ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Current and Emerging Approaches for Management of Primary Sclerosing Cholangitis

Kris V. Kowdley, MD
Director, Liver Institute Northwest
Professor
Elson S. Floyd College of Medicine
Washington State University
Seattle, Washington

G&H How are patients with primary sclerosing cholangitis typically managed currently?

KK There is no approved medical therapy for primary sclerosing cholangitis (PSC), so we are in a position of anticipatory management, recognizing that patients with PSC have multiple comorbidities and competing risks to their health because PSC is very frequently associated with inflammatory bowel disease (IBD). Patients who have PSC and colitis have much higher rates of colon cancer, so surveillance is needed. It is often recommended that a colonoscopy with biopsies be performed annually for PSC patients with IBD. Similarly, patients with PSC also have high rates of gallbladder cancer, so surveillance for gallbladder polyps is recommended in this patient population. If patients have a polyp larger than 8 mm, a cholecystectomy is generally recommended even if the patient does not have any symptoms. Additionally, patients with PSC have an increased risk of bile duct cancer, which can be particularly challenging to diagnose because of underlying abnormalities of their bile ducts. It can also be very difficult to differentiate a benign stricture from a malignant stricture caused by a tumor blockage. Although there is currently no ideal surveillance strategy to identify patients with bile duct cancers, PSC patients are generally recommended to undergo some type of imaging periodically to screen for changes in their bile ducts. For example, if a high-grade stricture is becoming progressively tighter with upstream dilation of the bile ducts, that might be an indication to perform endoscopic retrograde cholangiopancreatography (ERCP) to obtain brushings, scrapings, or biopsies of any strictures. In addition, patients with PSC who have cirrhosis are at increased risk for hepatocellular carcinoma, so imaging surveillance is needed for that as well. Thus, patients with PSC have a number of premalignant conditions, so one of the key points about PSC management is being aware of these risks and surveying patients appropriately. Additionally, there is a lot of research currently underway in PSC trying to identify new therapies, largely focused on either symptom control or trying to slow down the progression of the disease.

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G&H What has research found regarding the use of ursodeoxycholic acid in PSC?

KK A number of therapies have been studied in PSC, including ursodeoxycholic acid (UDCA). This agent has been around for decades to treat primary biliary cholangitis (PBC), which is a very different disease from PSC

but is similar in some ways. UDCA is established as first-line therapy for PBC. The data with using UDCA for PSC have been more mixed. Earlier studies suggested that standard doses of UDCA may not be effective in reducing the risk of complications of end-stage cirrhosis or decompensated liver disease. Intriguing studies from Scandinavia and the United Kingdom suggested that using higher doses of UDCA showed some trends toward possible clinical benefit. My colleagues and I subsequently carried out a National Institutes of Health–sponsored clinical trial examining whether high-dose (28-30 mg/kg/day) UDCA might provide clinical benefit in PSC. Unexpectedly, high-dose UDCA was associated with a greater risk of adverse liver-related outcomes, and the study was stopped early because of this finding. Therefore, the data with regard to UDCA use remain somewhat controversial. Some experts recommend that UDCA may be considered early in the diagnosis of a PSC patient to see whether it may lead to normalization of blood tests, particularly alkaline phosphatase. If that were to occur, it has been recommended that perhaps UDCA could be continued for those patients. However, by and large, the data with regard to UDCA for PSC have been mixed, and at the present time, there is no evidence that UDCA improves long-term outcomes in PSC.

G&H What is the current status of farnesoid X receptors in PSC?

KK Farnesoid X receptor (FXR) agonists work in the liver and have shown promise to treat PBC. One such drug, obeticholic acid, was approved to treat PBC almost 10 years ago but was recently withdrawn voluntarily by the manufacturer because of concerns raised by the US Food and Drug Administration (FDA) about safety as well as lack of efficacy. Other FXR agonists have been in clinical trials. For example, cilofexor was shown to be promising in a phase 2 trial. A phase 3 trial was conducted on the likelihood of developing cirrhosis in patients treated with this drug. Unfortunately, that study did not show benefit with cilofexor, and further development of cilofexor for PSC appears unlikely.

G&H Could you discuss any recent PSC research involving peroxisome proliferator-activated receptor agonists?

KK Two peroxisome proliferator-activated receptor (PPAR) agonists, elafibranor (Iqirvo, Ipsen) and seladelpar (Livdelzi, Gilead), are now approved to treat PBC. Elafibranor, a PPAR-alpha and -delta dual agonist, was recently studied in a phase 2 trial in patients with PSC. This was a short-term study with an open-label, follow-up safety extension. Patients were randomized to either 80 mg, 120 mg, or placebo. The primary endpoint was safety and tolerability, and secondary endpoints were change from baseline in liver biochemistries and symptoms of PSC. There were significant and dose-related reductions in alkaline phosphatase in patients treated with elafibranor compared with placebo. Patients then entered the long-term safety extension, which showed that response was sustained and that the drug was well tolerated. There was also improvement in itch among patients treated with elafibranor. These early results are promising and, in my opinion, warrant further examination in longer-term studies of clinical outcomes, which will be necessary for full approval by the FDA and other regulatory agencies. As for the PPAR-delta agonist seladelpar, this drug has not yet been studied in the treatment of PSC despite its recent approval for PBC.

Fibrates such as fenofibrate and bezafibrate also target PPAR and have been used for the treatment of dyslipidemia for many years. These compounds have also been studied in PSC. Bezafibrate, which is not available in the United States but is available in Canada, Europe, and Japan, has been recommended by European guidelines to treat itching related to PSC. Itching can be a severe and disabling symptom in some patients with PSC and can dramatically reduce quality of life.

G&H Do ileal bile acid transport inhibitors show promise in the management of patients with PSC?

KK Ileal bile acid transport (IBAT) inhibitors block the reabsorption of bile acids in the terminal ileum, the lowest part of the small intestine, before it joins the colon. Blocking the reabsorption of these bile acids can cause a net loss of bile acids from the body. Because they are not reabsorbed and recirculated, but rather eliminated via feces, it is thought that continuing therapy with these medications can reduce the bile acid pool. Although it is still not exactly clear how blocking bile acid reabsorption or reducing bile acid content may relieve itching in PSC or PBC, we know clinically that when patients are treated with these medications, they appear to respond well. These IBAT inhibitors are already approved to treat rare pediatric diseases such as Alagille syndrome and progressive familial intrahepatic cholestasis. In fact, they have been shown to improve not just symptoms, but even outcomes in pediatric patients with severe itching. A clinical trial is currently underway with an IBAT inhibitor with the goal of improving itching in PSC. There is some evidence that IBAT inhibitors may even have possible effects on modulating the disease in the liver and bile ducts, which would be welcome news for patients.

G&H What is the current role of liver transplant in PSC?

KK When patients with PSC develop end-stage liver disease, liver transplant is an effective treatment and remains the only accepted definitive therapy for PSC. Of course, access to liver transplant is not easy with the current state of organ allocation and availability, there are risks associated with the procedure, and the patient needs lifelong immunosuppression that may be associated with complications. Patients need to have severe disease, with sufficiently high Model for End-Stage Liver Disease (MELD) scores, to be eligible to receive a transplant. A subset (10%-25%) of PSC patients who undergo liver transplant experience recurrent disease; therefore, there is a need to monitor patients after the procedure to see whether they have evidence of recurrent disease. However, patients with PSC who undergo liver transplant generally have very good outcomes and can expect to do well for many years.

G&H What other therapeutic approaches and drugs are being explored in PSC?

KK There is a growing recognition of the connection between the gut and the liver in PSC, so modulating the microbiome in the colon may be a therapeutic option. A trial is currently underway with a compound that uses LB-P8 (LISCure Biosciences), which is a microbiome-modulating approach based on a derivative of kimchi. Our institution is one of the sites examining this compound (NCT06699121).

Another medication that has captivated the interest of patients and is being used clinically is vancomycin. Advocates of vancomycin point out that it is safe and improves liver biochemistries and that it may provide clinical benefit in PSC modulating the microbiome. The lack of randomized controlled trial data showing that vancomycin is safe and effective has limited widespread adoption of vancomycin as an established treatment. We do have some anecdotal experience treating selected patients with vancomycin in our clinic. These patients appear to be tolerating this medication well and have demonstrated reduction in liver biochemical tests.

Additionally, norucholic acid, an engineered bile acid derivative that is resistant to amidation, has been studied in a phase 3 trial that reported positive results in terms of biochemical parameters and biopsy. This drug undergoes cholehepatic shunting and is postulated to have anti-inflammatory and immunomodulating features.

G&H Is there anything else to keep in mind when managing patients with PSC?

KK It is important to note that PSC may not occur in isolation, particularly in the pediatric population. Young patients with PSC frequently may have overlap syndromes with autoimmune hepatitis. Therefore, it is always important to make sure that the patient has been evaluated for concomitant diseases such as autoimmune hepatitis, in which case they would be treated with immunosuppressive drugs to treat the autoimmune component.

Some patients with PSC who have symptoms such as itching or recurrent symptoms because of bile duct blockage may benefit from endoscopic interventions via ERCP with balloon dilation of strictures and, if necessary, stent placement.

In my experience, patients can do very well for long periods of time with good medical care, which includes managing nutrition and making sure they are adequately supplemented if needed with fat-soluble vitamins, making sure their bone density is measured and corrected as necessary, and undergoing proper cancer surveillance.

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Occasionally, patients may have severe recurrent cholangitis, where they have repeated infections in the bile ducts because the biliary tree is constantly being exposed to bacteria that may accumulate with bile stasis owing to strictures or blockages. The development of severe cholangitis may require admission to the hospital and intravenous antibiotics as well as endoscopic procedures to open bile duct strictures. Occasionally, patients with severe recurrent cholangitis may be eligible for MELD exception points to allow them to undergo liver transplant in an expeditious manner.

PSC is a complicated disease in which many different organs can be involved. It can be very disruptive for patients because it often strikes in the prime of their life, and patients often have to deal with not one diagnosis but multiple diagnoses. Some patients are diagnosed with IBD after the diagnosis of PSC, which was not apparent

clinically and this can be quite overwhelming. It is very important to stay positive and reassure patients that the vast majority do very well. Although at this point we do not have any medical therapies that cure or slow down the progression of the disease definitively, we are hopeful to be able to offer patients such therapies in the future.

G&H What are the priorities of research regarding PSC?

KK A very high priority is to simplify the pathway for drug approval. The pathway for approval of drugs in rare diseases such as PSC involves going through an accelerated or conditional approval process with the requirement that the medication should be shown to improve hard outcomes such as transplant-free survival or severe complications of liver disease. Such studies may take years to complete and result in a long delay in the approval of medications that might be life-changing for patients. Although we need to balance efficacy with safety, which is a priority for the FDA and other regulatory agencies, we also need to make pathways for drug approval more flexible and find more creative ways of bringing new therapies to the clinic. Several therapies that were in development for PSC have now been paused or are not moving forward because of the very high burden of proof required to show efficacy and safety. Of course, we do not want to bring therapies too early to the clinic that might potentially be associated with unrecognized risks. At the same time, we want to be able to streamline the pathway for drug development so that patients can get more therapies when there is evidence of safety and efficacy to an adequate degree.

Disclosures

Dr Kowdley has served as a consultant to Arbormed, Boehringer Ingelheim, CymaBay, Genfit, Gilead, GSK, HighTide, Inipharm, Intercept, Ipsen, Madrigal, Mirum, NGM, Novo Nordisk, Orphalan, Pfizer, Zydus, and 89bio; has received research support from Akero, AstraZeneca, Boehringer Ingelheim, Boston Pharmaceuticals, Corcept, Gilead, GSK, Hanmi, Inventiva, Ipsen, Janssen, Madrigal, Mirum, NGM, Novo Nordisk, Pfizer, Pliant, Terns, Viking, Zydus, and 89bio; has served on the speakers bureau for Gilead, Ipsen, and Madrigal; and has received stock options for Inipharm.

Suggested Reading

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