Editorial note on paroxysmal nocturnal hemoglobinuria.

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Editorial Note

Paroxysmal nocturnal hemoglobinuria (PNH) is an uncommon bone marrow disorder related to haemolytic anaemia, thrombosis, and cytopenias. Treatment for PNH was limited and patients with PNH were treated with corticosteroids, anticoagulation for thrombosis, and iron supplementation for chronic iron deficiency secondary to intravascular hemolysis. The Important feature of PNH was an iron deficiency and iron supplementation continues to be recommended as a treatment for the manifestations of PNH. With the introduction of C5 complement factor inhibitor treatments, potential long-term manifestations of treatment focused to decrease greater iron content.

An acquired mutation in phosphatidylinositol glycan class A (PIGA) gene results in two missing glycosylphosphatidylinositol (GPI) anchored proteins including CD55 and CD59. A deficiency of those complement regulatory proteins in red Blood cells leads to increased complement activation resulting in intravascular hemolysis with iron loss. Therefore, many PNH patients at initial stages have signs and symptoms of intravascular hemolysis and resultant iron deficiency. While extravascular hemolysis is additionally increased at disease onset, intravascular hemolysis signs and symptoms predominate before treatment with complement inhibitors.

Treatment options and management for PNH were revolutionized with the approval of the C5 complement inhibitors eculizumab in 2007 and subsequently with ravulizumab in 2018. Both complement inhibitors block terminal complement by binding to C5 and preventing formation of the membrane attack complex. Therefore, intravascular hemolysis subsides with initiation of those treatments. These patients have improvements in their hemoglobin o greater extent without the use of Blood Transfusion. Notably, patients on these treatments will still experience significant extravascular hemolysis because the complement inhibitors will not effect on CD55 deficiency and thus cause C3d deposition on PNH red cells. The effect of treatment on iron metabolism has not been well studied, but with reduction in intravascular hemolysis renal iron clearance should decline; in contrast, extravascular hemolysis usually leads to retention of total body iron by the RES.

Hepcidin is produced within the liver and regulates iron uptake because it inhibits the activity of ferroporotin-1, which is major significant cellular iron exporter.Hepcidin is suppressed when more iron is required to support increased red blood corpuscle production. Under usual conditions, hepcidin is elevated in setting of infection, inflammation, and normal iron stores. Suppression of hepcidin can cause hemochromatosis in setting of ineffective erythropoiesis, hereditary hemochromatosis, and hemolytic anemias.

Recent Studies suggest that longitudinal assessment (Fe, TIBC, ferritin) be reduced in PNH patients being treated with C5 complement inhibitors which iron supplementation be stopped once patients are iron replete. In those demonstrating evidence for hemochromatosis, assessment of hepatic iron should be considered. It's certainly unclear whether treatment (iron chelators, therapeutic phlebotomy if tolerated, or future hepcidin agonists) is indicated to scale back the hemochromatosis. Novel inhibitors of Complement Factor B, Complement Factor D or C3 might provide protection against both intravascular and extravascular hemolysis therefore mitigating the potential for hemochromatosis. Hemochromatosis remains a potentially unrecognized complication of novel treatments for PNH and warrants further investigation.

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