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

Comprehensive Care in PBC: Balancing Symptom Management and Disease Progression

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:
Welcome to *GI Insights* on ReachMD. I'm Dr. Brian McDonough, and today I'm joined by Dr. Robert Gish to discuss how we can approach disease progression and symptom management in primary biliary cholangitis, or PBC for short. Dr. Gish is a Professor of Medicine at Loma Linda University in California, and the Medical Director of the Hepatitis B Foundation and the American Pacific Health Foundation. Dr. Gish, thanks for being here today.

Dr. Gish:
Glad to join you. This is very nice, Brian. Appreciate it.

Dr. McDonough:
To start us off, Dr. Gish, could you provide some background on PBC and its symptoms?

Dr. Gish:
Okay, so PBC stands for primary biliary cholangitis. It used to be called primary biliary cirrhosis, but the name change was implemented in approximately 2014 because most people didn't have cirrhosis, and there was a lot of stigma and discrimination around the word cirrhosis. This is an autoimmune disease. And autoimmune disease is T and B cell mediated. These are special immune cells that attack the very small bile ducts in the liver. They're really attacking an antigen that overlaps with other antigens that are found in our environment, such as what we see with E. coli. And this autoimmune process builds up toxic bile acids. And there's a number of other inflammatory changes, cytokines that lead to an inflammatory response, but much more of a fibrotic response that eventually results in a large liver, not a small liver like we see with other patients. And that rule is 90 percent of patients will progress to end-stage liver disease. There is a small fraction who have mild disease who don't progress. But we really talk about this as a universally progressive autoimmune liver disease that results in liver transplant, liver failure, death, and also the possibility of liver cancer.

Dr. McDonough:
When it comes to treating PBC, why is it so important to address not only those symptoms, but also the disease progression that you speak of?

Dr. Gish:
Let's go down this symptom pathway just for a moment. And there is some misinformation out there that 70 percent of patients present without symptoms, and I think it's the inverse, 70 percent of people present with symptoms, typically fatigue and/or itching. But there are a number of other symptoms that can happen, and also signs on physical exams, such as too much cholesterol in the skin, dry eyes, dry mouth, but this fatigue is really a central issue. And the itching is also very interesting, because itching is present in 70 percent of people if you take a good history. And that itching appears to be mediated not just by bile acids, but another pathway called the autotaxin pathway, and the third pathway is interleukin 31.

So there is all about quality of life. There's issues about de-stigmatizing this disease. Then there's the issue about the natural history of the disease and progressing to cirrhosis and end-stage liver disease. So early diagnosis means we can intervene and improve people's quality of life. And early diagnosis means we can intervene with our different forms of treatment, because the earlier we intervene, the

more successful, the more likely we are to halt progression and potentially even reverse the disease.

Dr. McDonough:
With that in mind, can you explain how we can achieve biochemical response within a shorter timeframe?

Dr. Gish:
Let's define biochemical response, Brian. This is super important. In the old days, the previous days, we used all these different systems—the Mayo, the Rotterdam. There's a long list of normalizing ALT to less than 1.67 times upper limits of normal. Well, that's not normal; it's a bit of an oxymoron. And also a normal bilirubin, that's super important. But now the new normal, the new healthy is getting that alkaline phosphatase under 115. That's the healthy level for alkaline phosphatase. But I want to really emphasize that every person in this space should be measuring GGT with every liver panel. In a liver panel, we have liver enzymes—AST, ALT, alk phos, and GGT. These are not LFTs, they are not liver function tests; they're liver enzymes. Function is bilirubin. And anybody with chronic liver disease, we should be fractionating the bilirubin and following not total bilirubin, totally. We're supposed to be measuring and monitoring direct bilirubin in these patients. And of course, albumin. And eventually, as disease progresses, INR. So the new normal, the new healthy, is a normal bilirubin 0.6 or less, direct bilirubin 0.3 or less, alkaline phosphatase 115 or less, and GGT 35 or less. So this is the new target because we know this is the safest level of liver enzymes and function, indicating a very, very low risk of progressing to cirrhosis, end-stage liver disease, liver transplant, death. The new normal.

Dr. McDonough:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Dr. Robert Gish about comprehensive care for patients with primary biliary cholangitis.

So, Dr. Gish, if we switch gears a bit and zero in on managing the pruritus you were speaking of in these patients, what does the current therapeutic landscape look like?

Dr. Gish:
Oh, fantastic question, Dr. McDonough. So number one, going back just a tiny bit in history, we had a list of 15 different anti-itch drugs, bile acid binding resins such as cholestyramine, which everybody hates, it tastes like eating beach sand. Now we have a very long list of other medications which could be naltrexone or an SSRI, gabapentin, there's a variety of anti-itch medicines that are really repurposed. And we do want to approach this itch very aggressively because this really disrupts people's sleep, their quality of life. And believe it or not, there is a stigma associated with itch that goes back 600 years, because if you're in the 14th century and you're scratching, you probably have lice or crabs or something else that's infectious. So there is still a stigma with itching, that something's wrong with that person. So we want to improve their quality of life internally, but also so they can be more active in their family and society.

Now we have new options for itch. Obviously, we start out treating with urso for every patient with PBC—that's first-line therapy—and that can decrease the itch in some patients, can make it worse in others. And then we have newer therapies that treat itch. Now we're going to go down the PBC pathway just for a moment. We have a number of second-line therapies. What's been on the market for over 7 years now is obeticholic acid— we pronounce it OCA or O-C-A. This can worsen itch in some patients. It can be standard or the itch may improve in some patients, but it does have a history of worsening itch. Although about 5 percent of people come off because of itch. But of course, they would like to take one pill and have their itch better, or much better. Another medication just approved this last summer, elafibranor, is itch neutral to itch better —although that did not reach statistical significance, It definitely, in my opinion, doesn't make itch worse, and that's been my experience clinically since I started using this. And then seladelpar, that was also a medication that was approved this last summer. This medication has an interesting package insert and product information indication, both in terms of improving liver enzymes, normalizing liver enzymes, but improving itch. So it's really the first PBC drug that had that anti-itch formula in their package.

And I do want to wrap this up with two other medications that are called IBAT inhibitors—ileal bile acid transport inhibitors—that were originally developed for different pediatric diseases but have a profound effect on itch. They don't have data for PBC specifically, but they have very good data for itch. One is called maralixibat, and the other one's called odevixibat. And these really can profoundly change itch. And I have used those as fourth-line therapy in patients who have PBC who didn't respond to first, second, or third-line. So I have experience with all these medications, and each one has its place. Brian, this has been amazing what's changed in the last few years.

Dr. McDonough:
Thinking about a comprehensive approach to treating PBC, how might newer therapies help address both disease progression and symptoms like the pruritus?

Dr. Gish:

So if I have a patient who's itch dominant and they're not responding to some very simple first-line therapies, I would go down that urso and then seladelpar pathway and think about adding a drug that helps their itch and can stabilize or improve liver disease. And in some patients, up to a third, it can normalize alkaline phosphatase. If they're itch neutral, elafibranor would be a good choice because elafibranor is itch neutral, or it may improve itching slightly. And if they have no itch at all, I would consider OCA, or obeticholic acid as my second-line therapy.

I do need to bring up off-label, two drugs called fibrates that are being used, especially in Europe, called bezafibrate, off label. There's no really phase 3 randomized controlled trial with bezafibrate, although there's some in progress right now. But the emerging data on bezafibrate is it improves enzymes and improves itch. But also, the real-world data is 1 out of 4 people on bezafibrate come off because of side effects. In the US, we don't have bezafibrate. You can order it from Canada, but that's a lot of work.

We have fenofibrate, which is also one of these PPAR family drugs. I didn't talk much about mechanism here, but PPAR is that pathway that each of these drugs works down. But fenofibrate has a black box warning, do not use in people with liver disease. People say, “Oh, it's cheap, I'm going to use it off label.” But you really have to be careful with fenofibrate, because of toxicity issues. There's GI, there's kidney, there's liver, so there's other issues with fenofibrate, we have to be quite cautious. I tend to use medications on label first, and then I go to off-label use if I am in a desperate situation and my first and second-line on-label therapies are failing.

Dr. McDonough:
Before we close, Dr. Gish, do you have any final thoughts about how we can better care for patients with PBC?

Dr. Gish:
Well, I'd like to go way, way, way back to the beginning and comment on advocating anti-mitochondrial antibody in any patient presenting with elevated liver enzymes that are cholestatic. That means alk phos and GGT elevated above AST and ALT. Anybody with an AMA positive should see a hepatologist or gastrohepatologist – we call them gastroheps – so they are staged correctly. And we really didn't talk about staging much, but every patient with PBC should be staged once a year—that's with non-invasive testing, such as APRI or FIB-4, elastography. There's seven competitors in the elastography space. And also evaluate your patients for fatty liver. I have really backed off from doing liver biopsies for the last decade, but more recently I'm doing more liver biopsies because obesity overlaps with patients with PBC, and I need to know what's dominant. Is it metabolic syndrome? MASH? Or is it PBC? Or both? What pathway do I need to go down to think about treating this patient who's sitting in front of me?

Early interventions. Super important concept, F0 to F1, I'm going to watch those people typically with urso. But once they hit F2 I'm going to be stepwise moving through my second-line therapies, occasionally thinking maybe about triple therapy in my patients. I really don't think anybody should be progressing to F3 or F4; that's when the response rate to these drugs really falls down. So it's a staging algorithm. You don't have to give every patient every medicine, but this is a progressive disease. We need to find those patients, stop progression, and maybe even reverse their disease.

Dr. McDonough:
With those key takeaways in mind, I want to thank my guest, Dr. Robert Gish, for joining me to discuss how we can address both disease progression and symptom control in patients with primary biliary cholangitis. Dr. Gish, it was great having you on the program.

Dr. Gish:
Dr. McDonough, thanks for having me and thanks to your whole team. I appreciate it.

Dr. McDonough:
Thank you.

Announcer:
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