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C5 and C3 – Translating Acronyms to Actionable Targets for the Treatment of PNH

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Dr. Patel:
Hello. My name is Bhumika Patel. I'm from Prisma Health Cancer Institute, affiliated with the University of South Carolina School of Medicine in Greenville, South Carolina. I'll be discussing the current treatments for paroxysmal nocturnal hemoglobinuria. PNH is a hemolytic anemia that arises from a somatic mutation in the PIGA gene, which causes defective synthesis of the GPI anchor proteins leading to the development of PNH and its associated clinical manifestations. Keep in mind, PNH can arise de novo or arise from aplastic anemia. PNH is characterized by chronic intravascular hemolysis due to the action of the complement on the abnormal red blood cells, lacking CD55 and 59. PNH RBC's lyse more readily in the presence of activated complement. Similarly, granulocytes and platelets are sensitive to the complement as well in PNH.

The complement system plays a pivotal role in the pathophysiology of PNH. Complement is a group of proteins that are part of our immune system. It circulates in an inactive form. However, many different events can activate the complement system, including trauma, infection, and stress. In PNH, activated complement will attack red blood cells causing them to lyse.

Here, Dr. Gerber and colleagues illustrate the most important components of the complement system in PNH. CD55 regulates the proximal components of the complement system, C3 convertase and C5. Where CD59 regulates the membrane attack complex assembly. Lack of CD55 and 59 leads to chronic uncontrolled complement activation leading to intravascular hemolysis, leading to the causes of morbidity and mortality in patients with PNH such as thrombosis and organ damage. Currently, there's three FDA-approved therapies for patients with PNH. The first approved therapy for PNH was a C5 inhibitor Eculizumab, subsequently followed by its derivative ravulizumab, which is a C5 inhibitor. And most recently Pegcetacoplan, which is a C3 inhibitor, was approved for patients with PNH, which we'll get into details in the next few slides.

When we think about PNH therapeutics we look at it from three different aspects. What can we do to support these patients? How can we help improve red blood cell production? And how can we manage the hemolysis? From supportive measures, we think about transfusional support for our patients. How do we treat iron overload if progressive? The role of anticoagulation after an acute thrombotic episode. In patients, when we think about red blood cell production, we're looking at ways how we can optimize red blood cell production in these patients with ESA therapies, treating iron deficiency anemia, use of immunosuppressive therapy, if reticulocyte or platelet count is low, because many patients with PNH may have a component of aplastic anemia. And the role of anabolic steroids. For hemolysis, we use our complement inhibitors, our C5 and C3, which is our current standard of care.

Eculizumab and ravulizumab are humanized monoclonal antibodies that bind to the complement component C5, thereby inhibiting terminal complement activation. It decreases hemolysis of red blood cells and tendency of thrombosis, but it does not fix the defect in hematopoiesis. It reduces intravascular hemolysis, but not extravascular hemolysis, based upon its mechanism action in the complement system. It's important to vaccinate patients two weeks prior to treatment with meningococcal vaccine due to the risk of

meningitis secondary to complement inhibition. Then revaccinate every three to five years.

Eculizumab and ravulizumab target C5. And here we'll discuss the route of administration in dosing. Eculizumab is given IV 600 milligrams weekly for four doses and then maintenance 900 milligrams every two weeks. Whereas ravulizumab is given IV weight-based loading dose and then maintenance two weeks later weight-based and then every eight weeks making it more convenient for patients due to its longer half-life, which is currently our standard of care.

However, most recently, Pegcetacoplan which is a pegylated pentadecapeptide which was approved for patients with PNH. It binds to a complement component C3, thereby inhibiting proximal complement activation, decreasing hemolysis of red blood cells and tendency of thrombosis, but does not fix the defect in hematopoiesis. It reduces intravascular and extravascular hemolysis, which is different than the C5 inhibitors. It's important to vaccinate patients two weeks prior to treatment for Strep pneumo, Strep meningitis, and H. influenzae type B secondary complement inhibition. Then vaccinate every three to five years per guideline. Pegcetacoplan is a pegylated pentadecapeptide targeting C3 which is administered subcutaneously. When converting patients from C5 to C3 therapy, it's important to overlap a C5 therapy for four weeks. Or in some patients it is being used up front in treatment-naive patients where you'll start 1080 milligrams twice weekly subcutaneously. However, it can be given every three days if the LDH remains two times upper the middle of normal.

In conclusion, PNH is an acquired clonal disorder characterized by deficiency of the GPI-linked proteins CD55 and 59 diagnosed by flow cytometry. It's characterized by chronic hemolytic anemia due to uncontrolled complement activation and its associated complications. Currently, there's three FDA-approved therapies available: eculizumab, ravulizumab or pegcetacoplan. More choices for therapy to come. Thank you.

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