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Paroxysmal Nocturnal Hemoglobinuria (PNH) in the Era of New Therapies

Announcer:
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Dr. Patel:
Hello, my name is Dr. Bhumika Patel, and I'm from Prisma Health Cancer Institute, affiliated with the University of South Carolina School of Medicine in Greenville, South Carolina. We'll be discussing, "PNH in the Era of New Therapies." The complement system plays an important role in regulating our immune system. It has three major functions. Number one, optimization of phagocytosis, number two, inflammatory reactions and number three, complement mediated cell lysis. The classical, lectin and alternate pathway, converge at C3 leading to C5 in the assembly of the membrane attack complex. The complement system can be divided into proximal or terminal. In PNH, the lack of regulatory protein CD55 and 59, leads to dysregulation of the complement system, causing chronic intravascular hemolysis and its associated clinical complications.

Currently, we have three FDA-approved therapies for PNH. The first approved therapy was eculizumab, followed by its derivative ravulizumab, which targets C5 in the terminal complement system. C5 inhibitors are the standard of care for PNH. They have shown to improve quality of life, decrease transfusions, and the risk of thrombosis. Most patients become transfusion-independent on C5 therapy. However, most patients have some degree of C3-mediated extravascular hemolysis. Up to a third of PNH patients treated with C5 inhibitors, will remain transfusion dependent or have symptomatic anemia and could potentially benefit from proximal inhibitors. This leads us to the most recent FDA-approved therapy of pegcetacoplan, which is proximal C3 inhibitor, which targets intravascular and extravascular hemolysis. With persistent anemia due to C3-mediated extravascular hemolysis, other complement inhibitors are being investigated, such as oral factor B and D inhibitors, along with C5 and C3 inhibitors. Let's take a closer look.

Eculizumab and ravulizumab remain the standard of care for the treatment of PNH. Both are IV monoclonal antibodies targeting C5 in the terminal complement pathway, inhibiting the formation of the membrane attack complex in controlling intravascular hemolysis. Both of these agents have shown to improve quality of life, anemia and decrease the risk of thrombosis. However, both of these treatments are lifelong treatments and not all patients treated with these agents have full responses and some patients may remain refractory. It remains an inconvenience due to the frequency of treatment and there's a small risk of meningitis with complement inhibition therapy. Prior to initiating therapy on a patient with a C5 inhibitor, it's important to discuss the risk and benefits and personal goals and fears. Other C5 inhibitors that are currently being investigated that are self injectables are crovalimab and pozelimab. They may be similar or have better efficacy as the current C5 inhibitors, but are unlikely to rescue eculizumab non-responders and have similar safety considerations as with eculizumab. We will have to await the results of the COMMODORE and ACCESS trials to see how these agents will fit into the treatment paradigm of PNH.

The first approved C3 inhibitor, pegcetacoplan, was approved for the treatment of PNH in the frontline in the US and in the Europe for patients who remain anemic, despite C5 therapy. The PEGASUS trial noted that pegcetacoplan was superior in non-responders to eculizumab and can replace the IV infusion of anti-C5 therapy as an initial therapy and has been noted to improve patients' quality of life

because it's a self-injectable. Pegcetacoplan has shown to improve intravascular and extravascular hemolysis. However, we have limited long term safety data compared to C5 inhibitors. We will have to await the results of the PRINTS trial also, to see how C3 inhibitors will be continued to be utilized in the treatment of PNH. Other targeted therapies for C3 are also in development. Other proximal inhibitors that are being investigated are oral inhibitors. So factor B inhibitors, such as BCX9930, danicopan, and ALXN2050, are oral drugs that are given twice or three times a day. So far they've been shown to be effective in combination with C5 inhibitors or as monotherapy. Danicopan is being investigated as an add on therapy to C5 inhibitors. BCX9930 is under investigation and will likely be developed as a single agent.

Both drugs rescue refractory patients and improve intravascular and extravascular hemolysis. However, there is limited long term safety data compared to C5 inhibitors, and we will have to await the results of these trials to see how they'll fit into the current treatment for PNH. Other oral proximal inhibitors that are being investigated are factor B inhibitors. It's a oral drug twice a day, so far has shown to be very effective in combination with C5 inhibitors and as monotherapy. It appears to be effective with rapid and durable reduction in LDH and improvement in markers of hemolysis in most patients. Will likely be developed as a single agent or to rescue non-responders to other therapies. It has been shown that LNP023 improves intravascular and extravascular hemolysis but note, there's limited long term safety data compared to C5 inhibitors, as with other investigational agents. We will have to await the results of the APPLY and APPOINT trial to see how they'll fit into the treatment paradigm of PNH.

In conclusion, there will be choices for therapy for patients with PNH. Patients may have preferences and we would bet on oral agents in the future. However, we'll have to await the safety data for these agents. While cure is not in sight, new drugs will convert this disease into a more manageable condition. Curative treatments are being conceptualized: there is more hope. Thank you for participating.

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