G&H How were bile acids first used in a therapeutic role?

SK Bile acids are a class of molecules that are involved in a variety of biological processes, such as digestion and basic liver functions, as well as with adaptation to liver disease. Bile acid therapy was essentially first systematically used for certain types of gallstones; in addition, bile extracts have had homeopathic historic and regional uses. Bile acid therapy was also tried in the 1920s to 1930s for a variety of inflammatory conditions, mainly rheumatoid arthritis. It has taken some time, but to date, several bile acids have been approved by the US Food and Drug Administration (FDA) for primary biliary cholangitis (PBC), cholesterol gallstones, and, recently, specific rare genetic disorders of bile acid synthesis. In the last disease group, individuals do not make primary bile acids due to defects in genes that encode certain enzymes, so the machinery within the liver cells ends up creating intermediate molecules that, by accumulation, become damaging.

G&H What novel bile acid therapies and targets have been studied recently in the setting of liver disease?

SK Over the past several years, researchers have been wondering whether natural or modified bile acids may address problems in patients with liver disease, targeting hepatocytes, cholangiocytes, and the immune system. The modified bile acid obeticholic acid (Ocaliva, Intercept Pharmaceuticals) has been approved by the FDA for the treatment of PBC in adult patients. Clinical trials have shown that this drug has positive effects on PBC and, in research studies, nonalcoholic steatohepatitis (NASH). Although these diseases are very different, obeticholic acid seems to be beneficial in both diseases, and ongoing larger studies are poised to help determine whether it is safe and effective in broad populations of both diseases. This drug is the first to directly target a key nuclear regulator of other genes involved in bile flow and formation—the farnesoid X receptor (FXR; \( NR1H4 \) gene), a molecule in liver cells and bile duct cells. When FXR is activated essentially as a hormone, the liganded FXR engages a number of hepatoprotective pathways by regulating the expression of dozens of genes in a manner that mimics, but enhances, the efficacy of natural primary bile acids on FXR’s activity. Obeticholic acid therapy should be considered for patients who are unresponsive or poorly responsive to ursodeoxycholic acid, the current therapy for PBC, which is a bile acid that is not synthesized in humans and works in a non-FXR mechanism in PBC (ClinicalTrials.gov Identifier: NCT01473524).

A side-chain shortened bile acid, norursodeoxycholic acid (norUDCA), has recently been studied in another cholestatic liver disease, primary sclerosing cholangitis (PSC). This bile acid cannot be amidated by glycine or taurine, and may work by participating in choledhepatic shunting of bile acids. In a phase 2 trial by Fickert and colleagues, norUDCA improved serum levels of an accepted index of biliary tract disease in PSC—alkaline phosphatase.

Another target for bile acid–based therapy involves alterations of bile acid recirculation pathways, rather...
than the modification of bile acids themselves. Bile acids are recirculated, meaning that they are excreted into the bile ducts, gallbladder, common duct, and then the intestines to help with digestion of fats and fat-soluble vitamins. Nearly all bile acids are reclaimed at the lower end of the intestine by the ileal bile acid transporter (IBAT, also known as apical sodium-dependent bile acid transporter; SLC10A2 gene). When the IBAT protein is inhibited, improvements have been seen in some features of cholestatic liver disease such as pruritus (according to Hegade and colleagues and ClinicalTrials.gov Identifier: NCT01899703), as well as in a variety of genetic and acquired animal models of progressive hepatic fibrosis.

**G&H** Are there other clinical trial data on the use of these novel bile acid therapies in adult liver disease patients?

**SK** Several studies have shown that obeticholic acid improves the chemistries of PBC and PSC patients, primarily in terms of serum alkaline phosphatase levels. Obeticholic acid has also been studied in NASH patients. In the FLINT trial, patients underwent biopsy at the beginning and end of the treatment period with obeticholic acid, and reported improvement in the histologic score for NASH as well as improvement in fibrosis. The global long-term phase 3 REGENERATE trial of obeticholic acid in over 2000 NASH patients is in progress, and we await its results (ClinicalTrials.gov Identifier: NCT02548351).

In addition, there is currently an ongoing trial with the IBAT inhibitor volixibat (SHP626, Shire; ClinicalTrials.gov Identifier: NCT02787304) in NASH patients.

**G&H** Has there been any research on novel bile acid therapies in pediatric liver disease patients?

**SK** Mixed results have recently been reported in abstract form from the short-term small trials of 2 IBAT inhibitors for the treatment of pruritus in rare pediatric liver diseases (ClinicalTrials.gov Identifiers: NCT02057692 and NCT02630875). There is a small phase 2 initial trial of obeticholic acid currently being conducted in patients with biliary atresia in Europe. To my knowledge, there have not been any studies with FXR agonists or IBAT inhibitors in children with NASH.

**G&H** What adverse events have been associated with these novel bile acid therapies?

**SK** In the first obeticholic acid PBC study, some patients became more pruritic, particularly on higher doses of the drug. In addition, after approval and wider use of the drug in this population, several patients had quite significant adverse events, including progression to liver failure and death, more so, but not exclusively, on higher doses of obeticholic acid. These reports led to an FDA warning that PBC patients on obeticholic acid need to be followed closely by clinicians for signs of worsening liver disease and that considerations for dosage adjustment or cessation should be weighed on an individual basis.

In addition, the first studies of obeticholic acid in patients with NASH showed a slight increase in serum low-density lipoprotein cholesterol levels. Further follow-up is needed to determine whether this problem is persistent and whether it could be addressed with either diet or other medications.

As for IBAT inhibitors, early research in patients with cholestatic liver disease and those with NASH shows that inhibiting the return of bile acids in the ileum leads to residence in the colon, which can result in diarrhea in some patients. Although most of the diarrhea seems to be self-limited and the colon appears to adapt—at least according to what has been presented to date mainly from pediatric studies—some patients may not adapt well and may need a dose reduction. Thus, gastrointestinal issues, especially if persistent, should be monitored carefully on a patient-by-patient basis. Longer-term and larger studies are awaited to determine whether there are any characteristics of patients and diseases in which adverse events can be predicted or attenuated.

**G&H** Why has there been a recent revival in bile acid therapies for liver disease?

**SK** Approximately 30 or 40 years ago, there was enthusiasm for exploring different bile acids for treatment, but due to a lack of knowledge of therapeutic molecular targets and etiologies for several liver diseases, these treatments had only limited efficacies, which reduced the enthusiasm for general use for any bile acid–based therapies. However, this was before knowledge of diseases caused by mutations in bile acid transporter genes and FXR, as well as a marked explosion of knowledge of hepatoprotective FXR-mediated pathways in hepatocytes, cholangiocytes, and even ileocytes. Now that there are several defined biological targets, the pharmaceutical industry has started to design various molecules that specifically target these proteins and cells.

Among the key reasons that IBAT inhibitors are experiencing a revival are that there are now several different IBAT inhibitors, perhaps with varying efficacies, and that there is a single target, IBAT, on the apical surface of ileocytes. Moreover, IBAT inhibitors are limited to the intestinal lumen and are not absorbed. Thus, the overall effects on the body follow from local inhibition in the
gastrointestinal tract—in other words, these are drugs that target the intestinal surface to address a liver problem. That is why there have been several new molecules as well as new knowledge that has led to somewhat of a revival in bile acid therapies.

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

**SK** Not enough is known about the breadth of consequences of FXR agonism, norUDCA, and IBAT inhibition, nor do we know if clinically there should be modulation of efficacy or tailoring to a specific tissue or cell type. As we have seen in many diseases, perhaps there is a combination of drugs that could unite the aspects of FXR agonism as well as reduce the return of bile acids to the liver (ie, inhibit IBAT). I think that combination therapies of bile acid–based targeting with non–bile acid drugs, such as antifibrotic agents or drugs that address lipid synthesis, may be highly beneficial in patients with NASH or progressive fibrotic cholestatic diseases.

Finally, there may be genetic differences between patients who will respond to some of these therapies and those who will not. Thus, there could be a role for a limited set of genotyping to help inform the next steps, especially for patients who have an unclear cause for cholestasis.

**Dr Karpen is a consultant for Intercept Pharmaceuticals (manufacturer of obeticholic acid), Albireo (manufacturer of an IBAT inhibitor), Regulus, and Retrophin (manufacturer of cholic acid, which is used for bile acid synthesis disorders).**

**Suggested Reading**


