ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Current and Emerging Treatment Options for Primary Biliary Cholangitis

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G&H What is the current first-line therapy for primary biliary cholangitis, and what percentage of patients do not respond to it?

AB Currently, the only first-line therapy for primary biliary cholangitis (PBC) approved by the US Food and Drug Administration (FDA) is ursodeoxycholic acid. This treatment is weight-based; current guidelines recommend starting at a dose of 13 to 15 mg/kg, divided in 2 to 3 doses per day. Based on current data, between 30% and 40% of patients do not respond to this therapy.

G&H How can we define a patient who does not respond to ursodeoxycholic acid?

AB Many different scores and models have been developed. Most of these scores use the patient's laboratory findings and other patient information from different lengths of ursodeoxycholic acid therapy. This includes the patient's alkaline phosphatase, albumin, gamma-glutamyl transferase, bilirubin, aspartate aminotransferase, platelet count, and age. For example, the Rochester score looks at the patient's alkaline phosphatase after 6 months of treatment. Another example is the Toronto score, which defines a nonresponder as a patient with alkaline phosphatase above 1.67 times the upper limit of normal after 2 years of therapy. Most of these scores have only been used and validated in clinical trials. In clinical practice, most hepatologists define nonresponders to ursodeoxycholic acid as patients with alkaline phosphatase that does not fall below 1.67 times the upper limit of normal after 1 year of therapy.

G&H Should anything else be considered when monitoring response to therapy?

AB I think an important marker of progression is the stage of fibrosis. So far, only one clinical study has explored this as a secondary outcome. It should be kept in mind that patients with normal liver function tests can also have increased fibrosis and cirrhosis and be at increased risk for decompensation and the need for liver transplantation. Therefore, I recommend using a noninvasive marker of liver fibrosis on patients on presentation and then following them every 2 to 3 years.

G&H What is the current second-line therapy for PBC?

AB Currently, obeticholic acid (Ocaliva, Intercept Pharmaceuticals) is the only medication approved by the FDA for second-line therapy of patients with PBC who do not respond to conventional therapy. Obeticholic acid is a farnesoid X receptor (FXR) agonist. Findings from the clinical trial on this drug were published by Dr Frederik Nevens and colleagues in *The New England Journal of Medicine* in 2016.

G&H How many patients respond to this therapy?

AB In the aforementioned obeticholic acid clinical trial, both arms of treatment showed superior results compared to the placebo arm. These results were more significant after 12 months of therapy, when 46% of patients in the 5- to 10-mg arm and 47% of patients in the 10-mg arm responded, compared to 10% in the placebo arm. In the open-label part of the trial, the researchers found that after 12 months, close to 60% of the patients in the treatment arm achieved the primary outcome.

> In all of the patients who received obeticholic acid and bezafibrate, alkaline phosphatase and all markers of inflammation normalized.

G&H What were the most common side effects in the trial?

AB The most common side effect was pruritus, which was present in 68% of the patients in the 10-mg arm. Other side effects included nasopharyngitis (28%), headache (19%), and fatigue (26%).

G&H Are there any limitations associated with using this drug?

AB Recently, the FDA issued a black-box warning. Health care providers should determine the severity of the patient's liver disease before giving him or her this treatment. Patients who have Child-Pugh B and C should start with 5 mg once weekly, which is the approved dosing schedule, instead of 5 mg daily, which is used for other PBC patients. If needed, providers can increase dosing to a maximum of 10 mg twice weekly. Patients should be monitored frequently for disease progression, and the dose should be reduced to once or twice a week if a patient develops moderate or severe liver impairment.

G&H What are the PBC treatments in development that target peroxisome proliferator-activated receptors?

AB Peroxisome proliferator-activated receptor (PPAR) agonists, which are the newest medications that have been studied for the treatment of PBC, have 3 different receptors: alpha, gamma, and delta. Bezafibrate is a pan-PPAR agonist. In a study recently published in *The New England Journal of Medicine*, the primary outcome was normal biochemical response in patients who were treated for 1 year. The study included a total of 100 patients, 50 in each arm. The researchers found that 31% of the patients treated with bezafibrate achieved the primary outcome compared to 0% of the placebo arm. Up to 67% of the patients in the bezafibrate arm achieved normal alkaline phosphatase. Another important outcome was improvement in liver stiffness (measured by elastography). Liver stiffness decreased by 15% in the treatment group and increased by 22% in the placebo group. Finally, bezafibrate helped with pruritus and fatigue compared to placebo.

Elafibranor (GFT505, Genfit), which is a PPAR-alpha and -delta agonist, recently completed a phase 2 clinical trial that compared doses of 80 mg and 120 mg vs placebo. A decrease in alkaline phosphatase was seen in 48% of patients in the 80-mg arm and in 41% of patients in the 120-mg arm, the latter of which was significant compared to placebo (3%). In addition, elafibranor was able to help with pruritus. In the 80-mg arm, 24% of patients experienced improvement in their pruritus as well as 49% of patients in the 120-mg arm; in contrast, only 7% of patients improved with placebo.

Seladelpar (MBX-8025, CymaBay Therapeutics), a PPAR-delta agonist, showed promising phase 2 results for the treatment of PBC. However, in a phase 2b clinical trial for nonalcoholic steatohepatitis, the presence of histologic features of autoimmune hepatitis caused the trial to be stopped prematurely last fall.

G&H Could you discuss any clinical trial data on the new FXR agonists that are being studied for the treatment of PBC?

AB So far, there have been 2 promising drugs. A phase 2 trial of EDP-305 (Enanta) was recently completed. The INTREPID study was a 12-week trial in which the primary outcome was a reduction of alkaline phosphatase of 20% from baseline. Preliminary data showed an alkaline phosphatase reduction of 45% vs 11% in the placebo group. Most of the side effects were mild based on preliminary reports.

Cilofexor (Gilead) is in a phase 2 clinical trial. Results of this study were presented at last year's meeting of the American Association for the Study of Liver Diseases. The primary outcome was an alkaline phosphatase reduction of 25%.

G&H Has there been any research on combining an FXR agonist with a PPAR agonist?

AB Yes, this combination has been studied in a small cohort of patients. In the aforementioned obeticholic acid clinical trial, 11 patients were also given bezafibrate. In all of the patients who received obeticholic acid and bezafibrate, alkaline phosphatase and all markers of inflammation normalized. There are plans to start a phase 3 trial with an FXR agonist and a PPAR agonist to study a combination that uses 2 different mechanisms of action.

G&H Are there any other promising PBC drugs in the pipeline?

AB The NOX-14 inhibitor GKT831 (Genkyotex) was examined in a 24-week trial with 3 arms: 400 mg twice daily, 400 mg once daily, and placebo. Results of the trial should be released soon. In an interim analysis conducted 6 weeks after starting therapy, both treatment arms were superior to placebo at lowering alkaline phosphatase, 17% in the twice-daily arm and 8% in the once-daily arm, compared to the placebo arm, which increased by 2%. A significant difference was also seen in the measurement of gamma-glutamyl transferase.

G&H Overall, what are the most significant challenges of developing therapies for PBC?

AB Out of every 10 patients with the disease, only 6 respond to first-line therapy, so there is a limited number of patients who can enter clinical trials. In addition, most of the clinical trials are currently excluding patients with advanced stages of fibrosis and cirrhosis. Therefore, it is difficult to select patients for clinical trials.

G&H What are the next steps in research in this area?

AB In my opinion, there should be more focus on the degree of fibrosis. The bezafibrate trial noted a decrease in elastography values, but most of the clinical trials have not been including fibrosis as an outcome. This would be an interesting endpoint for future clinical trials. Also, as transplant hepatologists who work in a referral center, my colleagues and I are evaluating the most complicated PBC patients, most of whom have advanced fibrosis or cirrhosis. There are currently limited treatment options for these patients. Hopefully in the future, most clinical trials will include patients with advanced liver disease, so we can have options for nonresponders.

Disclosures

Dr Bonder has no relevant conflicts of interest to disclose.

Suggested Reading

Corpechot C, Chazouillères O, Rousseau A, et al. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. *N Engl J Med*. 2018;378(23):2171-2181.

Jones D, Boudes PF, Swain MG, et al. Seladelpar (MBX-8025), a selective PPAR-δ agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study. *Lancet Gastroenterol Hepatol*. 2017;2(10):716-726.

Nevens F, Andreone P, Mazzella G, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med*. 2016;375(7):631-643.

Trivedi HD, Lizaola B, Tapper EB, Bonder A. Management of pruritus in primary biliary cholangitis: a narrative review. *Am J Med*. 2017;130(6):744.e1-e7.

Trivedi HD, Lizaola B, Tapper EB, Bonder A. Primary biliary cholangitis: new treatments for an old disease. *Frontline Gastroenterol*. 2017;8(1):29-36.