBC destruction

# Testing for PNH-indications

- When patients have a blood clot and are destroying red blood cells
- Destroying red blood cells and iron deficiency
- Abnormal blood counts without other causes
- Bone marrow with aplastic anemia, certain types of MDS, or a marrow with less than normal amount of cells
- Blood clots in rare sites

# Testing for PNH

- The test is done with blood. It is very specific and can tell you the PNH clone size
- We want to know the granulocyte clone size
- Clones above 8% usually cause hemolysis

# Treatment indications

- When there is a blood clot
- When there is anemia requiring blood transfusions or near requiring transfusions
- When symptoms are debilitating or interfering with normal activities
- Some American experts treat when the clone is too large due to high risk of clots. British experts don't do it

# Treatment- Eculizumab

- Eculizumab blocks C5 in the complement cascade, so prevents destruction of the red blood cells
- None of the treatments improve white blood cells or platelets
- Eculizumab is an IV medication given weekly x 5 weeks, then every 2 weeks
- Life expectancy is the same as the population when treated with it

# Eculizumab

- Side effects:

- Risk of infection with Meningococcus. You need vaccines and we offer Penicillin prophylaxis
- Headaches, nose congestion, sore throat, aches, diarrhea. Most are very rare

# Ravulizumab

- Inhibits C5 in the complement cascade. Just like Eculizumab
- Compared to Eculizumab and it was not inferior
- It is given IV every 8 weeks after a couple of infusions 2 weeks apart
- Same side effects as Eculizumab
- No data during pregnancy

# Pegcetacoplan

- Not FDA approved yet. It is subcutaneous
- It inhibits C3 at the complement cascade, not C5
- Risk of infection seems similar to approved medications
- With C5 inhibition, sometimes some red blood cells still get destroyed. Potential benefit is the addition of RBC destruction prevention due to C3

# Crovalimab

- It inhibits C5 but in a slightly different place than the already approved medications
- The early studies use IV and subcutaneous administration with different schedules
- Well tolerated in early studies. Studies are ongoing
- Not approved yet

# LFG316

- Anti-C5 antibody under investigation
- It is able to inhibit C5 that is resistant to Eculizumab. This resistance is seen usually in Japanese patients

# REGN3918

- It is given IV and then subcutaneously
- It seems to work in normal C5 as well as a variant of C5 that may be missed by current treatments

# ACH-4471

- Oral medication
- It inhibits the alternative pathway of the complement cascade
- Studies have been done alone or in combination with Eculizumab

# LPN023

- Oral agents being investigated as an addition to Eculizumab

# AMY-101

- It binds to C3 and C3b
- Very well tolerated in early studies
- Given subcutaneously every 48 hrs

- Questions