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Advancing PBC Care: A Closer Look at Second-Line Therapies

Announcer:
You're listening to *GI Insights* on ReachMD, and this episode is sponsored by Gilead Sciences, Inc. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *GI Insights* on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss second-line treatment options for primary biliary cholangitis is Dr. Alan Bonder, who's the Director of Liver Transplantation at Beth Israel Deaconess Medical Center and an Associate Professor of Medicine at Harvard Medical School. Dr. Bonder, welcome to the program.

Dr. Bonder:
Thank you, Dr. Turck. It's a pleasure to be with you guys again.

Dr. Turck:
So to begin our discussion, Dr. Bonder, how do you determine when second-line treatment is appropriate for a patient with primary biliary cholangitis?

Dr. Bonder:
That's a great question. The first thing we need to consider is, who do we consider a non-responder? So currently, the guidelines say that any patient with PBC that we started first-line therapy UDCA, should be evaluated for at least 6 to 12 months, where we see an alkaline phosphatase—one of the liver enzymes—when we say responder is as the liver enzyme gets better. If it goes below a threshold, and the threshold is 1.67 of the upper limit of normal, which is called the POISE results, if it's below that, we call those patients responders, and they don't need a second-line therapy. For those patients who do not get below this threshold, we call them non-responders, and we start thinking about second-line therapies, clinical trials, or other new approved medications that we have available.

Dr. Turck:
And would you tell us about the mechanisms of action and efficacy of currently approved second-line therapies?

Dr. Bonder:
So as everyone is aware, the FDA just approved two medications, and I'm going to call them the PPAR. This is a peroxisome receptor agonist. The first one that we're going to talk about is called seladelpar. Seladelpar is a selective delta agonist. And how they do this is basically, seladelpar is released by the activation of the delta receptor. You release growth factor 21, FGF21, from the hepatocytes, which, in turn, reduces the accumulation of bile acids. Again, meaning it reduces that toxicity of the bile acids. In that way, it functions as a very specific receptor agonist targeting the disease.

And the other therapy that was approved is called elafibranor. Elafibranor is a dual PPAR agonist. It's a delta, but also it's an alpha. So both medications that were just recently published and, again, recently approved by the FDA have shown similar effects on getting the disease under control.

Dr. Turck:
And what else can you, in the literature, tell us about emerging second-line treatment options?

Dr. Bonder:
I would say this is very exciting for the PBC world. We went from having almost nothing. So if you look back to 2016, we had only UDCA,

or ursodiol, as part of the therapies; in 2016, obeticholic acid was approved as a second-line therapy and the only approved medication until 2024, when we got these two new medications approved. But right now, we have at least another five to seven different medications with very similar mechanisms that are undergoing phase 2 or even going into phase 3, that will be approved, and in the studies, have shown very, very interesting and significant improvement on the liver enzymes. So I think PBC is in a good spot, and I think we are seeing promising results in those patients who will hopefully get treated soon.

Dr. Turck:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Alan Bonder about second-line therapies for primary biliary cholangitis.

So Dr. Bonder, now that we know about what the second-line treatment options are and how they work, what should we know about their adverse effects and associated monitoring recommendations?

Dr. Bonder:
Great question, Dr. Turck. And I want to go specifically into the safety profile for each medication. In the seladelpar part of things, we know that seladelpar has a pretty safety adverse event profile. In the clinical trial, the most common side effects were nasopharyngitis, pharyngitis, and abdominal pain, which were not any different when we compared them to the placebo group. And then the elafibranor group—the most common side effects were abdominal pain, diarrhea, nausea, and urinary tract infections, which also were not any different than the placebo group.

So sending the message to these medications are very safe and very easy to use, but again, we do not have really significant amount of data or data in patients with advanced liver disease. So right now, these medications should only be used in patients with either advanced fibrosis or no fibrosis, or compensated cirrhosis.

Dr. Turck:
And when determining which treatment option is appropriate, what patient-specific factors should we consider?

Dr. Bonder:
This is the best question we ask all the time. If you ask me, “Is there any advantage of one to the other one?” The answer is no. And this goes to all kinds of patient profiles. For example, seladelpar—the study looked at patients with itching. So a patient who is itching a lot and who has bad disease activity from their PBC will be the right patient for seladelpar. But also for elafibranor. But then we go into, is there any drug-drug interactions? We know the elafibranor is a fibrate. And, for example, we see a lot of patients who are now getting treated with statins for their high cholesterol, so sometimes drug-drug interactions is a big, important decision to see what medications we're going to start with.

Also, as I told you, the advanced liver disease—there is no current data on decompensated liver disease, so any of those patients who have really advanced portal hypertension, we don't have any data, so we would not support using these medications until we get more data. But again, I want to point out that these medications are easy to use and easy to monitor.

Dr. Turck:
And to close out our program, Dr. Bonder, do you have any key takeaways you'd like to share?

Dr. Bonder:
I think a really important summary is the picture is very promising, as we have now, currently four new therapies approved for PBC. We know they work really well. And if you feel that you're not responding to UDCA, you should basically reach out to your gastroenterologist or hepatologist, asking for these medications. They are available for the general population. And as I said, these medications are very easy to use with minimal side effect profiles. So again, I was just going to reiterate it again, we have really new available therapies, and we are looking to treat everyone before they progress. And also, we are trying to treat everyone before they have poor quality of life related to the symptomatology from PBC.

Dr. Turck:
Well, with those final insights in mind, I want to thank my guest, Dr. Alan Bonder, for joining me to discuss second-line therapies for patients with primary biliary cholangitis. Dr. Bonder, it was great having you on the program.

Dr. Bonder:
Thank you, Dr. Turck. Hope this was some good information out there for patients and for physicians about how to treat patients with PBC.

Dr. Turck:
Absolutely.

Announcer:
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