Clinical Compendium:

Contemporary Issues in the Management of Patients With Primary Biliary Cholangitis: An Interprofessional Approach

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Diagnosis of PBC

James Boyer, MD: Welcome to module 1, diagnosis and identifying appropriate tests and support decision making in the diagnosis of PBC. I'm Jim Boyer. I'm a professor of medicine at Yale University School of Medicine and I've had a lifelong career with patients with PBC and I'm happy to be talking to you today.

A little background about the disease. It's a chronic cholestatic disorder, thought to be one of the most common in cholestatic diseases in the adult chronic disease. It has a low prevalence in the population, so it's known as an orphan disease. Prevalence is around, anywhere from 20 to 400 per million patients. It varies greatly geographically, and is said to cluster around environmental contamination sites, Super Fund sites in the United States, and also industrialized areas. There's some feeling that it's caused by heavy metal contamination that triggers the disease in somebody who is genetically predisposed to get this. It's predominantly a disease in middle-aged women and 1 out of 10 are males.

It can present both asymptomatically or symptomatically and when it presents with symptoms, they're usually fatigue or pruritus. There can be associated symptoms, dry mouth, dry eyes or sometimes they can develop fluid retention in the ankles and abdomen. And, as shown in the figure to the right, patients can develop fatty deposits of cholesterol in the skin and the eyes, known as xanthoma or xanthelasma. The picture shows the skin here where the eruption of cholesterol deposits in these patients. This is an uncommon finding now, as the disease is usually picked up before this problem occurs. Associated disorders in PBC include Sjogren's, which is the dry eyes and mouth, hypothyroidism, celiac disease, a rheumatoid-like arthritis, and these patients often get cholesterol gallstones.

To make the diagnosis in this disorder, you have to have at least 2 of the following: the most important one is the elevation of alkaline phosphatase. If you don't have an elevation of this enzyme in your blood, then it's very unlikely that you have a cholestatic disorder. The alkaline phosphatase is also a marker of prognosis. The hallmark of PBC is the presence of antimitochondrial antibodies in the serum and 95% of patients will have a positive AMA. Liver biopsies show what is shown in the right-hand panel here, and that is what we call a florid bile duct lesion. This isn't the bile itself. This is hepatic artery over here and this bile duct is surrounded by a chronic inflammatory infiltrate that is destroying the duct system itself. And there's also associated macrophages here, the beginning of what we call a granuloma. This is the classic florid duct lesion that's essentially pathognomonic of PBC.

Now, occasionally patients have negative AMAs. These patients can be often detected with another type of antimitochondrial antibody called SP100 or GP210.

The laboratory evaluations of the disease are typically that the alkaline phosphatase is elevated. There are usually only mild elevations of the liver enzymes, the aminotransferases. The bilirubin is usually normal at diagnosis but increases as the disease progresses. As I already indicated, the AMA is positive in 95% of patients. The antinuclear

antibody is also positive in these patients, maybe in half of the cases. It does not mean that there's an overlap of autoimmune hepatitis. It's just another autoimmune marker. Now, there are some patients who have overlap disease, but it's not based on the presence of ANA.

Smooth muscle antibodies are another antibody that can be detected in about half the cases. And the immunoglobulins, immunoglobulin M, may be elevated because there is a defect in conversion of immunoglobulin M to mature globulins.

Now, what about imaging modalities? It's often useful to get an ultrasound since these patients often have gallbladder disease, form gallstones, and ultrasound is very useful in picking this abnormality up. If the patients have cirrhosis, however, you would want to image them with MRI on an annual basis to detect liver cancer. But liver cancer is very unusual, particularly in females, a little more common in the males with PBC. But, and, of course, it can detect other processes going on and there is an increased incidence of colon cancer and some other malignancies in PBC.

What about transient elastography and FibroScan? These modalities detect the stiffness of the liver and therefore are a reflection of the amount of scarring or fibrosis in the liver. Every physician's office ought to have a FibroScan where you can make a measurement right away and they're useful for detecting the progression of the disease. And FibroScan should be done, or transient elastography, really on an annual basis.

So, in summary, PBC is an orphan disease, chronic cholestatic disease, most common in women and progresses usually over years until the liver is decompensated and needs to have liver transplantation.

One question arises which is when should a patient with PBC be referred to a specialist and usually the specialists are a gastroenterologist or most particularly a liver specialist, a hepatologist. If you're a primary care physician and you have a patient, middle-aged woman, with an elevated alkaline phosphatase, you're going to want to perform some of the diagnostic tests. And if you suspect PBC, I think you should send the patient on to a hepatologist or gastroenterologist because the treatment decisions that need to be made are really the purview and based on the expertise of these subspecialists. If you're a gastroenterologist and if you don't feel comfortable with the management of the disease, then also send the patient to a hepatologist. This is bread and butter for most hepatologists and they're the best ones to follow your patient.

Prognosis

Seth Sclair, MD: Hello, my name is Seth Sclair, from University Hospitals and Cleveland Medical Center, and I will be discussing prognosis in primary biliary cholangitis.

I'd like to open our discussion by reviewing some of the original data on the natural history of primary biliary cholangitis, of course prior to the introduction of treatment and therapy with ursodiol. PBC was shown to have a mild disease presentation with approximately half of patients presenting with asymptomatic disease and those presenting with symptoms, the most common symptoms being fatigue and pruritus. One of the very challenging aspects to primary biliary cholangitis is that it has a very variable course and progressive disease course. Some of the original studies demonstrated this nicely where over a third of patients would become symptomatic over periods of time and, as time goes on, this would encompass the majority of patients. However, we do know that presenting with asymptomatic disease at the time of diagnosis is, overall, associated with better survival, with median survival shown in some of the initial studies as high as 16 years. Some patients will remain asymptomatic

and have a very stable disease course. However, even in asymptomatic PBC, many patients will become symptomatic over time and experience more progressive disease. And the median time to symptoms can be as short as 2 to 4 years.

In contrast, patients who present with symptomatic disease at the time of diagnosis have diminished survival and the worst prognosis. And that survival can be, just with onset of symptoms, 5 to 8 years, as demonstrated in some of these initial studies.

With regard to the variable course of PBC, what's interesting is that patients who remain asymptomatic over time have a very similar prognosis to the general population without PBC. Even in those who begin with asymptomatic primary biliary cholangitis, and then develop symptoms over several years, there's clearly a diminished survival in that patient group who progress to symptoms and then progressive disease.

Further, there are other important clinical predictors of prognosis that were established years ago, and here I'd like to highlight 2 clinical factors. First, the importance of fibrosis at the time of diagnosis. So, when there was advanced and bridging fibrosis or even cirrhosis at the time of diagnosis, this was first established 40 years ago in Dr. Boyer's landmark *New England Journal of Medicine* study in 1983, that just the presence of bridging fibrosis and cirrhosis at initial biopsy clearly impacts long-term survival. The other clinical predictor at the time of diagnosis is the bilirubin level, and this also remains very important today where this study also showed that a bilirubin level greater than 5 mg/dL at the time of diagnosis was also associated with poor long-term outcomes.

Studies that have analyzed serial biopsies, over time, in patients with primary biliary cholangitis have shown that the median time to the development of extensive fibrosis, which is greater than fibrosis stage 3 or advanced bridging fibrosis, could be as little as 2 years. At 4 years, only a small proportion of patients, 29%, will remain in early stages of PBC. Whereas as many as 50% of patients who did not have fibrosis at the establishment of diagnosis, or at baseline, will develop cirrhosis. And therefore the estimated histologic stage progression would be 1 stage of liver fibrosis or hepatic fibrosis over 1½ years of follow-up.

With regard to clinical disease progression, there are a few studies that have informed on the risk of developing hepatic decompensation and by that I mean ascites, hepatic encephalopathy, variceal bleeding and hyperbilirubinemia. And the 5-year risk of hepatic decompensation in some of these studies have ranged between 15% and 25% and these are cohorts that were comprised of 50% cirrhotic patients at the entry of these observational studies. Also, the development of esophageal varices and variceal bleeding is very important in the clinical progression of disease. And studies have shown a 31% rate of developing esophageal varices over a 5-year period of time. And this was in a group of patients where only about a quarter were cirrhotic at entry or at baseline of these observational studies, and, clearly, once there's a presence of and the development of esophageal varices, there is diminished survival and that 3-year survival rate has been established to be 59% once varices have developed.

Here, I'd like to discuss how ursodiol has had a tremendous impact in improving outcomes in primary biliary cholangitis and delaying disease progression, as we discussed in the prior part of this talk. So, ursodiol has clearly changed the course of PBC. Treatment with ursodiol improves biochemical indices, it delays histologic progression and improves survival without transplantation. And this has been shown over and over again in many clinical studies. For example, in this clinical trial, I highlight the risk of fibrosis progression per year. In patients treated with ursodiol, the fibrosis progression was only 7% per year, whereas patients treated with placebo had

a far greater risk of fibrosis progression, on an annual basis, at 34%. Likewise, the risk of developing varices has changed significantly with the treatment of ursodiol. Over a 4-year period of time, the risk of developing varices in patients treated with ursodiol was only 16%, whereas that risk at 4 years in patients treated with placebo, was as great as 58%.

The data over and over again show overall survival benefits with treatment of PBC with ursodiol. In as little as 48 months, you can see superior patient outcomes, with patients treated with ursodiol compared to patients treated with placebo. And here I just want to reiterate some of these points. The effect of ursodiol on mortality and on liver transplant risk is very impressive. The long-term use of ursodiol reduces death and the need for liver transplant and that risk reduction is close to 70%. Further, treatment with ursodiol will normalize survival rates when given at early stages of PBC. However, in patients with late-stage and very advanced disease, survival remains reduced despite treatment with ursodiol.

Next, I'd like to discuss some of the contemporary prognostic models that can be used in primary biliary cholangitis. First, I'd like to point out that bilirubin remains the best predictor of survival in all PBC prognostic models and this was established over 40 years ago in the landmark *New England Journal of Medicine* study by Dr. Boyer and his group, and remains the case today. Next, I'd like to introduce the 2 contemporary mathematic models that have been developed in PBC. And that's the UK-PBC Risk Score and the GLOBE score.

So, the UK-PBC Risk Score was derived and validated from an international group of 3,000 patients. It's comprised of baseline albumin and platelet count, plus bilirubin, ALT, AST, and alkaline phosphatase levels 1 year after initiation of treatment with ursodiol. And part of the power and usefulness of these scores is that, for example, the UK-PBC Risk Score provides very meaningful data just after 1 year of initiating therapy. And that calculator can be accessed through the UK-PBC website.

The GLOBE score, similarly, is a mathematical model that was derived and validated from over 4,000 international patients. And this index comprises the following variables: baseline age, bilirubin, alkaline phosphatase level, albumin and platelet count. Again, 1 year after initiating therapy with ursodiol. And the calculator can be accessed on the GLOBAL PBC website.

Here, I'd like to provide an example of how the GLOBE score can predict transplant-free survival just using a simple threshold. Using a threshold of 0.3, the transplant-free survival and the long-term survival is quite diminished, whereas GLOBE score of less than or equal to 0.3 has an excellent medium- and long-term survival rates.

Ursodiol as initial therapy

Case 1 background

A 37-year-old woman is evaluated during her annual physical examination. The patient has a history of type 2 diabetes mellitus controlled with metformin therapy, and rheumatoid arthritis somewhat controlled with methotrexate therapy. Her current concerns are dry, itchy skin of the legs and trunk and morning stiffness of the knees and elbows. Physical examination shows excoriations of the thighs and upper arms. Hematologic findings are normal. Significant biochemical findings are as follows:

Glucose 92 mg/dL Total bilirubin 1.2 mg/DL Alanine aminotransferase 42 U/L Aspartate aminotransferase 24 U/L Alkaline phosphatase 210 U/L
Question 1
Which of the following serologic tests would be the most appropriate next step in the evaluation of this patient? **A.** Antinuclear antibody B. Antimitochondrial antibody C. Anti-glycoprotein 210 D. Smooth muscle antibody
Answer rationale
The correct answer is: B • This patient most likely has primary biliary cholangitis (PBC). Measurement of serum antimitochondrial antibody (AMA) is highly sensitive and specific for this disorder, being present in nearly all patients. • Antinuclear antibody is found in more than 2 out of every 3 patients with PBC, but may suggest autoimmune hepatitis • Anti-glycoprotein 210 may be useful in AMA negative patients, but it is only present in 1 in every 4 patients with PBC • Smooth muscle antibodies are found in about half of patients with PBC, but have little diagnostic value

James Boyer, MD: The correct answer is B. This patient most likely has primary biliary cholangitis or PBC. The antimitochondrial antibody is a highly sensitive and specific test for this disorder and it's present in over 95% of patients with this condition. Patients with PBC also can have antinuclear antibodies and more than 2 out of 3 patients with PBC may have this antibody present. This really doesn't suggest autoimmune hepatitis as some people make out. It's just an associated antibody in the disease. Very rarely, though, the patient can overlap syndrome with autoimmune hepatitis and be ANA positive. And in patients who are AMA-negative, one can get an anti-glycoprotein 210 antibody, but it's present in only 1 in every 4 patients with PBC. Smooth muscle antibodies are also found in about half of the patients with PBC, but have very little diagnostic specificity.

Sarah Enslin, you're a PA, what is the importance of setting a laboratory and symptom baseline for the patient?

Sarah Enslin, PA-C: A great question, and there's a few reasons for that. One is to evaluate their baseline status. Do they have advanced fibrosis or cirrhosis at the time of diagnosis? It's also helpful to get baseline fat soluble vitamins and lipids before you start treatment. It's also helpful for prognosis. So, many of the prognostic scores, such as UK-PBC or the Globe Risk Score, are going to use those baseline lab values and then compare them to 1 year after treatment. We also know that patients who have elevated AST and ALT may have more disease severity at the time of diagnosis. And then finally, those baseline labs are important so that when we start treatment, we can monitor their therapeutic response.

James Boyer, MD: Donald Gardenier, you're a nurse practitioner, how do you help patients keep track of their baseline as they navigate care?

Donald Gardenier, DNP: It can be challenging, to be honest. I personally work with an older population and probably for most of them, and certainly my PBC patients, I'm taking over their care as they have moved to our area from someplace else. And very often they don't come with their records and so it's a matter of piecing things together. Some people are meticulous about keeping their records; some are not. In a situation

where you're diagnosing someone from the beginning, I think it's as much as anything else, a matter of patient education and letting people know.

Generally speaking, though, I set up all sorts of ways of sharing information with patients through patient portals and so on and so forth. I kind of set up a grid for them so they can track their progress and I set up sort of a portable record that will go with them as they continue to treat their disease.

James Boyer, MD: And Dr. Sclair, what other laboratory markers do you use routinely, and do you collect at baseline?

Seth Sclair, MD: In addition to what Sarah just outlined, I like to establish the serologic profile for the patient at baseline. In addition to obtaining the antimitochondrial antibody, ANA, the antinuclear antibody and the smooth muscle antibody and serum immunoglobulins, specifically the serum immunoglobulin G and M levels, that helps, I believe, to clarify how likely a diagnosis is or is there more work-up evaluation that needs to be pursued? And this sometimes can inform the need to do further testing like a liver biopsy to be most confident with the diagnosis of primary biliary cholangitis.

Case 1 background
Serologic testing in this patient shows a positive result for antimitochondrial antibody and a negative result for antinuclear antibody. Diagnosis of asymptomatic, AMA-positive, ANA-negative primary biliary cholangitis is made.
Question 2
For which of the following disorders associated with primary biliary cholangitis should this patient be monitored? A. Hypercholesterolemia B. Hypertension C. Glaucoma D. Renal failure

Answer rationale
The correct answer is: A • Autoimmune diseases are associated with PBC, which the patient already has. • PBC is considered to be an organ-specific disorder. • Hypercholesterolemia affects upwards of 90% of patients with PBC • Other common comorbid conditions include anxiety, and depression

Donald Gardenier, DNP: The correct answer is A, hypercholesterolemia. Autoimmune diseases are common in PBC. This patient already has associated autoimmune disorders. PBC, however, is considered organ-specific to the liver. Hypercholesterolemia is an issue in patients with PBC, upward of 90%, so an overwhelmingly common disorder. Other comorbid conditions with PBC include depression and anxiety. Dr. Boyer, what other related disorders do you commonly see in your patients with PBC?

James Boyer, MD: Other autoimmune diseases can be seen in patients with PBC. They can have hypothyroidism. They can have dry eyes and dry mouths syndrome, called Sjogren's disease. Rarely, intestinal issues such as celiac disease can be associated, and they can have an arthritis that's very much like rheumatoid arthritis, as well. These are the major other autoimmune-associated disorders.

Donald Gardenier, DNP: Sarah, are there any cultural considerations that come to the fore when you're dealing with your patients with PBC?

Sarah Enslin, PA-C: There's a couple of things that I think about. We know that these cases are mostly females, but they're also most prevalent in Northern European, North America. There's probably some component of both genetic and environmental factors or triggers that are contributing to that. It's an area that's relatively new in research, but we see that geographic clustering and then there's the

consideration of whether there are some socioeconomical factors that are in it. Definitely more common in people with identical twins or families, particularly those with female first-degree relatives with the diagnosis. And once we have that diagnosis, I think the other part of it is the adherence to medications and so, certainly looking at the patient's background and providing any education that might be needed from that standpoint.

Donald Gardenier, DNP: Dr. Bhat, from a pharmacist perspective, we just heard about adherence to medications. Are there any other sort of pharmacy-related issues that you look for in patients with PBC?

Shubha Bhat, PharmD: I'd like to just emphasize that there might be some questions or considerations around medications and their liver-related effects. In this particular patient's case, the hypercholesterolemia, there might be concerns or questions about statin use, but, however, studies have demonstrated that statins are effective at lowering low-density lipoprotein or LDL cholesterol, but it is important to emphasize that use in decompensated cirrhosis is not ideal. Fibrates are another medicine that we could potentially consider, but they are not as effective at lowering LDL cholesterol. And there's another medication class called proprotein convertase subtilisin/kexin 9 or PCSK9 inhibitors. These can also be safe and effective in chronic liver disease. Some other medications to consider not using in patients that have PBC would also be nonsteroidal medications, so ibuprofen and naproxen. There's a concern that if the liver is damaged, they could potentially cause greater injury. So there are some other medication-related considerations that relate to PBC.

Donald Gardenier, DNP: Dr. Sclair, could you comment about the difference between people who are asymptomatic vs those who are symptomatic at diagnosis with PBC?

Seth Sclair, MD: I think that's a very important question. Actually, Dr. Boyer answered a very important literature and data for this question many years ago which I think is very pertinent. Before treatment, there are definitely some key points in patients with asymptomatic disease vs symptomatic disease and, in general, patients with asymptomatic disease are shown to have an excellent prognosis and a better prognosis. Outcomes were better than patients who had symptomatic disease. But there are a couple of other points that are very important too. A proportion of patients will likely remain asymptomatic and have a stable course over time, but there's a large proportion of patients who will go from an asymptomatic state or condition and they will later become symptomatic over time and develop more progressive disease. And that can happen as early as the first few years after diagnosis.

Case 1 background
After further discussion with the patient regarding likelihood of response to therapy and prognosis, the decision is made to start treatment with ursodiol.
Question 3
Which one of the following is a criterion of response to ursodiol therapy? A. Stabilization of aminotransferases at 6 months B. Normalization of aminotransferases and symptoms at 12 months C. Normalization of alkaline phosphatase and bilirubin at 12 months D. Resolution of symptoms at 6 months
Answer rationale
The correct answer is: C • The primary target of treatment in PBC is a normalization of alkaline phosphatase and bilirubin. These lab values at 1 year have been associated with prognosis such as reductions in liver transplant and

mortality. In early disease, bilirubin may be normal.
- Other laboratory values such as aminotransferases may or may not be elevated in patients with PBC.
- Symptoms, while important to patients, are not the primary outcome, but should resolve with response to therapy.

Sarah Enslin, PA-C: The correct answer is C, normalization of alkaline phosphatase and bilirubin at 12 months. The primary target of treatment in PBC is that normalization of alkaline phosphatase and bilirubin. Many patients are not going to have elevations in the AST or ALT. We know that normalization of phosphatase and bilirubin at 1 year has been associated with improved prognosis, such as reductions in liver transplant and mortality. We have many different studies that are out there that show that there's a reduction in fibrosis in these patients as well. Symptoms, while they're really important to patients, they really are not the primary outcome. They should resolve. If you have reduction of the alkaline phosphatase, we'd expect that something like pruritus and even fatigue is going to get better, but that is not our primary target for therapy. So, Donald, it's clear that patients who adhere to ursodiol therapy for 12 months have better outcomes. How do you help support your patients so that they're able to adhere to that ursodiol regimen?

Donald Gardenier, DNP: It's always the challenge, isn't it, in chronic diseases, especially for asymptomatic patients to keep them sort of steady going on therapy. And I would say all the usual things that we do in terms of counseling and making sure that prescriptions are filled and emphasizing the importance of follow-up. In PBC specifically, I would say I often use the data.

We alluded to that earlier, the difference between survival and generally in outcomes in patients whose disease is managed vs those who are not. And the change in nomenclature some years ago from primary biliary cirrhosis to primary biliary cholangitis tells a lot of the story, because I think mostly we called it cirrhosis because most of the patients were cirrhotic by the time we diagnosed them. And changes in practice have led to improved outcomes despite some uptick in the prevalence of the disease.

So, I try to use the data to my advantage in this case. It's also helpful that ursodiol is generally very well-tolerated.

Sarah Enslin, PA-C: Building upon that, Dr. Bhat, what are some of the common side effects with ursodiol, and what education should the patients be given prior to starting therapy?

Shubha Bhat, PharmD: I think Donald had brought up a lot of pertinent points as they relate to ursodiol treatment. As he had mentioned, it is generally well-tolerated. We do try to titrate to an optimal dose based on body weight, between 13 to 15 mg/kg/day and the doses can be administered in 2 to 4 divided doses. And it should be taken with food. There are some educational points that the patients should be informed about. The medication works by moving bile through the liver. As you had mentioned before, the treatment goal is to really slow down disease progression and reduce the need for liver transplantation. And so there might not be improvement with itching or fatigue, however the end goal, again, is to try to minimize the need for transplant. I do often emphasize that the treatment is lifelong, and some other important considerations are that there are drug interactions that can affect how well the medication works. So, for patients who are on bile acid sequestering medications, such as cholestyramine or colestipol, it's important to space those out so that the ursodiol should be taken 1 hour before or 4 hours after the bile acid sequestering agent and, similarly, there's another interaction to be noted with aluminum-based antacids. For that, the administration instruction for ursodiol is to be 1 hour before or 2 hours after the aluminum-based antacid. So, I think there are some important things

to just highlight in terms of making the medication a little bit more effective.

Obeticholic acid and emerging therapies

Case 2 background
A 46-year-old woman with a 6-year history of primary biliary cholangitis is evaluated after 1-year of ursodiol therapy. The patient's disease has not responded to therapy: the serum alkaline phosphatase is 375 IU/L (more than 3 times the upper limit of normal). The patient has fatigue and pruritus and such symptoms of early compensated cirrhosis as upper abdominal pain and nausea, but without evidence of portal hypertension.
Question 1
In addition to continuing ursodiol, which one of the following therapies would be most appropriate for this patient now? A. Fenofibrate B. Obeticholic acid C. Budesonide D. Liver transplantation
Answer rationale
The correct answer is: B • Obeticholic acid may be used in patients who have not responded to or are intolerant of ursodiol. Obeticholic acid is indicated for adults with PBC without cirrhosis or with compensated cirrhosis without evidence of portal hypertension. The POISE trial showed nearly half of patients treated with obeticholic acid (vs 10% of placebo treated patients) achieved an alkaline phosphatase level l less than 1.67 times the upper limit of normal. Nearly all patients continued ursodiol. • Fibrates are investigational and do not carry a labeled indication for PBC but are sometimes used in patients who have not responded to or are intolerant of ursodiol. They are generally safe for patients with cirrhosis. Fibrates also have positive effects on fatigue and pruritus. The data are strongest for bezafibrate, which is not available in the United States. • Budesonide may be used in patients without cirrhosis who also have inflammatory changes, but the data on benefit are unclear. • The patient is not a liver transplant candidate at this time with compensated cirrhosis.

Seth Sclair, MD: The correct answer is B, obeticholic acid. Obeticholic acid may be used in patients who have not responded to or are intolerant to ursodiol. Obeticholic acid is indicated for adults with PBC without cirrhosis or with compensated cirrhosis without evidence of portal hypertension. The POISE trial showed nearly half of patients treated with obeticholic acid (vs 10% of placebo-treated patients) achieved an alkaline phosphatase level less than 1.67 times the upper limit of normal and nearly all patients continued ursodiol. Fibrates are investigational and do not carry a labeled indication for PBC but are sometimes used in patients who have not responded to or are intolerant of ursodiol. They are generally safe for patients with cirrhosis as well. Fibrates also have positive effects on fatigue and on pruritus. The data are strongest for bezafibrate, however bezafibrate is not currently available for use in the United States. Budesonide may be used in patients without cirrhosis but also have inflammatory changes. These are the changes that sometimes are present when there's overlapping autoimmune hepatitis, but the data on benefit of budesonide are not entirely clear. At this time, the patient is not a liver transplant candidate as the patient has compensated disease and compensated cirrhosis. Dr. Boyer, what risks of obeticholic acid and

fibrate therapy do you consider and how do you weigh them against the anticipated benefit?

James Boyer, MD: Well, starting with obeticholic acid, the major risks that we have with this drug are it's used in more advanced cirrhosis. In fact, it should not be prescribed in patients with decompensated cirrhosis and those with portal hypertension because not only has liver failure been described, but also a few deaths that required the FDA to put a black box warning and these were due to inappropriate dosages of the drug when it was used. That's the major risk factor of obeticholic acid. Of course, there are other side effects that are significant. Many of these patients will develop pruritus. As had been mentioned, hypercholesterolemia can be aggravated and these are the major concerns for obeticholic acid. Fibrates, on the other hand, are relatively safe. Their side effects, and this is in the United States, fenofibrate has been on the market for a number of years for hyperlipidemia and so it has a very strong safety record in that regard. But it can lead to increases in creatinine. This is a dose-related complication and if you halve the dose, the creatinine should come back to its previous levels. Very rarely one can have a severe inflammation in the muscles with a rhabdomyolysis-like syndrome. This is a very rare serious complication that can lead to kidney failure. Those are the main concerns, I think, and the general safety profile for the 2 drugs tends to favor the fibrates.

Seth Sclair, MD: Dr. Bhat, what side effects or intolerances to ursodiol do you commonly see that trigger you to consider a different therapy?

Shubha Bhat, PharmD: As mentioned before, ursodiol is generally well-tolerated, however patients may experience contrary weight gain or mild gastrointestinal discomfort, like diarrhea, nausea, vomiting, as well as, potentially, hair loss. So, these might be situations to potentially consider changing therapy. I would also like to reiterate and emphasize in the presentation that it is common for patients to not have treatment response and we have found a factor predictive of the ursodiol failure does include high serum bilirubin, high total serum bile acid concentration, low serum albumin, hepatomegaly and splenomegaly. So, there might be some additional considerations, more from an efficacy standpoint, to consider in terms of changing to a different treatment option.

Case 2 background
A 46-year-old woman with a 6-year history of primary biliary cholangitis is evaluated after 1-year of ursodiol therapy. The patient's disease has not responded to therapy: the serum alkaline phosphatase is 375 IU/L (more than 3 times the upper limit of normal). The patient has fatigue and pruritus and such symptoms of early compensated cirrhosis as upper abdominal pain and nausea, but without evidence of portal hypertension.
Question 2
At what point in therapy for this patient would a full response to obeticholic acid be expected? A. 3 months B. 6 months C. 9 months D. 12 months

Answer rationale

The correct answer is: D

- Monitoring of response may occur at 3-to-6-month intervals with repeat at 12 months
- Biochemical response has been shown to be significant at 12 months, and as far out as 36 months, for those patients treated with obeticholic add-on therapy.
- The POISE trial showed that patients began to show response at 3 months, however, the primary composite endpoint was month 12.

James Boyer, MD: The correct answer is 12 months, D. Of course, one can monitor the response earlier and many of these patients will respond within the 3 to 6 months period. And you would repeat it again at 12 months. The biochemical response has been shown to be significant at 12 months, and as far out as 36 months, for these patients treated with obeticholic acid add-on therapy. And the POISE trial, which was the phase 3 trial for this drug, showed that patients began to show response at 3 months, but the primary composite endpoint was month 12. Now, the composite endpoint includes a reduction of the alkaline phosphatase below 1.67 upper limits of normal. It consists of maintaining a normal serum bilirubin and it also means that alkaline phosphatase should be greater than 15% below the starting level. That's the so-called primary composite endpoint for cholestatic disease with this drug. Now, Dr. Sclair, what survival benefits do you see in patients treated with obeticholic acid?

Seth Sclair, MD: And so the POISE trial initially informed on the biochemical response from obeticholic acid, but now there is emerging data from the POISE trial, from the open-label extension of the POISE trial, which is starting to inform on some of the long-term outcomes of patients who have been using obeticholic acid as well. And I'd like to point out 2 points which I believe can inform on this topic. So, for example, a portion of patients on, from the open-label extension part of the POISE trial, have undergone repeat biopsy at the 3-year mark and 70% of those patients have improvements or stabilization of fibrosis, which I think is very encouraging and shows that obeticholic acid can stabilize the liver disease in PBC and perhaps improve it. I think even more recently some of the long-term follow-up data from the open-label extension is now also demonstrating greater transplant-free survival in patients who are receiving obeticholic acid for PBC. And I think this also supports and reflects what we learned many years ago from the ursodiol studies. So, these, I think, are very important. This is very important data that's beginning to emerge from the initial POISE trial showing some of the long-term benefits of therapy.

James Boyer, MD: Sarah, as a PA, what are the things that you routinely discuss with patients who are about to start obeticholic acid?

Sarah Enslin, PA-C: I think this is a really important point. A lot of the medications that we're going to use, not just for PBC but really any disease state, require the patient to be committed to the therapy, whether that's for a finite period of time or indefinitely. So, when I have conversations with patients about obeticholic acid, my first point is if this is effective for you, we're going to continue this indefinitely. I also have to acknowledge that, for some patients, this is costly and so making sure that we're looking at ways that we can make this more cost effective for them. If they feel like they're having some side effects or some issues with it or if cost is a matter that they want to discuss, I ask that they reach out to me and they don't self-discontinue medications. We talk about the reason that we're using it so that they have a good understanding for that. I always try to go through what are we going to do for monitoring and so, in this case, I'm looking at blood work, we're watching the alkaline phosphatase and hoping that it's starting to improve. And so trying to give them some expectations and if it hasn't reached where I want it to reach within 6

months, we may consider going up on the dose. This way, they have those expectations ahead of time. I also like to talk about side effects. So, obeticholic acid, pruritus being the biggest side effect. We talk a little bit about that. If they have pruritus to start with, then it may not be a great option for them. If they don't have it and they start to get it, they could think it's from any number of things and so, having those expectations ahead of time I think is really important. And then finally, that emphasis on compliance. So, you're taking this medication for this reason, this is how you're going to take it, this is how we're going to follow it and if you have any issues, reach out to me.

James Boyer, MD: Donald Gardenier, how do you support patients with adherence to obeticholic acid?

Donald Gardenier, DNP: I think Sarah did a great job just now covering the main points. Alert to side effects, I think, is the key with obeticholic acid and Sarah hit the nail on the head with the pruritus. As we know, patients these days do a lot of their own information gathering and so they frequently confuse—and it's confusing, I acknowledge that with them—the side effects of the medication vs the symptoms of the disease. And it can be the single most challenging part of managing PBC, in my experience, given the chronic nature of the disease and the indication for lifelong therapy. So, in addition to knowing all the facts and all the patient education that Sarah covered so well, I would say, generally speaking, being alert, being a good listener, being available to patients, not being above the point of providing sort of a creative approach to treating the side effects and/or the symptoms of the disease and the occasional pep talk, honestly, is what a lot of these patient visits turn into. And that's okay. It's all part of taking care of someone with PBC, I should say.

James Boyer, MD: Dr. Bhat, can you discuss some of the common side effects with obeticholic acid?

Shubha Bhat, PharmD: I think everyone on the panel has discussed this, but pruritus or itching is the most common side effect that we typically tend to see with obeticholic acid. And I would like to just briefly discuss how we can typically manage it. So, obeticholic acid is available in 5 and 10 mg tablets. The current recommendation is to start at 5 mg once a day for ideally up to 3 to 6 months and then titrate up to 10 mg daily, depending on how the patient is tolerating it and their response to the medication. We typically do not recommend to initiate at 10 mg daily because they are at increased risk for pruritus right off the bat. And if you do have a patient that does develop this, depending on the severity of their itching, there are ways to manage this and 1 thing that we can potentially do is to consider reducing the dose to 5 mg every other day or temporarily pausing the treatment for up to 2 weeks and then restart them at 5 mg every other day and then gradually do a dose titration. We can also consider adding on an antihistamine or a bile acid sequestrant, again like cholestyramine or colestipol. And then the other interesting thing is that the pharmaceutical company that makes obeticholic acid does provide a pruritus kit and, in that kit, there are some samples that can be used to soothe itching and that includes like an aloe gel, a lidocaine spray, an oatmeal bath and hydrocortisone ointment. So, there are resources to manage this, but it definitely can be a quality-of-life factor and so it's a very important side effect to assess for when starting on treatment. I'd also like to just briefly emphasize that it's important to monitor for hepatic decompensation or evidence of portal hypertension and that's another point that the faculty has been mentioning, so I just want to emphasize again that this is an important consideration to keep in mind and monitor for when using this therapy.

Case 2 background

The patient's medical team proposes that the patient's care be provided by a multidisciplinary, interprofessional care team consisting of a pharmacist, a nurse practitioner or physician's assistant who will coordinate with the patient's primary care provider, and others.

Question 3
Which of the following statements about the use of multidisciplinary, interprofessional care models in the management of primary biliary cholangitis is correct? A. Multidisciplinary care models are costly and inefficient B. Multidisciplinary care models are not addressed in current clinical guidelines. C. Multidisciplinary care models are safe and efficient D. Multidisciplinary care models are geographically limited
Answer rationale
The correct answer is: C • No data has emerged on the cost of multidisciplinary care models; however, care models in other diseases have shown them to be cost effective • Guidelines discuss, briefly, multidisciplinary team members and their potential roles • Multidisciplinary care models have been shown in early data to provide safe and efficient care • Multidisciplinary care models may be limited to certain centers, but telemedicine has provided expanded geographic reach

Seth Sclair, MD: The correct answer here is C, multidisciplinary care models are safe and efficient. No data has emerged on the cost of multidisciplinary care models, however care models in other diseases and chronic diseases have shown them to be cost effective. Guidelines discuss briefly the multidisciplinary care team members and their potential roles. Multidisciplinary care models have been shown in early data to provide safe and efficient care and multidisciplinary care models may be limited to certain centers, but telemedicine has also provided expanded geographic reach. Jim, what is the current practice model in which you operate?

James Boyer, MD: I operate within an academic medical center and most of my contacts with patients with PBC are in the outpatient clinic. I do see occasional patients within the hospital, but almost all of them are outpatient. When a patient does progress to decompensated cirrhosis, then I refer those patients to my colleagues who are transplant hepatologists for further follow-up. Unfortunately, we don't have a PA like Sarah Enslin, it would be terrific if we did, but that's one deficiency in our clinical operation. I practice with 2 other hepatologists in our autoimmune and cholestatic liver disease clinic and that's the focus of our model.

Seth Sclair, MD: Sarah, what is the current practice model in which you operate and what role do you play in the care of patients with primary biliary cholangitis?

Sarah Enslin, PA-C: I am in an academic practice. I have a collaborative practice with a physician. We are a relatively large group. There's over 20 advanced practice providers in total. I primarily am seeing patients with pancreaticobiliary disease and hepatologic liver diseases. And so, in our collaborative practice, I will see patients independently. I may see them as a new patient or I may see them more as a continuity visit. I do carry my own panel of patients and then I see patients who are more complex in shared visits with the physician. I think that our role certainly is, in the clinic, definitely patient care, but there's a lot of background work too that is important to the role of advanced practice providers and physicians as well. But it's making sure patients are getting the medications that they need, prescription refills and authorizations, managing any complaints or concerns that patients may have through phone calls or patient messaging, really working in conjunction with a care team and so reaching out to pharmacy when needed. I think that that a multidisciplinary team is important in many of these patients, especially those that have advanced liver disease. So, working with, potentially, transplant hepatologists, if

they get to advanced cirrhosis and end-stage liver disease.

Seth Sclair, MD: Donald, what is the current practice model in which you operate and what role do you play in the care of patients with PBC?

Donald Gardenier, DNP: I am 1 of 4 nurse practitioners and 7 gastroenterologists in a hospital-affiliated gastroenterology/hepatology practice. So, we're a community-based health system affiliated with a 500 or so bed hospital. We say our main catchment area is a population of about 200,000, but that can vary a lot. This part of Southern California where I work, we have a lot of snowbirds who spend part of their time here and part of their time somewhere else. We also had a lot of shifting of population, mostly into the area during the recent COVID pandemic so that has increased our patient population a lot and a lot of our trends are kind of upended by that. My gastroenterologist colleagues do a lot of different things. A lot of their time is spent doing procedures. The 4 nurse practitioners in our particular practice spend all of our time in the office seeing patients as outpatients. And so, generally speaking, I've certainly got those patients who are my own panel, but I spend probably at least half my time seeing patients who are primarily seen by 1 of the gastroenterologists, either for interim visits or urgent visits or rescheduled visits. We do have close relationships with our nearby transplant centers. The closest is about 50 miles away, but again this is Southern California, so there are several, and at least 2 of them run what they call outreach clinics. So, once a month or so, they travel to our area and see patients and, of course, remote telehealth visits have helped a lot just in terms of keeping everything moving.

Seth Sclair, MD: Shubha, what is the current practice model in which you operate and what role do you play in the care of patients with primary biliary cholangitis?

Shubha Bhat, PharmD: I'm always excited to talk about what a pharmacist does when I have the opportunity. So, similar to the rest of the panel, I also work in an academic center and I'm actually embedded as a pharmacist within the gastroenterology clinic. I work under a collaborative practice agreement, but I do have the ability to see patients alongside the physician and kind of more medication monitoring and management. Pharmacists can be embedded in a specialty pharmacy or they can also be embedded in a clinic. So, you'll kind of see that our practice settings can actually vary, depending on the institution. But in general, a pharmacist's role is really focused on medication education, definitely access and monitoring. We typically would do baseline assessments to include that we're making sure that labs are up to date, we're screening for potential contraindications as well as drug interactions and then we're definitely making sure to maintain medication adherence and ensuring that patients have regular follow-ups with assessment by the hepatology team. I'd like to point out in the context of PBC, that obeticholic acid is actually considered a specialty medication, so this means that it's not a medicine that you can send to your regular pharmacy and expect the patient to go pick it up like the next day. It actually does require a whole level of medication coordination and that comes in with prior authorization, copay assistance program or patient assistance program and then actually the medication being dispensed from a specialty pharmacy that has (access) and has the medication in supply or in stock. The other component that we can also do as pharmacists is to help out with adverse effects management. So, if patients are having side effects, we can tease out if that's related to the medication and then provide recommendations on how to address that. And really, our overall focus is really on optimizing the patient's medication regimen, access, and outcomes.

Case 3 background

A 53-year-old woman with a 4-year history of primary biliary cholangitis is evaluated after 1 year of ursodiol therapy. She has had minimal improvement in her fatigue and pruritus and has not had a biochemical response; the serum alkaline phosphatase is 425 IU/L (more than 3 times the upper limit of normal). She has symptoms of decompensated cirrhosis with mild ascites on physical examination. She also has evidence of mild portal hypertension.

Question 3

Which one of the following therapies would be most appropriate for this patient?

A. Add obeticholic acid
B. Add fenofibrate
C. Add budesonide
D. Refer for transplant

Answer rationale

The correct answer is: B

- The patient has had little biochemical response, so additional therapy is warranted at this time.
- Obeticholic acid may be used in appropriate patients who have not responded to or are intolerant of ursodiol. Obeticholic acid is indicated for adults with PBC without cirrhosis or with compensated cirrhosis without evidence of portal hypertension. Recently, the use of obeticholic acid in patients with cirrhosis has been reported to lead to liver failure. These reports have led to a change in the prescribing information for patients with cirrhosis with the addition of a contraindication for those with decompensated cirrhosis or portal hypertension.
- Fibrates are investigational and do not carry a labeled indication for PBC but are sometimes used in patients who have not responded to or are intolerant of ursodiol. They are generally safe for patients with cirrhosis. Fibrates also have positive effects on fatigue and pruritus. The data are strongest for bezafibrate, which is not available in the United States.
- Budesonide may be used in patients without cirrhosis who also have inflammatory changes, but the data regarding benefit are unclear.
- The patient is not a liver transplant candidate at this time, with compensated cirrhosis.

James Boyer, MD: The answer given here is B, to add fenofibrate. I have to say this is somewhat of a controversial answer and not all physicians would want to add therapy in a patient that has mild decompensation of cirrhosis since the efficacy and safety of drugs at this stage of the disease may not always be effective. In particular, one would not want to administer obeticholic acid where recent prescribing information has contraindicated the use of this drug in patients who have decompensated cirrhosis or portal hypertension. And we seem to have evidence of that to a mild degree in this patient. I have used fibrates in this situation as the safety profile of the fibrates is quite strong, but the efficacy of a fibrate at this stage may not be very effective. So, one has to monitor patients fairly carefully in this situation.

Fibrates are more effective than obeticholic acid, of course, in the treatment of pruritus. That's one of the distinct advantages of the fibrates. While obeticholic acid causes pruritus, fenofibrate and other fibrates usually improve that symptom. Bezafibrate has been studied in a phase 3 trial in France and was shown to be quite beneficial in terms of endpoints, the reduction of alkaline phosphatase, the normalization of pruritus percentage was quite high, the liver scan for fibrosis, FibroScan, also seemed to be improved but, unfortunately, we don't have bezafibrate in the United States. It's not yet been FDA approved. Budesonide is occasionally used in patients with PBC who have an inflammatory component as their transaminases tend to be higher.

Again, one wants to be sure you're not dealing with the overlap syndrome with autoimmune hepatitis in that situation, and a liver biopsy is usually necessary to make that determination. There's no hard data, evidence-based data, however for the use of this drug. While this patient is not a transplant candidate at the present time, I think the patient is definitely headed in that direction, so I would have a low threshold to refer this patient in the near future to my transplant colleagues. So, Dr. Sclair, when you're considering adding fibrates too, when are you considering adding fibrates to a patient's treatment plan?

Seth Sclair, MD: Dr. Boyer, I think you already hit on a few of the points and let me elaborate a little further. I think, if a patient has not fully had a response to ursodiol and meets criteria for adding adjunct therapy or adding on therapy and our choices are obeticholic acid and fibrate therapy, I think one factor might be access to obeticholic acid. Does the patient have access to it in terms of cost and coverage? Another might be someone suffering from pruritus, as you indicated. If the concern is that someone already with significant pruritus might not tolerate obeticholic acid due to the concern of worsening pruritus, then perhaps fibrate might be an option in that scenario. I think the other option is, in the patient where the safety of obeticholic acid in a patient with more advanced cirrhosis and portal hypertension, where you want to avoid some of the safety problems with obeticholic acid, fibrate might be an alternative as well. I think its use in more decompensated disease, I'd be careful and cautious in using even fibrate therapy in decompensated disease. I think, in this scenario where it's very early signs of decompensation, it might be worthwhile to consider fibrate therapy here.

James Boyer, MD: And Dr. Bhat, what side effects should patients who are started on fibrates be monitored for?

Shubha Bhat, PharmD: I think you have previously discussed about fibrates in an earlier question and you had alluded to some of the side effects there. This is generally another treatment that is well tolerated and we've seen that rates of discontinuation in clinical trials have been overall low. But some potential side effects to monitor for would include pruritus, myalgias, definitely elevation of serum creatinine phosphokinase and CPK levels, fatigue, and sometimes gastrointestinal intolerances, such as nausea, abdominal pain and bloating.

James Boyer, MD: Sarah, I'm interested to see you have your own practice, which is terrific, and when you add fibrates, do you continue or discontinue other therapies?

Sarah Enslin, PA-C: I think, as with everything, it's not a 1-size-fits-all and so I don't use fibrates often, but I have used them in both scenarios. I think if there's a patient who is intolerant to ursodiol and has early compensated cirrhosis or early signs of decompensation perhaps, fenofibrates is potentially our best option that's available currently. Most of the time though, if somebody has an incomplete response to ursodiol or no response, I'm looking to add it on as more of an adjunct and then I would continue them on ursodiol and start the fenofibrates. I've also used it in patients who have high triglycerides, particularly if it's worsening when they start therapy because it'll give us that little benefit. And then, for patients who may have some pruritus, again—particularly if they have high triglycerides—it can be helpful in that instance.

James Boyer, MD: And Donald Gardenier, are there any other considerations for patient care that we should be thinking of for our patients with PBC?

Donald Gardenier, DNP: A very thorough consideration by my colleagues here, but I would say that in PBC in particular, but with all of my patients with cirrhosis for one reason or another, because I don't work at a transplant center, I tend to refer or at least consult with my transplant colleagues early. And I say that because everybody's situation is a little

bit different. The transplant program, you may be the transplant program, but my patients have to travel. They tend to be able to make a day trip out of it and they tend to have the resources to do that, but there are plenty of people who are farther away from transplant and for whom it's a bigger deal. It's also a huge life consideration and a lot of times we refer people for transplant and they don't have all that much time to think about it and I try to imagine what they're going through. So, they get a very thorough work-up in the pretransplant evaluation and I think it's worth it to get that started early and get the patients known to the transplant team so that when the time comes, they're not only on board from a medical perspective, but also from a sort of a social, psychological perspective. And I let them know that I will still be involved and I'll be able to participate in their care, but that this is an important component to make sure that we're able to continue to take care of them.

James Boyer, MD: And Dr. Sclair, at what point now do you consider a liver transplant for your patients?

Seth Sclair, MD: An important question and an important aspect to PBC care. In general, the same indications that apply for other chronic liver disorders apply for PBC in this case. So, whenever a patient has started to experience a decompensating event, whether that may be a variceal bleed, the development of ascites, hepatic encephalopathy, the development of hepatocellular carcinoma, etc. So, that together with evidence that the liver function is beginning to deteriorate. So, if the MELD score is beginning to rise and approach 15 or the new iteration of MELD score, MELD 3.0 in the same way, I think that's when it's very important to begin considering a patient for liver transplant evaluation.

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