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Uncovering the Complications of Primary Biliary Cholangitis

**Dr. Buch:**
This is *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch, and today we're joined by Dr. Alan Bonder. Dr. Bonder is an Assistant Professor of Medicine and the Medical Director of Liver Transplantation at Beth Israel Medical Center in Boston. Together, we'll be discussing primary biliary cholangitis, or PBC, and its complications.

Welcome back to the program, Dr. Bonder.

**Dr. Bonder:**
Thank you, Dr. Buch, for having me again. It's a pleasure to be again with you, and hopefully, we can get to the questions and answer them correctly.

**Dr. Buch:**
Thank you so much. Let's dive right in, Dr. Bonder. Can you tell us about the disease progression of PBC? And equally important, what are the strategies for assessing prognosis?

**Dr. Bonder:**
So PBC is defined as primary biliary cholangitis, Dr. Buch. It's an autoimmune liver disorder that affects mainly the small ducts of the liver. It is an autoimmune condition. It's a chronic disease. What we know currently is that PBC affects females, most likely in the fourth to the sixth decade of life, and what we've seen to date is we are diagnosing more PBC, so we are preventing, we are treating them early, and we are preventing them to actually progress to cirrhosis, end-stage liver disease and needing a liver transplant, which basically takes me to the next question. So, what do we do in the clinic to stratify them or to make sure that they're doing well?

So we do have three main, I would say, between labs and biological tools, that we can use to stratify patients. So now we have what's published in The Global PBC, which is basically the largest PBC consortium around the world, and it's shown two things. If your alkaline phosphatase bond with your liver enzymes, as you detect it and you treat it and it's coming down, that's a marker of good prognosis, so we would like to get the alkaline phosphatase as normal as they could get. The second one is the bilirubin. We should try to aim for a bilirubin less than 0.6 because, again, studies have shown that people who have bilirubin less than 0.6 progress slower. And most recently we have transient elastography, or as we call it, FibroScan. So we know that FibroScan results add diagnoses. If it's more than 10, we know that those patients are more at risk of having complications, but also, we know that treating those people with first-line therapy, second-line therapy, either off-label medication is if FibroScan comes down or stays the same, we know that those patients are not at risk for progressing with liver disease and needing a liver transplant.

So using those three tools in clinic for the first time can give us a lot of information. It can tell us what patients we need to get and way sooner and try to see if we can get those patients in second line there and either clinical trials before they progress to end-stage liver disease.

**Dr. Buch:**
And following up with that, Dr. Bonder, just a word to our primary care colleagues—what are the key elements we have to worry about when thinking about primary biliary cholangitis as opposed to other liver diseases? And this is for our primary care colleagues.

**Dr. Bonder:**
So for our primary care providers, Dr. Buch, I think the most important thing is diagnosis. And again, I want to stress the importance of anyone with abnormal liver tests, specifically with a cholestatic pattern and elevated alkaline phosphatase, most of them females, we should be sending an antimitochondrial antibody, or AMA, because then if you get an elevated alk-phos plus an AMA, you have a

diagnosis of PBC. And again, for primary care providers, the diagnosis is not actually a death sentence. We know if we get them earlier in treatment, they have the same life expectancy as any other patient who doesn't have the disease, so I think the message is if we can screen them in the community, we can catch them early; we can prevent them from progressing to end-stage liver disease.

**Dr. Buch:**
Thank you for that, and I think that's a very useful bit of information for our colleagues out there. And are there any concerns about using obeticholic acid in PBC patients who develop cirrhosis?

**Dr. Bonder:**
So we do have concerns about using obeticholic acid. In the PBC world, we call it OCA. So I want to just take a step back, Dr. Buch, and we need to talk a little bit about treatment options that we have. We have two approved therapies for PBC. First-line therapy is ursodeoxycholic acid. That treats 60 to 70 percent of the patients, so that means 60 to 70 percent of those patients will respond, meaning their liver tests will go back to normal or close to normal, and up to 30 to 40 percent of them will need a second-line therapy. The second approved therapy that we have available is obeticholic acid. And in the year of 2021, there were 17 deaths related to liver disease complications. In those 17 deaths, when the FDA analyzed them, showed that patients who were dying using obeticholic acid were patients who were decompensated, so patients who had either a Child B or Child C or they had portal hypertension. And based on that, the FDA just started a black box warning, which means any patient with cirrhosis who is decompensated or who has portal hypertension, meaning ascites or esophageal varices, should not be using obeticholic acid because the risk of liver death.

**Dr. Buch:**
And which PBC patients are most likely to develop hepatocellular carcinoma?

**Dr. Bonder:**
So most of the PBC patients will have a benign natural history, as I explained earlier, but patients do progress to cirrhosis, so we will only screen patients with cirrhosis for liver cancer. Any patient who does not have advanced fibrosis or scarring should not be screened for liver cancer because they are not at risk.

**Dr. Buch:**
And when we're talking about screening patients, should we be following the same protocol as for other cirrhotic patients? Every six-month evaluation?

**Dr. Bonder:**
That's correct, Dr. Buch. Any patient with PBC-related cirrhosis should follow the protocol of any patient with any other liver disease who actually ends up getting liver cirrhosis.

**Dr. Buch:**
And the other question for this is do you like to use alpha-fetoprotein in addition to routine ultrasounds?

**Dr. Bonder:**
I do. Most of my patients I use alpha-fetoprotein, and this is a little bit of a debate in the liver community. If you look at our guidelines, our guidelines recommend using an ultrasound every six months, and also, the alpha-fetoprotein is not as recommended because the evidence is not as clear, but what I do—this is more like a personal opinion—most of my patients who come to see me with cirrhosis will get an alpha-fetoprotein and send a liver ultrasound to screen for liver cancer.

**Dr. Buch:**
Thank you for that. So, what are your recommendations for managing pruritus in these patients?

**Dr. Bonder:**
I think, Dr. Buch, this is one of the really most interesting and intriguing answers that I'm going to give you. So now PBC patients have more options. So, there are close to 9 to 10 new medications coming on the pipeline in really advanced clinical trials, so I want to divide the answer into two parts. Let's say a patient comes to see me with diagnosis of PBC with an elevated alkaline phosphatase who I'm not able to control. So, in those patients, on top of using Ursodiol, then I might be interested in putting them on a clinical trial where we can use any PPAR agonists, so such as fibrates, or if a patient is not eligible for a clinical trial, then I can get them in other therapies, such as fenofibrate. Unfortunately, those patients are not very keen to use obeticholic acid because one of the main side effects of obeticholic acid is pruritus, itching. Up to 50 percent on a low dose and 70 percent at the high dose of patients with obeticholic acid will experience itching.

And then we have the second type of patient. Let's say a patient who has controlled PBC, normal alkaline phosphatase, normal bilirubin. Then we can actually use a little bit different medication, and we can start with, if the itching is not as severe, overnight antihistamines.

We can use antidepressives, such as sertraline. We can use rifampin, which is an inductor and is shown in studies that actually improves itching. But I want to emphasize that most of the medications that are coming out in the pipeline in clinical trials are treating both pruritus and disease at the same time with really great response.

**Dr. Buch:**
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Alan Bonder about the disease progression and prognosis of primary biliary cholangitis, or PBC.

Now let's switch over to treatment options, Dr. Bonder. What therapies are available for PBC? And could you talk a little bit further about fibrates and the risk and benefit of using fibrates?

**Dr. Bonder:**
So I would say the current available options—so we have the FDA-approved treatment options—which are two. The first one is ursodeoxycholic acid. And I want to emphasize the importance of the weight-based treatment option. So, it is 13 to 15 milligrams per killogram per day, and it's so important because I've seen so many patients considered as non-responders because they are not properly dosed based on their weight. So, we start that treatment, and we do consider non-responders after a year of treatment of ursodeoxycholic acid when we don't see an improvement in either the alkaline phosphatase and the bilirubin. After a year has passed by, then we will consider second-line therapy.

So obeticholic acid is the second-line therapy approved by the FDA. Again, as long as the patient does not have advanced cirrhosis or portal hypertension, they might use it, and we follow then their alkaline phosphatase. In those cases, I would say the ursodeoxycholic acid, 70 percent of the people will respond, and out of patients using obeticholic acid, I would say up to 46 to 50 percent of the people, we'll get them to normal, so that leaves us some patients who will not be able to get to normal, and this is when we actually start using either clinical trials or off-label fibrates.

So, in the United States, the fibrate that we have available is fenofibrate. It's a PPAR agonist, specifically an alpha agonist. And in the studies, there's a small open-label study of 20 patients that shows improvement in both the alkaline phosphatase and itching. We currently have a lot of patients in clinical trials. Elafibranor, which was a study that was published last year, 12 weeks looked at—really promising—decreasing by close to 60 percent the alkaline phosphatase. The Phase 3 clinical trial is undergoing. Then we have Seladelpar, which is another PPAR agonist, which also is undergoing. And then we have other types of different therapies out there.

So, I just want to mention that fibrates will become the second-line therapy for patients with PBC, but also, I want to stress the importance that not everyone responds to fibrates and some of those patients will have side effects. In some cases, we will be mixing medications, for example obeticholic acid, ursodeoxycholic acid, and fibrates at the same time to try to get them to normal.

**Dr. Buch:**
That's extremely exciting. And what should we know about liver transplantation in PBC?

**Dr. Bonder:**
I would say the first thing that we need to understand about PBC in transplant is we are seeing less and less patients going with end-stage liver disease complications, liver disease to transplant centers with PBC because I just mentioned we have so many good, new therapies; but unfortunately, there are still some patients that are still progressing despite everything that we have out there, and they need a liver transplant.

I would say, Dr. Buch, it's very important to know that even after liver transplant there is a chance that PBC will come back. The quoting numbers in different clinical trials show between 20 to 30 percent of patients with PBC will have recurrent PBC in the allograft. So, what are we doing right now is any patient who, unfortunately, goes to transplant—after transplant we start preemptively ursodeoxycholic acid because in studies that has shown to decrease the recurrence of PBC but also decreasing the chances of needing another transplant in the future.

**Dr. Buch:**
This was an excellent review of the complications of primary biliary cholangitis. I want to thank my guest, Dr. Alan Bonder, for sharing his insights.

Dr. Bonder, thanks so very much for joining us today.

**Dr. Bonder:**
Thank you, Dr. Buch, and I will be happy to join you again in the future for any questions that you guys have for me.

**Dr. Buch:**

For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/*GIInsights* where you can Be Part of the Knowledge. Thanks for listening, and I look forward to learning with you next time.