ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Novel Therapies for Cholestatic Liver Disease

Cynthia Levy, MD
Professor of Medicine
Arthur Hertz Chair in Liver Diseases
Associate Director, Schiff Center for Liver Diseases
Division of Hepatology
University of Miami Miller School of Medicine
Miami, Florida

G&H Currently, how is cholestatic liver disease in adults typically treated?

CL Cholestatic liver disease in adults mainly consists of primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). For PBC, the traditional first-line treatment is ursodeoxycholic acid (UDCA), starting at a dose of 13 to 15 mg/kg/day. In May 2016, obeticholic acid (Ocaliva, Intercept Pharmaceuticals) was approved by the US Food and Drug Administration (FDA) for second-line treatment of PBC patients who either do not respond to UDCA therapy or who are intolerant of it. Dosing for noncirrhotic or well-compensated cirrhotic patients is 5 mg daily, which can be increased to 10 mg daily after 3 months of therapy if it is well tolerated. However, if a patient has decompensated cirrhosis (Child-Pugh class B or C), the dose should be reduced to 5 mg once a week and, after 3 months, can be increased to 5 mg twice a week, at least 3 days apart (for a maximum dose of 10 mg twice a week).

As for PSC, no treatment is currently approved by the FDA. However, it is still important to monitor PSC patients clinically and perform surveillance, as PSC is a premalignant condition. In addition, although the literature does not definitively support or refute this, many experts believe that there is a subgroup of patients who may benefit from UDCA treatment. If a patient is unable or unwilling to participate in a clinical trial, it is worth trying medium doses of UDCA (17-23 mg/kg/day) to see if there is an improvement in biochemistries and closely follow these patients.

G&H What are the limitations of the therapies currently being used?

CL Up to 40% of patients with PBC may not respond to UDCA therapy, meaning that they will not have significant biochemical improvement in alkaline phosphatase, which will remain elevated above 1.5 or 2 times the upper limit of normal. In addition, in the PBC clinical trials for obeticholic acid, only half of the patients met the primary endpoint. Furthermore, as previously mentioned, there is no FDA-approved treatment for PSC. Therefore, there are unmet needs for PBC and PSC treatment, which have led to a plethora of ongoing clinical trials exploring drugs of various mechanisms of action. Promising drugs include new farnesoid X receptor (FXR) agonists, peroxisome proliferator-activated receptor (PPAR) agonists, and, possibly, fibroblast growth factor (FGF) 19 mimetics, among other classes of drugs under evaluation.

G&H Why are new FXR agonists being studied?

CL FXR is a well-established target for PBC, as obeticholic acid, the current second-line therapy for this disease, is an FXR agonist. Activation of this nuclear receptor leads to modulation of bile acid homeostasis as well as inflammatory pathways, and may also have antifibrotic effects. Newer FXR agonists are being developed to increase potency and selectivity and minimize the occurrence of the side effects classically associated with obeticholic acid, such as itching, decrease in high-density

lipoprotein cholesterol, and increase in low-density lipoprotein cholesterol. One such newer FXR agonist under development is cilofexor (Gilead). A 12-week study of cilofexor in PSC showed dose-dependent reduction in liver biochemistries, especially alkaline phosphatase, with similar rates of adverse events between patients on cilofexor and those on placebo. This drug is now under evaluation for regression of fibrosis in an ongoing phase 3 study for PSC patients. A phase 2 study of PBC patients with inadequate response to UDCA therapy has been completed, but results are not available. Two other FXR agonists (LJN 452, Novartis and EDP-305, Enanta Pharmaceuticals) are also undergoing studies at this time.

G&H Which PPAR agonists are being studied for the treatment of cholestatic liver disease?

CL PPARs can occur in 3 isoforms (alpha, delta, and gamma). PPAR agonists regulate bile acid homeostasis as well as lipid and glucose metabolism and inflammation, and several of these agents are currently under evaluation. The PPAR delta agonist seladelpar (CymaBay Therapeutics) was first evaluated in a 12-week, phase 2, randomized, controlled study comparing placebo to 2 doses of the drug: 50 mg/day and 200 mg/day. Although the study was terminated early due to 3 cases of elevation in serum alanine aminotransferase level, all patients who completed the 12 weeks of seladelpar therapy had normalized alkaline phosphatase levels at the end of the study. Subsequently, the effect of seladelpar was evaluated in open-label studies using lower doses of 2 mg, 5 mg, and 10 mg daily, with major improvements in alkaline phosphatase levels. Importantly, analysis of a subset of 26 cirrhotic patients exposed to seladelpar confirmed its safety and tolerability as well as anticholestatic effects even among patients with advanced disease. Seladelpar is currently undergoing phase 3 evaluation. Preliminary results for elafibranor (Genfit), a dual PPAR alpha and delta agonist, have shown significant decreases in alkaline phosphatase and gamma-glutamyl transferase levels as well as in serum lipids and anti-inflammatory markers after a 12-week treatment period. Furthermore, a trend toward improvement in pruritus was observed. A phase 3 trial of this drug is expected.

In addition, bezafibrate (a pan-PPAR agonist) and fenofibrate (a PPAR alpha agonist) have been studied in small clinical trials (mostly in Europe and Japan, although one was conducted in the United States). These fibrates have been shown to improve alkaline phosphatase levels. Last year, the *New England Journal of Medicine* published results from a French study that evaluated 200 PBC patients who were incomplete responders to UDCA therapy and were randomized to UDCA plus bezafibrate vs UDCA plus placebo for 2 years. The study reported normalization of all liver biochemistries in 31% of the bezafibrate-treated patients compared with 0% of the placebo group, which is a very significant biochemical response. Furthermore, fibrates appear to improve pruritus. Other phase 3 studies on these agents are underway at this time outside the United States. According to both US and European guidance documents, off-label use of fibrates can be considered in select PBC cases in nonresponders to UDCA therapy.

G&H What research is available thus far on FGF 19 mimetics?

CL Results of phase 2 trials on FGF 19 mimetics have been presented for both PBC and PSC. For PBC, improvement was seen in alkaline phosphatase levels and other liver biochemistries as well as in immunoglobulins and markers of inflammation. Approximately half of the treated patients achieved a 15% reduction in alkaline phosphatase level, compared with 7% of placebo-treated patients. The drug was generally well tolerated, and most side effects were related to loose stools and increased stool frequency. Such improvement was not demonstrated in PSC patients, as alkaline phosphatase levels did not change much. Nevertheless, reductions in the serum levels of transaminases and bile acids were observed, along with decreases in noninvasive markers of fibrosis.

G&H What other targets are being considered?

CL 24-norursodeoxycholic acid (norUDCA), a derivative of UDCA, is a bile acid therapy that has been studied for PSC, but not yet for PBC. In phase 2 trials in Europe, norUDCA has been shown to improve alkaline phosphatase levels in a dose-dependent fashion. Treatment was very well tolerated, and phase 3 evaluation is underway.

Treatments modulating the gut microbiome in patients with PSC have been discussed. Earlier this year, results from a small open-label clinical trial evaluating fecal microbiota transplantation in 10 patients with PSC and inflammatory bowel disease were published. Three patients had a greater than 50% reduction in serum alkaline phosphatase level. However, these results are very preliminary, and further research is needed. Studies have also examined the use of antibiotics to manipulate the gut microbiome. Vancomycin, the most-studied antibiotic, has been shown to improve gamma-glutamyl transferase in children and was associated with an

immunomodulatory effect. In adults, only small studies have been conducted thus far, but they have shown improvement in alkaline phosphatase levels and Mayo Risk Score. A phase 3 study is currently underway to further evaluate potential benefits of vancomycin in adult patients with PSC.

A novel target being explored for PBC is the selective inhibition of NOX 1 and NOX 4 enzymes by setanaxib (GKT831, Genkyotex), which affects transforming growth factor beta and nuclear factor kappa beta signaling pathways and leads to antifibrotic effects. Preliminary results have shown an improvement in gamma-glutamyltransferase and alkaline phosphatase levels over a 24-week treatment period in PBC patients.

Simtuzumab (Gilead), a lysyl oxidase–like 2 inhibitor with antifibrotic properties observed in animal models, failed to reduce hepatic collagen concentration in patients with PSC treated for 2 years. However, other antifibrotics are likely to be evaluated in the near future.

There is also hope that modulation of the immune system may change the course of chronic cholestatic liver disease. However, this has not been demonstrated thus far. To date, there have been negative studies with ustekinumab (Stelara, Janssen) and abatacept (Orencia, Bristol-Myers Squibb).

G&H Are any new drugs being studied specifically to treat symptoms of cholestatic liver disease such as pruritus?

CL There are several drugs currently under evaluation for the treatment of pruritus, which is common in PBC patients and can be very distressing. Linerixibat (GlaxoSmithKline) is a promising ileal apical sodium-dependent bile acid transporter inhibitor that interferes with bile acid reabsorption in the ileum. Phase 2 studies in PBC patients were very successful, showing improvement in pruritus and quality of life. A subsequent larger phase 2 study with this drug is currently enrolling patients, and the results are greatly anticipated. The other drug being evaluated is the kappa opioid receptor agonist difelikefalin (CR845, Cara Therapeutics). Unlike morphine and demerol, this drug does not affect mu receptors; therefore, it has a low potential for crossing the blood-brain barrier, which reduces the possibility for addiction. This drug has been evaluated in uremic patients with pruritus and has shown very successful results.

Of note, maralixibat (Mirum Pharmaceuticals) is another selective ileal apical sodium-dependent bile acid transporter inhibitor that was evaluated for the treatment of pruritus in patients with PBC. Unfortunately, in that study the reduction in pruritus intensity was not different between maralixibat- and placebo-treated patients, and the drug failed to meet the primary endpoint. This drug was also evaluated in patients with PSC, and results will be presented at the upcoming American Association for the Study of Liver Diseases meeting.

G&H How do the safety profiles of the new PBC and PSC drugs appear to compare with those of the current drugs?

CL UDCA is a very safe drug with minimal side effects. Patients taking UDCA may occasionally complain of gastrointestinal intolerance (eg, nausea), and sometimes may report hair thinning, a little weight gain in the first year, and, rarely, worsening of pruritus. Very rarely is treatment discontinued due to intolerance.

Obeticholic acid is very safe in patients with well-preserved hepatic function. The most common side effect is pruritus, as probably more than half of patients develop some degree of itching on treatment. However, it is usually mild, and clinicians can manage patients through it. Occasionally, some patients need to discontinue treatment because of pruritus, but clinicians should be familiar with ways to treat it and, specifically for patients taking obeticholic acid, how to address drug-drug interactions and how to manipulate the drug to maintain efficacy while treating the pruritus. For example, if obeticholic acid is being given in doses of 10 mg daily, the dose can be reduced to 5 mg daily. If the dose is already 5 mg daily, then rifampin can be used if it is not contraindicated, or cholestyramine can be used with the caveat that it has to be given at least 3 hours apart from obeticholic acid. Patients who still have significant pruritus despite these measures can take obeticholic acid every other day or take drug holidays.

In addition, there is concern about potential worsening of hepatic function in patients with advanced cirrhosis who take obeticholic acid. There were a few reports of decompensation and death. However, it should be noted that the patients who experienced these complications were receiving an incorrect dose in the setting of decompensated cirrhosis. In this setting, obeticholic acid should be reduced to 5 mg a week, and the patient's liver function should be monitored closely. If there is any evidence of decompensation, the drug should be discontinued.

As for the drugs currently under evaluation, there are also safety considerations with fibrates. Hepatotoxicity has been reported, with cases of both acute and chronic drug-induced liver injury. In addition, both fenofibrate and bezafibrate have been associated with an increase in creatinine, although this is usually not accompanied by a drop in glomerular filtration rate. There also have been reports of rhabdomyolysis, especially when these drugs

are used in combination with a statin. However, this was more common with first-generation fibrates, and is not often seen with fenofibrate or bezafibrate.

Seladelpar has been associated with myalgia and elevation in transaminases, although the latter was seen predominantly with doses of 50 mg/day and higher. Therefore, although patients will also need to be monitored, the drug seems to be quite safe. Pruritus is not reported as a side effect for any of the PPAR agonists. In fact, pruritus tends to improve with use of these medications.

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

CL Phase 3 studies need to be completed. The drug that is the furthest along is seladelpar. In addition, we are waiting for results of phase 4 studies and postmarketing studies of obeticholic acid to determine if the drug can improve long-term outcomes, such as preventing progression to cirrhosis, decompensation of liver disease, need for liver transplantation, and death. Ultimately, these are the endpoints that really matter.

Further research is particularly important in PSC, as there is currently no approved therapy. As previously mentioned, there are several ongoing clinical trials investigating FXR agonists, PPAR agonists, and fecal microbiome modification. There is also a study looking at the combination of UDCA and the natural supplement berberine. Successfully completing these studies and defining endpoints that can be evaluated in these trials and in future clinical trials are important goals.

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Suggested Reading

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