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Crossroads in PBC Care: When First-Line Therapy Falls Short

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

Dr. McDonough:
This is *GI Insights* on ReachMD. I'm Dr. Brian McDonough, and today I'm joined by Dr. Aparna Goel to discuss how she cares for patients with primary biliary cholangitis, or PBC, who have partial responses to first-line therapy. Dr. Goel is a Clinical Associate Professor of Medicine in Gastroenterology and Hepatology at Stanford University. Dr. Goel, thanks for being here today.

Dr. Goel:
Thank you for having me today.

Dr. McDonough:
So let's just dive right in, Dr. Goel. What are the current criteria and biochemical markers used to assess a patient's response to first-line therapy at different points in time?

Dr. Goel:
So there have been many, many criteria that have been proposed to define biochemical response. All of them will take into account alkaline phosphatase levels. So I will anchor on that one, because in the recent past, in the criteria that have been used in clinical trials to have drugs approved, we've used what's called the POISE criteria. And that criteria is having an alkaline phosphatase that's less than 1.67 times the upper limit of normal, having a greater than 15 percent decline in the alkaline phosphatase after 1 year of starting therapy, and having a total bilirubin response that's less than normal.

So the POISE criteria are what we've used in the last several years when we're designing clinical trials to understand whether or not patients have had an effective response to therapy. The key is definitely the cholestatic parameters, so you're really thinking about alkaline phosphatase and bilirubin. I will say that for our biochemical goals in this evolving landscape, there is suggestion and data that perhaps achieving biochemical response should be redefined as a normalization of the alkaline phosphatase and even a total bilirubin level that's less than 0.6 times the upper limit of normal. And the reason for that is because we do see that there is a difference in liver disease-related mortality or the need for liver transplantation in those that are able to normalize those tests versus those that meet the POISE criteria versus those that don't meet the POISE criteria. So what we ultimately might settle on in terms of a biochemical response might change, but right now, we're relying on the POISE criteria to define it in the US.

Dr. McDonough:
And can you tell me about the different ways you've seen partial response to first-line therapy present in patients?

Dr. Goel:
Yeah, the most common reason why I will identify a patient in my clinic as having a partial response is if they're starting alkaline phosphatase. I'll give you an example. Say their starting alkaline phosphatase is 300 when I diagnose them with PBC and I start them on first-line therapy, which is ursodeoxycholic acid—an appropriate weight-based therapy—so 13 mg/kg/day of ursodeoxycholic acid. And I'll monitor them for a year on that therapy, and ideally they have good compliance during that year. And after a year of therapy, if they still don't meet that improvement in alkaline phosphatase by over 15 percent, if their alkaline phosphatase is still over 1.67 times the upper limit of normal, or if their bilirubin level is elevated, then that will define them as a partial response.

Now, a few caveats: I feel like a lot of people get labeled as having a partial response because their compliance with ursodeoxycholic acid, or their dose of ursodeoxycholic acid, might not be appropriate. So remember that the total daily dose of ursodeoxycholic acid should be 13 to 15 mg per kg per day. Most GI physicians and hepatologists tend to prescribe this as divided dosing—three times a day dosing, or twice a day dosing—and that can be challenging for patients. So the dose can actually be clustered as just a single dose if patients are able to tolerate it. And then the other big reason why I see potentially inadequate treatment with ursodeoxycholic acid is that it's not being appropriately weight dosed. So making sure that you meet that 13 to 15 mg/kg/day is key.

So once I'm able to confidently say that on the appropriate dose and the appropriate compliance of ursodeoxycholic acid, that they haven't met the POISE criteria, then I will categorize them as having a partial response to UDCA. And that's by far the most common reason why someone has a partial response.

Dr. McDonough:
Now, how is partial response related to risk of disease progression in these patients?

Dr. Goel:
What we've seen in some large population-based cohort studies now—this is from global PBC data—is that patients who tend to maintain a normal alkaline phosphatase end up having a much higher transplant-free survival, so they progress to needing liver transplantation and developing complications from their liver disease at a much slower rate compared to those that have an abnormal alkaline phosphatase.

And we see this stratified in three different ways. So you have the patients that have abnormal alkaline phosphatase that do very, very well and almost never need a liver transplantation. And then you have those that have this mild elevation in their liver tests. So they're not meeting the full biochemical response criteria, but their alkaline phosphatase levels might still be a little bit below—they're a little bit above normal, but they're below that 1.67 times the upper limit of normal. So they're sort of at this mild elevation in their alkaline phosphatase. And you see that their rates of transplant-free survival, so disease-free progression, is good, but it's a little bit lower than it is if you have normal liver tests.

And then lastly, you have the patients that are unable to meet a biochemical response altogether based on POISE criteria. So you have patients that have ongoing elevations in their alkaline phosphatase greater than 1.67 times the upper limit of normal, and those patients tend to have the highest risk of progressing in terms of developing complications with a liver disease or needing a transplant down the line.

So the important thing, when somebody has a partial response at a certain timepoint one year after therapy, is really thinking about what additional therapies you might be able to start for them to really try to get their liver tests to ideally normalize or definitely to get them below that 1.67 times the upper limit of normal.

Dr. McDonough:
For those just joining us, this is *GI Insights* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Dr. Aparna Goel about her experience with primary biliary cholangitis patients who have partial response to first-line therapy.

So Dr. Goel, now that we have a better understanding of partial responders, let's zero in on second-line treatment. What does the current therapeutic landscape look like?

Dr. Goel:
So there are now several approved second-line therapies. 2024 was a big year for primary biliary cholangitis. One of the previously approved second-line therapies is obeticholic acid, and that's been approved since 2016 as an add-on therapy for those that have an incomplete response to ursodeoxycholic acid, or to those that are intolerant to ursodeoxycholic acid.

There are now two other therapies to consider in the US for those patients that have an incomplete response. The first is seladelpar and the second is elafibranor. These are both PPAR agonists. Seladelpar is a selective delta agonist. And there's some who want us to think about both of them, but both of them have shown pretty good efficacy in terms of second-line therapy, with 50-60 percent response rates for meeting that POISE criteria. Importantly, these are patients that are, again, incomplete responders or intolerant to ursodeoxycholic acid.

Dr. McDonough:
And what factors do you consider when determining the right therapeutic approach for each patient?

Dr. Goel:
So now that we have a lot of different options for second-line therapy, I will be using the FDA approved option. I do not intend to use

things off label anymore. With obeticholic acid, the biggest reason why people tend to discontinue is because of the development of itchiness. And there's some data that suggests that if you have itchiness when you start obeticholic acid and it's not necessarily adequately managed, then patients can develop worsening itchiness. So unfortunately, pruritus, or itch, is something that our PBC patients experience. And up to 70 to 80 percent of patients that have PBC suffer from itch. So in a patient that has baseline itch to begin with, I am unlikely to consider obeticholic acid as my first option for second-line therapy.

In thinking about seladelpar or elafibranor, these are both newer agents to the market, so we're still trying to learn more about them. Importantly, for both of these medications, we do not recommend using them for patients that have decompensated cirrhosis. So for patients that have jaundice, ascites, encephalopathy, or history of variceal bleeding, it is not recommended that these medications be started. It is safe to consider it in patients that have compensated cirrhosis—so Child's A cirrhosis or cirrhosis without any of those complications.

Deciding between seladelpar and elafibranor, there's many small nuances, and we have to learn more as these drugs are on the market for a longer period of time so that we learn more about their long-term safety data and some of the things that might make you consider one or the other. Elafibranor is contraindicated in pregnancy and not recommended if you're breastfeeding. So if you have a younger woman that might be considering that, you probably need to use seladelpar instead, or use another agent instead.

There is some data that seladelpar might improve itch and it improves interleukin 31 levels. And there were signals in the RESPONSE study, which led to the accelerated approval of seladelpar, that PBC patients who had itch to start with, 30 percent of them, had a decline or an improvement in their itch by the end of the study. And this might be more prominent in those that have more moderate to severe itch. So in a patient that has PBC with itch that's really complicating them, because you're already giving them medications to help them with their itchiness, and you need to add a second-line therapy, adding something like seladelpar might be able to kill two birds with one stone. You might be able to treat their itch, and you also might be able to offer better disease control. So that's something to consider. While elafibranor's data didn't necessarily meet that key secondary endpoint for improvement in itch based on the numerical rating scale, there are some suggestions that itch could improve on elafibranor as well.

The other things to consider are in all patients that have PBC, it's important to consider bone health. PBC affects the bile duct, so fat-soluble vitamins might be affected. We know that there's a higher incidence of osteoporosis in these patients, so all patients should be getting bone density scans. In the seladelpar study, the RESPONSE study, there were a few fractures that were noted, but most of them did not seem like they were related to the study drug. That's something that we will need to monitor over time.

And in elafibranor's latest study that led to its accelerated approval, there were instances of rhabdomyolysis—breakdown of muscle—that were noted. Those instances seemed to be related to a concurrent use of statins—high-dose statins. So in the elafibranor label, there are recommendations for statin dosing. And that's important to take into consideration if you're going to be starting elafibranor in a patient that's on a statin—just make sure that you're adjusting the dose of the statin appropriately to potentially reduce that risk. And again, this is something that we'll need to monitor closely as we start to use these drugs more and have more data on the drugs too.

Dr. McDonough:
As we reach the end of our program, Dr. Goel, can you explain why it's important for us to make these decisions about second-line therapies in a timely manner?

Dr. Goel:
Yeah, it's very important to consider adding second-line therapy if a patient is not a complete responder because you can change their overall long-term trajectory of developing complications for liver disease. If you do not treat adequately, and if patients do not ultimately get a complete biochemical response if they do not ultimately even meet the POISE criteria, the risk of progressing to having more complications from their liver disease or needing a liver transplantation is quite high. So I recommend that in patients that are first diagnosed with PBC that we stage their disease and understand how much hepatic fibrosis they might have. This can be done with something as simple as a FibroScan. And in those that have advanced disease, really being aggressive about trying to normalize their biochemistries could make a big difference in terms of their long-term trajectories. In those that don't have advanced fibrosis, those that have no fibrosis,you have a little bit more time to really get to biochemical remission. And whether or not you're trying to get to normal or 1.67 times the upper limit of normal, and which criteria you want to follow, you have some options that you can weigh there. But in those that have advanced fibrosis, identifying the severity of the liver disease to begin with and then really making sure that you're trying to reduce the risk of their disease progressing is key. So really trying to get adequate control the disease can prevent complications.

Dr. McDonough:
That's a great way to round out our discussion. I want to thank my guest, Dr. Aparna Goel, for joining me to discuss management strategies for primary biliary cholangitis patients with partial responses to first-line therapy. Dr. Goel, it was great having you on the

program.

Dr. Goel:
Thank you very much. Appreciate it.

Announcer:
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