Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/what-are-the-data-supporting-first-line-c3-inhibitor-treatment-of-pnh/16111/

Released: 09/22/2023
Valid until: 09/22/2024
Time needed to complete: 41m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

What Are the Data Supporting First Line C3 Inhibitor Treatment of PNH?

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. de Castro:
Hello, welcome to this talk entitled: What Are the Data Supporting First Line C3 Inhibitor Treatment of PNH? I'm Carlos de Castro. I'm a Professor of Medicine at Duke University in Durham, North Carolina.

With treatment of PNH with C5 inhibitors, which were the standard of care for many, many years, we learned of the consequence of extravascular hemolysis. When a PNH red cell is not treated with any drug, it is quickly lysed through the membrane attack complex, which forms a pore in the cell, and leads to intravascular hemolysis with increased LDH, anemia, and hemoglobinuria, and marked fatigue. Once a patient is put on a C5 inhibitor such as eculizumab, these PNH red cells will survive in the circulation, as they are not destroyed through the MAC complex, which eculizumab blocks. But we've learned that they have C3 fragment deposition on their surface, which can lead to uptake in the liver and spleen, and extravascular hemolysis with consequences of a return of anemia, not much of an increase in LDH, and usually with fatigue.

With this, we've learned that about 10 to 20% of patients on C5 inhibitors have a suboptimal response to therapy, that is they're still anemic or needing transfusions. So other targets are being investigated that block the proximal pathway at C3 or earlier. The one that's been FDA approved that we'll talk about is pegcetacoplan. But others such danicopan and iptacopan are in clinical trials now.

Pegcetacoplan was compared to eculizumab in PNH in a phase 3 trial entitled PEGASUS published in the *New England Journal*. pegcetacoplan is a pegylated pentadecapeptide that targets C3, it's given subcutaneously by a pump twice a week. PEGASUS, as I mentioned was this phase 3 randomized multicenter trial, comparing pegcetacoplan to eculizumab in PNH patients who were on treatment with eculizumab and had a hemoglobin level less than 10.5. The primary endpoint of the study was the change in hemoglobin at week 16. And we'll show you that pegcetacoplan was clearly superior to eculizumab in this patient population in terms of that primary outcome. We'll talk about adverse events. This drug was FDA approved in May of 2021, and is now available.

So in this graph, you see patients who were - PNH patients who had a suboptimal response to eculizumab, their average hemoglobin at baseline was 8.7. There was a 4-week period where they got both drugs to prevent any hemolysis while they were transitioning, and then they were randomized to monotherapy with one or the other. All patients in the 4-week run-up had a rise in hemoglobin to almost 12, and then those that were maintained on pegcetacoplan maintain that hemoglobin at a level of about 11.5 to 11.7. Whereas those on eculizumab, they returned to their baseline around 8.5.

We now have data on the long-term extension study after week 48. And you see patients who were kept on pegcetacoplan at week 48 still had a hemoglobin a mean of 11.3, whereas those that were switched over to pegcetacoplan for the extension study, their hemoglobin at week 48 was up to 11.6. The number of secondary outputs were looked at including transfusion freedom, change in reticulocyte counts which went down on the pegcetacoplan as we blocked more hemolysis, and changing the FACIT-Fatigue score. And

all of these seem to be superior in the pegcetacoplan arm, although this was a non-inferiority study. The LDH however, remained about the same.

Safety outcomes were looked at. We saw breakthrough hemolysis in both groups; more in the eculizumab than the pegcetacoplan, but 3 patients had to stop the pegcetacoplan because of the breakthrough hemolysis, as we didn't build in anything to account for this, and they had to be given a dose eculizumab. There were injection site reactions that were mild, and diarrhea that was mild on this study.

So in summary, pegcetacoplan was superior to eculizumab with respect to change and baseline at week 16, the primary endpoint. And then improvements in key hematological and clinical variables such as freedom from transfusion. Adverse events were very mild. And in this patient population, pegcetacoplan, by preventing intravascular and extravascular hemolysis, provided better control of the disease than treatment with eculizumab.

We now have data coming from the PRINCE study. PRINCE is a trial looking at PNH patients who are treatment naive. They are being treated with standard of care in whatever country they are living in. And this may or may not include a C5 inhibitor, and you can see again that the pegcetacoplan arm had a rise in hemoglobin to 12 by week 30 on average, whereas those on standard of care maintained their anemia at about baseline.

With that, I'd like to thank you for attending this talk.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, LLC. and is part of our MinuteCE curriculum.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.