ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Management of Suboptimal Response in Primary Biliary Cholangitis Treatment

Gideon M. Hirschfield, MB BChir, PhD
Lily and Terry Horner Chair in Autoimmune Liver Disease Research
Professor of Medicine, Division of Gastroenterology and Hepatology
University of Toronto
The Autoimmune and Rare Liver Disease Programme
Toronto General Hospital
Toronto, Ontario, Canada

G&H Currently, what are the main treatment goals for primary biliary cholangitis?

GH The goals of primary biliary cholangitis (PBC) treatment are evolving and becoming more aspirational. Current guidelines highlight biochemical control of the disease and getting alkaline phosphatase in patients with PBC to less than 1.67 times the upper limit of normal. That is a classic treatment goal for PBC and has been used in clinical trials. However, there has been an evolution in the thought processes associated with PBC treatment. Intuition says providers should be aiming for normal alkaline phosphatase, which is the best marker of biliary inflammation in PBC. Intuition also says that providers should be aiming for the best quality of life for their patients, which includes the treatment of symptoms, particularly itch or pruritus. Thus, PBC treatment goals are evolving from just using ursodeoxycholic acid (UDCA) as our longstanding first-line therapy to thinking proactively about second-line therapies in patients who do not respond adequately to first-line treatment. With the recent increase in choice for second-line agents, I think there will be more focus on the aspirational goals of trying to normalize patients' blood tests and improving their quality of life as much as possible, especially in terms of itch.

G&H What scoring system should be used to assess response to first-line treatment in PBC?

GH One of the challenges for clinicians is that there are too many scoring systems. An advantage of just going with intuition is that it is easier to explain what to do; aiming for normal is an easy message. The scoring systems that have been developed can be described as either dichotomous or continuous. With dichotomous scoring systems, a number is chosen for alkaline phosphatase, for example, less than 1.67 times the upper limit of normal. Continuous scoring systems for PBC, such as the GLOBE Score, are similar to the Model for End-Stage Liver Disease score in that the doctor uses patient information to obtain a continuous risk assessment for the patient.

These scoring systems work and can essentially predict who is at greatest risk of disease progression. When first-line treatment fails, patients should be considered for a second-line therapy promptly. However, for the average practicing clinician, these scoring systems can be difficult to remember because of the relative rarity of PBC. I have always advised that doctors choose one scoring system that they like. As tools and drugs improve, messaging will be easier. Clinicians will be able to use the drugs most likely to normalize alkaline phosphatase and improve symptoms. That will be easier for practicing clinicians to use on a day-to-day basis, rather than having to find a scoring system for a disease that is relatively uncommon in their day-to-day practice.

G&H How many PBC patients experience suboptimal response, and should it be assessed at 6 months rather than 12 months?

GH On average, approximately one-third of patients treated with UDCA do not obtain sufficient biochemical response and are at risk for further progressive liver disease. That is important because one of the goals of being a hepatologist is preventing end-stage liver disease.

When considering completely normal alkaline phosphatase, the proportion of patients experiencing suboptimal response increases. In general, clinicians have always used 12 months for responding to PBC treatment because the data used to generate that answer come from studies where blood tests were available at 12 months. However, the same information can be obtained at 3 and 6 months. Waiting 12 months is just an arbitrary number that has traditionally been used in clinics. I think it is perfectly reasonable to think about additional treatment choices at 6 months. When a PBC patient with high alkaline phosphatase takes UDCA, a clinician can tell at 6 months whether the patient is on a trajectory to lowering their alkaline phosphatase to less than 1.67 times the upper limit of normal, or closer to normal if using aspirational therapeutic goals, so it is not necessary to wait 12 months. The tradition of waiting 12 months will likely be uprooted with the addition of second-line treatment choices. With more and more treatment choices, it is not going to be logical to make people wait.

G&H What are the main risk factors for suboptimal response to first-line PBC treatment?

GH The risk factors can be separated into pretreatment and on-treatment factors, although they can overlap. Pretreatment, I look at the age of the patient, the height of the alkaline phosphatase at diagnosis, and the stage of disease as assessed by liver biopsy or FibroScan. That is not a bad way to identify who is going to have the hardest time normalizing their alkaline phosphatase. If a patient is diagnosed with PBC under the age of 50 years, there is a 50% chance they are not going to be an adequate responder by any criteria. Those patients will likely need their livers for more than 30 years, so it is important to do something to prevent end-stage liver disease.

As for on-treatment risk factors, clinicians should first check that the treatment is being dosed correctly. Stage of disease at diagnosis and during treatment is a predictor of response. Male sex may be a predictor of worse disease, but it is slightly complicated by the fact that men often present late. Clinicians sometimes look at serologic patterns of the disease and may be able to identify subgroups of patients at higher risk.

G&H When should second-line treatment be considered?

GH Patients should be managed holistically. Clinicians should make sure their patients only have PBC and do not have superimposed fatty liver (from obesity or alcohol use, for example), which can of course be quite common. Clinicians need to understand the stage of disease and how much scarring there is. They should also be sure that UDCA has been optimally dosed, at 13 to 15 mg/kg, and that the patient is adherent to the medication. If a clinician has given first-line treatment, 6 or 12 months of UDCA, and is worried, for example, because the patient is younger or has more scarring than the average PBC patient and their alkaline phosphate is not following a downward trajectory, the clinician should consider second-line treatment.

Factoring in symptoms, especially itch, is relevant as well. Symptoms are complex in PBC because there are many of them, but itch is one of the most common. A patient who has persistent pruritus is probably not responding to treatment as well as would be liked. That is not always the case, though, as a patient can have itch with normal test results.

G&H What second-line options are now available for PBC treatment?

GH Currently, 3 agents have received approval from the US Food and Drug Administration (FDA) for the treatment of PBC as a second-line agent in the United States. The one that has been around the longest, since 2016, is the farnesoid X receptor agonist obeticholic acid (Ocaliva, Intercept), which has a composite biochemical response of approximately 48% in phase 3 clinical trials. However, in some patients, itch becomes worse.

Two phase 3 clinical trials led to FDA approval this year for PBC drugs in the peroxisome proliferator-activated receptor (PPAR) class. The first to receive FDA approval was the PPAR-alpha and -delta agonist elafibranor (Iqirvo, Ipsen), based on the results of a phase 3 clinical trial published earlier this year in *The New England Journal of Medicine* by Dr Kris V. Kowdley and colleagues. In that clinical trial, composite biochemical response for 80 mg of elafibranor was 51%. The key secondary endpoint for itch was not met, but some secondary analysis suggested that itch became better with elafibranor.

More recently, results of a phase 3 clinical trial of the selective PPAR-delta agonist seladelpar (Livdelzi, Gilead) were also published in *The New England Journal of Medicine*, leading to FDA approval. That clinical trial, which I contributed to, reported 61.7% composite biochemical response at 12 months with 10 mg of seladelpar, and the key secondary endpoint for itch was met. In patients who had moderate to severe itch, seladelpar led to a statistically significant improvement.

Looking at these agents in the context of normalizing alkaline phosphatase, which constitutes more intuitive PBC treatment, the drug most likely to induce such an effect is potentially the one having the most potent anti-

cholestatic effect. Such normalization is quite uncommon with obeticholic acid. In the elafibranor study, 15% of patients normalized their alkaline phosphatase, whereas that endpoint was reached in 25% in the seladelpar study. It should be noted that those two phase 3 clinical trials were very similar in design.

G&H How can clinicians choose among these second-line options?

GH When selecting among these PBC drugs, it is important to consider which are most likely to normalize the patient's alkaline phosphate as well as most likely to improve their symptoms. The stage of disease should also be kept in mind. None of these drugs should be used in patients with Child-Pugh B or C liver disease, and obeticholic acid should not be used in patients who have portal hypertension. Although seladelpar has a higher rate of normalization and met the key secondary endpoint for itch in its pivotal trial, it will be important to see whether those advantages are also seen in real-world practice.

G&H If second-line treatment does not achieve adequate response, what is the next step?

GH In Toronto, because of different access to medications, our group uses second-line therapy and then adds a third drug if the patient still has a suboptimal response. Triple therapy is still in development, but combinations of UDCA and obeticholic acid with a PPAR agonist, in this case bezafibrate, have been reported. With such a combination, alkaline phosphatase normalization rates will likely increase. It is not impossible that US practice will see a combination of a PPAR agonist and obeticholic acid, as well as UDCA, in this particularly difficult-to-treat, at-risk population, where clinicians are trying their best to prevent end-stage liver disease.

G&H Should obeticholic acid be stopped or switched?

GH That depends on how the patient is doing. If a patient is doing well on obeticholic acid and is meeting treatment targets, then I do not think I can envisage a good reason to stop the therapy. If the patient has not responded sufficiently or has side effects or itch, then new agents should probably be considered on an individual basis. It should also be kept in mind that patients do not like switching drugs often. If they are doing well and are happy to stay on a drug, clinicians should respect that.

Additionally, it should be noted that the FDA continues to evaluate the efficacy of obeticholic acid through its regulatory process mandated for drugs conditionally approved based on a surrogate endpoint. The final result of that assessment is awaited.

G&H Is there still a role for fenofibrate with the recently approved PPAR agonists?

GH I do not think there is a role for off-label therapy in the United States if there are 2 licensed drugs in that class that have been approved by the FDA. My personal opinion would be that patients who are receiving off-label therapy in the United States should be moved to labeled therapy. That makes the most sense to me. The point of the FDA process is to help clinicians use drugs safely.

G&H What drugs are in the pipeline for PBC treatment?

GH There has been a lot of interest in ileal bile acid transporter inhibitors, with phase 2 and 3 clinical trials ongoing. There is hope that phase 3 data from the anti-itch drug linerixibat will be released in 2025. It is exciting that we are starting to get closer and closer to individualized, personalized care. There are also studies underway on other PPAR agonists and antifibrotic agents. Eventually, we would like to treat the disease immunologically, of course.

Disclosures

Dr Hirschfield has consulted for Intercept, Advanz, Ipsen, CymaBay, Gilead, GSK, Falk, Mirum, Pliant, Kowa, and Escient.

Suggested Reading

Hirschfield GM, Bowlus CL, Mayo MJ, et al; RESPONSE Study Group. A phase 3 trial of seladelpar in primary biliary cholangitis. *N Engl J Med*. 2024;390(9):783-794.

Jones DEJ, Beuers U, Bonder A, et al. Primary biliary cholangitis drug evaluation and regulatory approval: where do we go from here? *Hepatology*. 2024;80(5):1291-1300.

Jones DEJ, Wetten A, Barron-Millar B, et al; UK-PBC Research Consortium. The relationship between disease activity and UDCA response criteria in primary biliary cholangitis: a cohort study. *EBioMedicine*. 2022;80:104068.

Kowdley KV, Bowlus CL, Levy C, et al; ELATIVE Study Investigators' Group. Efficacy and safety of elafibranor in primary biliary cholangitis. *N Engl J Med*. 2024;390(9):795-805.

Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2021 practice guidance update from the American Association for the Study of Liver Diseases. *Hepatology*. 2022;75(4):1012-1013.

Murillo Perez CF, Harms MH, Lindor KD, et al; GLOBAL PBC Study Group. Goals of treatment for improved survival in primary biliary cholangitis: treatment target should be bilirubin within the normal range and normalization of alkaline phosphatase. *Am J Gastroenterol*. 2020;115(7):1066-1074.