ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Emerging Treatment Strategies for Patients With Primary Biliary Cholangitis

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G&H What are the current first- and second-line treatments for patients with primary biliary cholangitis?

MM First-line treatment of patients with primary biliary cholangitis (PBC) currently consists of ursodeoxycholic acid (UDCA) at 13 to 15 mg/kg per day, usually divided in twice-daily doses. It may take up to 12 months for UDCA to reach its full benefit; however, up to 40% of patients treated with UDCA will not have an adequate biochemical response after 1 year. In those patients, the farnesoid X receptor (FXR) agonist obeticholic acid (Ocaliva, Intercept) is typically added for second-line treatment. The double-blind, placebo-controlled, phase 3 POISE trial showed that patients on UDCA who also received obeticholic acid were approximately 5 times more likely (46% vs 10% with placebo) to achieve the composite primary endpoint (defined as alkaline phosphatase ≤1.67 × the upper limit of normal, ≥15% reduction in alkaline phosphatase, and normalization of bilirubin) than patients on UDCA alone. Thus, this drug combination significantly reduced alkaline phosphatase and bilirubin, which have been accepted as important surrogate markers for endpoints such as death and need for liver transplantation. As a result of these important data, the US Food and Drug Administration (FDA) granted accelerated approval for obeticholic acid in 2016. In patients intolerant to UDCA, obeticholic acid may be used as a monotherapy.

G&H Why is there still a need for new therapeutic strategies for patients with PBC?

MM Current treatment is limited by inadequate biochemical response and side effects. As mentioned, as much as 40% of patients receiving UDCA will not have an adequate biochemical response after 1 year and although the addition of obeticholic acid improves response, some patients still will not respond. In addition, both agents have some issues with tolerance. UDCA is associated with gastrointestinal side effects as well as hair loss and weight gain. Obeticholic acid is most commonly associated with dose-dependent pruritus and may be intolerable to certain patients despite dose reductions and interruptions. In May 2021, the FDA released a safety advisory restricting the use of obeticholic acid in patients who have cirrhosis with evidence of portal hypertension or have current or prior decompensation. For all of these reasons, new therapeutics are needed for the treatment of patients with PBC.

G&H What types of therapeutic approaches are being studied in patients with PBC?

MM The mainstay of PBC therapy has been to target bile acid physiology, as bile acids in excess can become cytotoxic. In patients with PBC, bile acid processes are thought to be dysregulated; to this end, UDCA has been used in an attempt to dilute the bile acid pool. UDCA affects FXR very weakly, so the addition of a potent FXR agonist such as obeticholic acid enhances biochemical response. FXR agonism leads to reduction of hepatocyte bile acid synthesis and promotes secretion of bile acids from hepatocytes. Despite the potential synergism of

these 2 mechanisms, not all patients achieve biochemical response, and therefore, concerns remain for death and the need for liver transplantation. As such, other targeted therapies are needed. One therapeutic target is peroxisome proliferator-activated receptor (PPAR) agonism. Some PPAR agonists selectively target alpha, delta, and/or gamma subclasses, whereas other PPAR agonists are nonselective. PPAR agonists have a number of effects and are thought to help in the regulation of bile acid homeostasis, suppressing hepatic bile acid synthesis and playing a role in bile acid transportation. Fibrates such as fenofibrate (a PPAR-alpha agonist) have been used off-label to treat patients with PBC. Fibrates have been shown to improve liver chemistries as well as pruritus and fatigue in patients who have PBC. However, the enthusiasm for fibrates has been tempered because of associated liver and kidney toxicities. Currently, a number of PPAR agonists are being studied.

Also being studied are second-generation FXR agonists. First-generation FXR agonists, including obeticholic acid, are bile-derived steroidal hydrophobic agents with inherent unpredictable pharmacokinetics and pharmacodynamics, as they rely on enterohepatic circulation for clearance. These agents also have undesirable off-target effects that lead to pruritus. Second-generation agents include non-bile acid–derived hydrophilic agonists that seek to be more selective and restrictive of FXR activation with predictable pharmacokinetics. Fibroblast growth factor (FGF)-19 analogues are another class of drugs that work to improve bile acid homeostasis by suppressing hepatocyte bile acid synthesis. Additionally, nicotinamide adenine dinucleotide phosphate oxidase (NOX) 1/4 inhibitors are of clinical interest, as these enzymes are thought to be a source of reactive oxygen species, which in turn are responsible for fibrogenesis. Ileal bile acid transporter (IBAT) inhibitors, also known as apical sodium-dependent bile acid transporter inhibitors, prevent bile acid resorption in the ileum, which lowers the bile acid pool and confers downstream effects on bile acid homeostasis. In addition, immunosuppressants (Janus kinase 1/2 inhibitors and sphingosine-1-phosphate receptor agonists) may have a potential role, as innate immune system dysregulation is thought to contribute to PBC pathogenesis. Many of these agents are still in early-stage development.

Right now, the drugs that are in late-phase development are PPAR agonists and FXR agonists.

G&H Which of these therapeutic strategies appear to be most promising for patients with PBC thus far?

MM Right now, the drugs that are in late-phase development are PPAR agonists and FXR agonists. The PPAR-delta agonist seladelpar (MBX-8025; CymaBay Therapeutics) is currently being studied in the phase 3 RESPONSE trial, which is comparing 5- and 10-mg doses of the drug vs placebo. Seladelpar was previously studied in a 12-week, double-blind, placebo-controlled, phase 2 trial of patients who did not respond to UDCA. Significant improvement in alkaline phosphatase was seen at 12 weeks in patients who received 50 or 200 mg daily of the drug compared with the placebo group. The PPAR-alpha/-delta agonist elafibranor (GFT505; Genfit), an 80-mg oral drug, is currently being investigated in the phase 3 ELATIVE trial. A previous multicenter, double-blind, randomized, placebo-controlled, phase 2 trial evaluating elafibranor demonstrated positive results after 12 weeks in patients who had inadequate response to UDCA. Patients who received a dose of 80 to 120 mg of elafibranor had a significant reduction in alkaline phosphatase compared with the placebo group. The panspecific PPAR agonist bezafibrate has been studied alone and in combination with UDCA, and is currently being studied in combination with obeticholic acid in a phase 2 study. The BEZURSO study was the first phase 3 study to use bezafibrate in patients who had an inadequate response to UDCA. In this study, patients treated with both UDCA and bezafibrate had a statistically significant improvement in biochemical response compared with placebo. In addition, the bezafibrate treatment arm had associated decreases in pruritus. A promising FXR agonist is tropifexor (LJN452; Novartis), a non–bile acid, nonsteroidal FXR agonist that completed its phase 2 trial. Final results have yet to be published, but a 4-week interim analysis has shown positive results with a significant decrease in gamma-glutamyl transferase in patients receiving 90 μg daily. Cilofexor (Gilead Sciences) was studied in PBC patients without cirrhosis in a phase 2 study; however, the study was terminated and patients experienced grade 2 to 3 pruritus.

Along similar lines of affecting bile acid homeostasis, the FGF-19 analogue aldafermin (NGM Biopharmaceuticals) has shown promising results in a 28-day, double-blind, placebo-controlled, phase 2 trial. Alkaline phosphatase was significantly decreased in a dose-dependent

fashion in patients who received the drug compared with patients who received placebo. Patients who received aldafermin also demonstrated significantly reduced transaminase and immunoglobulin levels. The most common adverse events were gastrointestinal symptoms.

G&H What other targets are being studied?

MM The antifibrotic therapy setanaxib (GKT137831; Genkyotex) is a NOX1/4 inhibitor that recently completed a randomized, placebo-controlled, phase 2 trial of once- or twice-daily treatment in patients with PBC who had an incomplete response to UDCA. An interim analysis found a decrease in gamma-glutamyl transferase and alkaline phosphatase at 6 weeks and no significant concomitant adverse events. Changes in alkaline phosphatase were statistically significant in the 400-mg twice-daily group vs placebo. A phase 2/3 study is currently being planned.

> Effective treatment of pruritus is an important unmet need in this patient population.

Immunomodulators theoretically make sense as agents of interest given the autoimmune nature of PBC and the associated immune dysregulation. These agents have been and currently are being studied, but the history of these compounds has unfortunately been mostly disappointing for PBC. Therapies that have been tried include budesonide, azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, and rituximab.

G&H How effective do these new agents appear to be for treating symptoms of PBC such as pruritus and fatigue?

MM Effective treatment of pruritus is an important unmet need in this patient population. Currently, off-label treatments are used for cholestatic pruritus, such as bile acid binding resins, antihistamines, selective serotonin reuptake inhibitors, opioid antagonists, and rifampin. A number of IBAT inhibitors have been studied to manage pruritus. Linerixibat (GSK2330672; GlaxoSmithKline) showed potential in improving pruritus in patients with PBC in the randomized, double-blind, multidose, placebo-controlled, phase 2 GLIMMER study, and a phase 3 trial (GLISTEN) is currently underway. Volixibat (Mirum Pharmaceuticals) is another IBAT inhibitor undergoing phase 2 study for cholestatic pruritus in patients with PBC. As mentioned, bezafibrate appears to be effective for the management of pruritus in addition to improving alkaline phosphatase. Difelikefalin (Cara Therapeutics) is a peripherally acting kappa opioid receptor agonist that is undergoing phase 2 study in PBC patients with moderate to severe pruritus.

In terms of fatigue, there have been several nonpharmacologic interventions, but pharmacologic agents have been limited. Modafinil has been used off-label based upon uncontrolled trials; however, a randomized controlled trial published in 2017 did not demonstrate benefit. It is important to exclude other etiologies for fatigue, such as hypothyroidism and obstructive sleep apnea. Importantly, UDCA and obeticholic acid do not influence fatigue. In a review of pharmacologic agents for treating fatigue, a single-center study in Denmark is looking at high doses of oral thiamine.

G&H What research is currently being conducted on the combination of different classes of drugs?

MM Combination therapy makes sense to employ, as different targets of bile acid homeostasis can be used (eg, FXR with PPAR). Additionally, combination therapy can mitigate some of the pruritus-associated adverse effects with bile acid–derived therapies (eg, IBAT with FXR, FXR with PPAR). A randomized, double-blind, phase 2 study of obeticholic acid in combination with bezafibrate is underway and expected to be completed soon. IBAT inhibitors have been, and currently are being, studied in combination with UDCA and obeticholic acid.

G&H What are the main challenges of drug development for patients with PBC?

MM The challenges are inherent given the complexity of the disease process of PBC. There are a number of pathways and downstream effects that lead to the genesis of this disease, which is why combination drugs are needed to treat patients with PBC; however, combination drugs can also lead to untoward side effects and possibly toxicity. For these reasons, it can be a challenge to navigate the treatment paradigm for PBC.

G&H Are any nonpharmacologic treatment approaches being studied in patients with PBC?

MM Nonpharmacologic treatments are being studied for some of the extrahepatic complications of PBC.

For example, fatigue has been shown to be improved with coping strategies or behavioral therapies, including mindfulness-based interventions. Modest exercise is thought to help with fatigue. Avoidance of social isolation is important, and there are a number of online support groups to aid patients with this disease.

G&H What are the priorities of research for PBC treatment?

MM The main priority is to use different classes of drugs to aid in the normalization of alkaline phosphatase, which, as previously noted, is an important surrogate marker. Given the relative rarity of this disease, it has been difficult to prove that the hard endpoints of prevention of death and need for liver transplantation are being met in patients receiving these novel therapeutics.

In addition, it is important to learn where to incorporate transient elastography and other noninvasive fibrosis testing into the management algorithm for patients with PBC. Another important management concern involves the monitoring of total bilirubin. Providers are often focused on alkaline phosphatase and may lose sight of the fact that total bilirubin is a late marker that increases in patients with PBC. Elevations of this marker should lead to stronger consideration of second-line and investigational treatment options.

Disclosures

Dr Moehlen is a speaker and consultant for Intercept Pharmaceuticals, is a speaker for Gilead Sciences, and has received relevant research grants from Novartis Pharmaceuticals, Gilead Sciences, Bristol Myers Squibb, and CymaBay Therapeutics.

Suggested Reading

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