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The Treatment Pipeline for Primary Biliary Cholangitis: IBAT Inhibition and Beyond

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. Kowdley:
This is CME on ReachMD, and I'm Dr. Kris Kowdley. Here with me today is Dr. Marlyn Mayo.

Dr. Mayo, we reviewed the PPAR clinical trial results in another episode, including the late-breaker presentations from the recently concluded AASLD meeting. What other clinical trials in PBC treatment should providers be aware of?

Dr. Mayo:
Another class of drugs that is hotly under investigation now in PBC is the IBAT inhibitors. These are drugs that bind to and inhibit the ileal bile acid transporter, and that's how they interrupt the enterohepatic circulation of bile acids and reduce the size of the bile acid pool. And there are 2 drugs in this category, odevixibat and maralixibat, that have been fairly recently approved by the FDA to treat itching in pediatric cholestatic diseases. And now there are 2 other IBAT inhibitors, linerixibat and volixibat, which are in Phase 3 and 2 trials, respectively, for treating itch in PBC.

Now, the phase 2 data for linerixibat has already been published, and they showed a dose-dependent reduction in itch in the per-protocol population, but the study did not meet its primary endpoint of a significant difference in itch compared to placebo in the intention-to-treat group. And mild diarrhea was a common adverse event.

There are also some novel approaches to PBC that are in phase 2 studies now. For example, there is a nanoparticle that induces tolerance to mitochondrial autoantigens in PBC that's in a phase 2a study, and that's going to be interesting to see if it impacts disease progression. There is setanaxib, which is a NOX1/4 inhibitor. This is a drug that reduces reactive oxygen species in the liver, and ROS are one of the main pathways by which cholestatic injury occurs from retained bile acids. This mechanism is anticipated to be antifibrotic in the liver. So there was a phase 2 study with setanaxib that was completed and they observed a reduction in alkaline phosphatase of about 50 points. It was a 6-month study.

Their primary endpoint was actually GGT. That endpoint was not met, but like I said, they did have a good reduction in alkaline phosphatase. What was interesting from that study was that fatigue actually improved in the treated group of about 10% versus 1% or 2% in the placebo group. So this is the first therapy we've seen that appears to have an effect potentially on fatigue. And then they also did a post hoc analysis where if they took patients that had high baseline stiffness, baseline liver stiffness, their liver stiffness was reduced by about 3 kPa. So they have a phase 3 trial that's underway. Again, it's going to be interesting to see those results.

Dr. Kowdley:
So I think what we learned is that not only do we have some exciting new therapies in development and late stage of development that appear to have disease-modifying properties and potentially favorable effect on pruritus that we discussed in a previous episode, we

now are seeing new therapies that are aimed predominantly at reducing the symptom burden for PBC patients, namely pruritus with regard to the IBAT inhibitors. And they seem to be very promising for patients who are really bothered by itching, which can be a major symptom that affects patients' quality of life.

So thank you Dr. Mayo, thank you to our listeners. I hope you learned something today that you can put into your practice tomorrow.

Announcer:
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