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Key Novel Considerations for Pegcetacoplan?

Announcer:

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Dr. Patel:

Hello, my name is Dr. Bhumika Patel, and I am from Prisma Health Cancer Institute, affiliated with the University of South Carolina School of Medicine in Greenville, South Carolina. We'll be discussing key novel considerations for pegcetacoplan. PNH is an acquired hemolytic anemia characterized by chronic intravascular hemolysis, high risk of thrombosis, and bone marrow impairment. It is a rare disease, with a prevalence of less than 10 cases per million. PNH is caused by somatic mutation in the X-linked PIGA gene. Hematopoietic stem cells in PNH are unable to synthesize GPI-anchored proteins that are protective against activated complement. In PNH in particular, the lack of CD 55 and 59 increase red blood cell susceptibility to complement activation, resulting in chronic intravascular hemolysis and its associated clinical complications.

Current FDA approved treatments for PNH include two C5 inhibitors, eculizumab and ravulizumab, categorized as terminal complement inhibitors, and the most recently approved therapy, C3 inhibitor pegcetacoplan, which is proximal complement inhibitor. We'll be discussing the review article about hemolysis and PNH by Dr. Notaro and colleagues, with the aim to compare the benefits and adverse effects of proximal versus terminal complement inhibition in PNH. In PNH, the lack of GPI-anchor protein CD 55 and 59 result in one of the cardinal features of PNH, intravascular hemolysis. This results in anemia, symptoms of smooth muscle dystonia, and high risk of thrombosis. Overall, intravascular hemolysis has been reduced with complement inhibition therapy with C5 inhibitors and C3 inhibitors. The first approved complement therapy for PNH was in 2007, the monoclonal antibody, eculizumab, targeting C5. This drug has been a major advance in the management of PNH, and the uses resulted in remarkable clinical improvements, including relief for anemia, reduction in the thrombotic risk, improved quality of life, and prolonged survival.

In comparison to terminal complement inhibitors, the duration of follow up is limited with the proximal complement inhibitors. And how the proximal complement inhibitors compare to terminal complement inhibitors in regards to the risk of thrombosis and other clinical factors, we will have to await future results. But as of now, we know both C5 inhibitors and C3 inhibitors are effective in treating patients with PNH and controlling intravascular hemolysis. Despite optimal complement therapy, breakthrough hemolysis can occur, which is characterized by sudden resurgence in signs and symptoms of intravascular hemolysis, including hemoglobinuria, marked increase in LDH, and sharp decrease in hemoglobin.

This may be caused by suboptimal C5 inhibition, which can be evaluated by looking at it from the pharmacokinetics due to low levels of monoclonal antibody, or pharmacodynamics, it could be related to inflammation or infection, resulting in strong complement activation breaking through C5 blockade. Another important clinical point to discuss is extravascular hemolysis in PNH. During C5 blockade, C3 fragments bind to PNH red blood cells because C3 activation is unrestricted. Opsonized red blood cells are targeted by macrophages, resulting in extravascular hemolysis, this is demonstrated by persistent reticulocytosis. Up to a third patients can remain transfusion dependent during C5 inhibitor therapy. Which brings us to the new approved therapy, pegcetacoplan, C3 inhibitor. Pegcetacoplan has been found to not only prevent intravascular hemolysis, but also extravascular hemolysis, it blocks the formation of the membrane attack

complex and prevents C3 deposition on red blood cells.

So, for patients up to a third that are not improving with C5 inhibitor therapy, pegcetacoplan would be a good option. Consequences of complement blockade is an important topic to discuss. Breakthrough hemolysis have been reported with eculizumab, rare cases report LDH up to five times upper limit of normal in the pegcetacoplan, where very severe cases reported LDH 10 to 15 times upper limit of normal. Authors theorize the etiology of the breakthrough hemolysis is different between proximal and terminal complement inhibition. Some of the reasons are as followed, in patients receiving pegcetacoplan in PNH, the red blood cells are larger than in patients receiving C5 inhibitors.

Another aspect to look at is that the half-life of pegcetacoplan is shorter, so plasma level may drop below its efficacy due to a missed dose, or injection related. But the third reason which is really important to consider is the intrinsic features of the complement system itself. The proximal compliment system is composed of multiple steps of enzyme activation, giving it a lot of compliment amplification potential. Whereas when you look at the terminal compliment system, the assembly of the membrane attack complex is completed in a one-to-one ratio, where one C5b recruits one molecule of the membrane attack complex, which may be limiting its breakthrough hemolysis in comparison to proximal inhibitor. Risk of breakthrough hemolysis applies to any drug targeting the proximal and terminal pathway, but the mechanism action may be unique, which will need to be further evaluated.

This brings us to combined terminal and proximal compliment inhibition. Combining therapies may provide advantages in treatment of PNH by synergistic efficacy in preventing C3 binding in PNH, and reduction of extravascular hemolysis. However, the downside of combined treatment is the risk of infection is largely unknown, and the financial toxicity, but this will need to be further be evaluated in clinical trials. Here is a great summary table of the complement inhibitor treatments for PNH, which are separated by terminal complement pathway and proximal complement pathway. As previously discussed, eculizumab and ravulizumab are two terminal complement pathway inhibitors that are approved for the treatment of PNH, and the most recently approved therapy is pegcetacoplan, which is proximal complement inhibitor. Other therapies that are being currently evaluated include: crovalimab, pozelimab, and nomacopan, which are terminal compliment pathway inhibitors, but we'll have to await future results to see how they'll fit into the treatment paradigm for PNH.

Also, other agents that are being evaluated are proximal complement inhibitor or oral therapies, which are factor B and D inhibitors, iptacopan and danicopan. Both of these drugs seem very promising, as either monotherapy, and as add-on therapy to C5 inhibitors, however we'll have to wait for future results to see how they'll fit, once again, in the treatment paradigm for PNH. In conclusion, the sequencing and combination of proximal and terminal complement inhibitors will need to be further investigated in clinical trials for the treatment of PNH. Combined approach may prevent extravascular hemolysis and breakthrough hemolysis, improving clinical care for the patients of PNH. Thank you.

Announcer:

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