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

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What Is the Impact of First line PNH Treatment Choice on Risk of Thrombosis

Announcer:
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Dr. de Castro:
Welcome to this talk entitled: What is the Impact of First Line PNH Treatment Choice on the Risk of Thrombosis? I'm Carlos de Castro. I'm a Professor of Medicine at Duke University in Durham, North Carolina.

Thrombosis, or blood clots, in PNH are one of the most feared complications of PNH, occurring in up to 40% of patients during their lifetime. They can contribute to end-organ damage including the lungs, liver, the kidney, the brain, and in earlier studies thrombotic events were the leading cause of death accounting to 40 to 67% of deaths in the U.S. and Europe. The first thrombotic event increased the risk for death 5- to 10-fold in patients with PNH. And the problem was always that once you had a blood clot, you tended to clot again, despite anticoagulant therapy. Thrombotic events can be the presenting symptoms in PNH, and about 20% of patients will present this way. And the first thrombotic event unfortunately can be fatal. Thrombotic events are correlated with the size of the white cell clone, or the PNH clone, that is, the larger the clone, the higher the risk of blood clots. And these blood clots can occur in very unusual locations.

In this pie graph you see about 1/3 of patients with thrombotic events occur as standard DVTs in their - in the leg or the extremity. But another 1/3 occur in the GI tract, including hepatic portal veins, Budd-Chiari syndrome, or mesenteric and splenic veins. Other clots can occur in cerebral veins, cerebral dural veins or superficial dermal veins, which are highly unusual locations. And they can be arterial clots such as stroke or myocardial infarctions.

We have data from the first treatment that was ever developed for PNH in complement inhibition as eculizumab where the rates of thrombotic events fell from about 39 in the pre-eculizumab treatment arm to 3 once they were on treatment. So overall, it was estimated that 92% fewer thrombotic events will occur with eculizumab treatment. And the majority of patients on this study had been receiving concomitant anticoagulants. There was no look at what happened if we withdrew anticoagulants. But we now believe you can safely do that. We now have newer drugs that are being developed to target complement. These include pegcetacoplan, which targets C3 and is now FDA approved, and factor D and B inhibitors which are in clinical trials.

So with eculizumab and ravulizumab, we know data now long-term on the thrombotic event rates and these range for eculizumab from about 1.07 to 2.14 events per 100 patient years. Depending on which study you look at, ravulizumab is similar, having a thrombotic rate of about 1.38 events per 100 patient years.

With pegcetacoplan, we have 2 studies that we can look at now to look at the thrombotic events. The 307 study is a long-term extension study for patients who were on pegcetacoplan in clinical trials. And thrombotic events occurred in 5 patients during the clinical trials, which is a rate of about 1.22 events per 100 patient years, in a total of about 409.4 years. And then post marketing in the U.S. there have been 2 events, again for a rate of about 1.17 events per 100 patients per given over 120.8 years.

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From PEGASUS and PRINCE trials, where we did a post hoc analysis looking at the incidence of thrombotic events along with anti-thrombotic therapy and D dimer levels, for pegcetacoplan there was 1.54 events per 100 patient years in 130 patient years being studied, whereas the eculizumab had 1.77 events per 100 patient years in the same study. So it looks like for pegcetacoplan, the thrombotic rates are very, very similar to what we see with eculizumab and ravulizumab, which is wonderful news.

We have some real world data from pegcetacoplan that was presented at the International PNH Interest Group Symposium in 2023 in England. Since its approval in May of 2021 by the FDA, pegcetacoplan appears to be very safe and effective in treating patients with PNH. There has been no increase in episodes of thrombotic events compared to historical rates with C5 inhibitors, which is what I just showed you. In addition, there's been no increase in meningococcal infections compared to the C5 inhibitors, no increase in other infection rates. The compliance rates on those drugs are very, very high, above 90%. And there have been improvements in other parameters such as transfusion requirements, symptoms, and quality of life. Surveys were done and the patient satisfaction levels on this drug are sky high.

With that, I'd like to thank you for your attention.

Announcer:
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