ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Targeting the Farnesoid X Receptor in Patients With Cholestatic Liver Disease

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G&H What diseases are included within the term *cholestatic liver disease*?

CL Cholestasis refers to impaired bile formation or bile flow. In the adult population, the term *cholestatic liver disease* is most commonly used to describe primary biliary cholangitis (PBC, formerly known as primary biliary cirrhosis) and primary sclerosing cholangitis (PSC), although drug-induced liver injury can also present with cholestasis. In children, the term *cholestatic liver disease* includes biliary atresia, cystic fibrosis, progressive familial intrahepatic cholestasis, Alagille syndrome, and even alpha-1 antitrypsin deficiency.

G&H How effective are the current treatment options for cholestatic liver disease?

CL The only treatment currently approved by the US Food and Drug Administration (FDA) for PBC is ursodeoxycholic acid (UDCA), given at a dose of 13 to 15 mg/kg per day. This therapy can and should be used in all patients with PBC. Intolerance to UDCA is rare, but gastrointestinal symptoms may develop in some patients. Approximately 1 in every 3 PBC patients treated with UDCA will not respond with a substantial drop in, or normalization of, serum alkaline phosphatase, and is considered an incomplete responder. Elevated serum alkaline phosphatase is associated with worse clinical outcomes, including increased risk of death or need for liver transplantation. In fact, even the risk of hepatocellular carcinoma appears increased in UDCA nonresponders. Thus, treatment of nonresponders to UDCA is an unmet need in PBC.

For PSC, the situation is even more critical because there is currently no FDA-approved medical therapy available. UDCA is often used off-label, but data showing improvement in clinical outcomes are lacking. Multiple clinical trials are currently being conducted to identify effective therapy for PSC.

G&H What are the consequences of untreated or insufficiently treated cholestatic liver disease?

CL When untreated, cholestatic liver disease progresses toward biliary cirrhosis at variable rates. Complications of biliary cirrhosis include the development of portal hypertension and end-stage liver disease, which often requires liver transplantation.

G&H What is the farnesoid X receptor?

CL The farnesoid X receptor (FXR) is a member of the nuclear receptor superfamily. Nuclear receptors are ligand-activated transcription factors that are able to regulate multiple key metabolic pathways. Bile acids are the natural ligands for the FXR. When activated, the FXR regulates the enterohepatic circulation of bile acids. As such, activation of the FXR leads to inhibition of basolateral uptake of bile acids into hepatocytes, suppression of bile acid synthesis, and upregulation of canalicular transporters that secrete bile acids into the canaliculi. The net effect is an increase in bile flow.

G&H What consequences can result from FXR dysfunction?

CL FXR dysfunction, or antagonism, results in the lack of tight regulation of bile acid metabolism and the accumulation of toxic bile acids in the liver. FXR dysfunction has not been clearly identified in patients with PBC or PSC, although several rare syndromes have been linked to FXR dysfunction.

Specific antagonists of the FXR include stigmasterol, a compound found in soy-based lipid formulations for total parenteral nutrition. This may contribute to total parenteral nutrition–induced liver injury.

G&H What is the current understanding of the relationship between the FXR and cholestatic liver disease?

CL Several animal models have demonstrated that the FXR has a protective effect in various diseases, including cholestatic and autoimmune liver diseases, alcoholic liver disease, fatty liver, gallstone formation, portal hypertension, and hepatocellular carcinoma. Specifically in the setting of cholestatic liver disease, FXR activation is thought to promote bile flow and alter bile composition due to increased secretion of phospholipids and glutathione. Furthermore, FXR activation has anti-inflammatory effects through inhibition of the nuclear factor–κB pathway, possibly coupled with antifibrotic properties. All of these actions are very attractive to counter the effects of long-standing cholestasis, including cytotoxicity from bile acid accumulation, portal inflammation, ductopenia, and fibrosis itself.

G&H What research has been conducted on targeting the FXR in the setting of cholestatic liver disease?

CL Both animal and human studies have been performed. Although there is no perfect animal model for PBC or PSC, investigators have used a model of cholestasis induced by bile duct ligation. In that setting, activation of the FXR reduced fibrosis. In addition, in models where cholestasis was induced by feeding mice with lithocholic acid, the administration of FXR agonists promoted improved bile flow and minimized cytotoxicity.

As for human studies, phase 2 and 3 trials of the FXR agonist obeticholic acid (Intercept Pharmaceuticals) have been conducted in patients with PBC with very favorable results in terms of improvement of serum alkaline phosphatase and other liver biochemistries. Interestingly, the use of obeticholic acid in patients with PBC was associated with smaller decreases in bone mineral density compared with patients who received placebo. A larger phase 3b study of obeticholic acid for PBC is ongoing, as is a phase 2 study for PSC.

In addition, studies have examined the use of obeticholic acid in patients with nonalcoholic steatohepatitis and those with alcoholic cirrhosis. In nonalcoholic steatohepatitis, use of obeticholic acid was associated with improved histology compared with placebo. In alcoholic cirrhosis, obeticholic acid caused a significant reduction in the hepatic venous portal gradient.

G&H Has obeticholic acid been studied as monotherapy or as combination therapy with UDCA?

CL Only 1 small monotherapy study has been conducted. It included 59 PBC patients who had been off UDCA therapy for more than 6 months. Patients were randomized to receive placebo vs 10 or 50 mg per day of obeticholic acid. Serum levels of alkaline phosphatase dropped by approximately 40% in both active treatment arms, and the response was not dose-dependent.

Subsequent studies were conducted in patients who had been taking UDCA but had an incomplete biochemical response. These patients received combination therapy of UDCA and obeticholic acid. In the first combination study, patients were randomized to placebo vs 10 or 25 mg per day of obeticholic acid for 12 weeks, and in the larger phase 3 study, called POISE (Phase 3 Study of Obeticholic Acid in Patients With Primary Biliary Cirrhosis), patients were randomized to placebo vs 5 or 10 mg per day of obeticholic acid for 1 year. In these combination studies, serum alkaline phosphatase levels fell approximately 20% from baseline in patients receiving active drug. In the POISE study, nearly half of all patients taking obeticholic acid reached the primary endpoint of achieving an alkaline phosphatase that was less than 1.67 times the upper limit of normal while maintaining a normal bilirubin, and with a reduction in alkaline phosphatase of at least 15% from baseline, compared with only 10% of patients receiving placebo. There have not been any drug-drug interactions reported between obeticholic acid and UDCA.

G&H Are there any significant side effects or concerns associated with the use of obeticholic acid?

CL The most common side effect in patients with PBC is itching, which is dose-dependent and can be problematic for some patients. However, there are ways to minimize this side effect, such as starting with a lower dose and then increasing the dose after 3 to 6 months if a biochemical response is not achieved and the patient is tolerating the medication well.

Also noted in the aforementioned studies was a mild decrease in total cholesterol attributed mainly to a decrease in high-density lipoprotein cholesterol, as well as a minimal increase in low-density lipoprotein cholesterol. However, the significance of these findings is unclear.

G&H Is obeticholic acid close to being ready for use in clinical practice?

CL Obeticholic acid is currently undergoing regulatory review by the FDA and may be approved soon as an adjunct therapy for patients with PBC who do not respond to UDCA.

G&H What studies are currently being conducted exploring the use of FXR agonists in cholestatic liver disease?

CL The following studies are currently enrolling patients: a phase 3b study of obeticholic acid evaluating clinical outcomes in patients with PBC (NCT02308111); a phase 2 study of obeticholic acid in patients with PSC (NCT02177136); a phase 3 study of obeticholic acid for patients with nonalcoholic steatohepatitis and fibrosis (NCT02548351); and a double-blind, placebo-controlled trial of obeticholic acid for moderately severe alcoholic hepatitis (NCT02039219), among others.

In addition, another potent FXR agonist, the Novartis molecule LJN452, is currently under evaluation in patients with PBC (A Multi-part, Double Blind Study to Assess Safety, Tolerability and Efficacy of LJN452 in PBC Patients; NCT02516605).

Dr Levy is a principal investigator in studies using the FXR agonist obeticholic acid in PBC and PSC, and has received research grants from Intercept and Novartis. She is also a consultant and has participated in advisory boards for Intercept.

Suggested Reading

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