ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Diagnosis, Prognosis, and Management of Primary Sclerosing Cholangitis

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G&H What underlies the symptoms of primary sclerosing cholangitis?

CP The symptoms of primary sclerosing cholangitis (PSC) relate to cholestasis, or frank obstruction of intrahepatic and extrahepatic bile ducts. Cholestasis can cause pruritus, fatigue, and, in advanced cases, jaundice. Obstruction of the larger bile ducts caused by strictures that are either too narrow to allow sufficient choleresis or bile ducts that are obliterated by biliary sludge is responsible for pain in the right upper quadrant of the abdomen, which is a common symptom of PSC. Secondary infection may occur because of bile buildup and damage to the bile ducts. Fever, thus, is a symptom of secondary infection and occurs in the context of suppurative cholangitis.

G&H What is the usual course of symptom manifestation as PSC progresses?

CP The disease can manifest with any of the main symptoms, which can include right upper quadrant pain, pruritus, jaundice, fatigue, and/or suppurative cholangitis. Over the course of years—as with all chronic progressive liver diseases—signs and symptoms of liver cirrhosis will occur. These signs and symptoms typically include splenomegaly, ascites, portal hypertension, and jaundice. Patients also are at increased risk for the development of cholangiocarcinoma (CCA), which can occur at any time. The presenting symptoms of CCA usually are progressive fatigue, weight loss, and jaundice.

G&H What is the general prognosis for patients with PSC?

CP Studies have suggested that the median transplant-free survival of patients with PSC ranges from 9.3–18 years; however, in a large population-based study on the epidemiology and natural history of PSC that we recently performed in The Netherlands, a median transplant-free survival of 21.3 years was found. Diagnosis of PSC was commonly preceded by a period of up to 5 years when, in retrospect, symptoms or abnormal laboratory values could be attributed to the disease. The findings from this population-based review were recently published in *Hepatology*.

With the availability of noninvasive magnetic resonance cholangiography (MRC), which is now thought to be preferable to endoscopic retrograde cholangiography (ERC) in the diagnosis of PSC because of its much lower adverse effect profile, diagnosis is being made earlier.

As for the prognosis of patients who undergo liver transplantation for PSC, the 5-year survival rate is approximately 85%.

G&H Who is at risk for PSC, and how can PSC be detected in early stages?

CP PSC is strongly associated with inflammatory bowel disease (IBD), especially ulcerative colitis and, to a lesser extent, Crohn's colitis. Upon diagnosis, 60% of patients with PSC have IBD. In time, this percentage rises to

80%. Conversely, PSC will develop in 3% of patients who have ulcerative colitis. There is also a familial factor, with a hazard ratio of PSC of 11 for offspring and siblings of patients who have ulcerative colitis. Currently, there are no screening guidelines for PSC in patients at risk, such as patients with ulcerative colitis. At our institution, we measure alkaline phosphatase levels on a yearly basis in patients who have ulcerative colitis to assess for the emergence of PSC. On the other side of the coin, because we have no effective treatment for PSC, the only action to be taken if presymptomatic disease is found is yearly colonoscopic surveillance from the time of diagnosis.

G&H Is there a way to predict which patients might be at risk for CCA?

CP Other than frank dysplasia in biliary brushings, there are currently no established biomarkers available to predict which patients with PSC are at risk for development of CCA. A study by Boberg and colleagues, published in the *Journal of Hepatology* in 2006, showed that dominant strictures that harbor low-grade or high-grade dysplasia are associated with a high risk for development of cancer. However, differentiating dysplasia from reactive changes due to inflammation in brush cytology material from a dominant stricture in the setting of PSC requires a highly experienced cytopathologist. CA19-9 has some merits as a tumor marker but not in indicating who is at risk for tumor development.

G&H Should PSC be regarded as a premalignant lesion?

CP Undoubtedly, PSC is a premalignant condition. Research by our collaborative Dutch PSC research group estimated that the risk of CCA within 30 years from diagnosis of comorbid PSC and ulcerative colitis amounts to about 20%. The risk of colorectal cancer within 30 years of diagnosis of comorbid PSC and ulcerative colitis is 15%. Patients with PSC also are at an increased risk for gallbladder carcinoma and hepatocellular carcinoma.

G&H What is the best diagnostic protocol, and is liver biopsy useful?

CP In 2010, the American Association for the Study of Liver Diseases (AASLD) issued practice guidelines for the diagnosis of PSC. In short, a nondiagnostic abdominal ultrasound and MRC are recommended in patients with a cholestatic liver enzyme profile and negative relevant serology results, such as the presence of antimitochondrial antibodies. When these procedures prove to be nondiagnostic or when there is disproportionate elevation of transaminase levels, a liver biopsy for the diagnosis of small duct PSC or autoimmune hepatitis is advised. ERC is recommended in some instances, such as when the sensitivity and specificity of MRC findings are in question.

G&H Is treatment basically symptomatic until liver transplant becomes a necessity?

CP At present, there is no medical or endoscopic therapy with proven efficacy to halt disease progression. This implies that therapy is directed to alleviate symptoms. Ursodeoxycholic acid (UDCA), a hydrophilic, dihydroxy bile acid, can ameliorate pruritus and fatigue. Pruritus that does not respond to resins such as cholestyramine can be treated with a low to medium dose of rifampicin, which is a pregnane X receptor agonist and enhances the metabolism of pruritogens probably by inducing biotransforming enzymes and transport molecules. As a third-line therapy, the opioid antagonist naltrexone can be used. When patients have increased cholestatic complaints and an increase in alkaline phosphatase and/or bilirubin levels, the a priori chance of existence of a symptomatic-dominant stricture is about 60%. MRC is indicated in this situation. When a dominant stricture is identified, ERC with either balloon dilatation or short-term stenting is warranted. Whichever of these ERC methods is more effective is the topic of an ongoing multinational clinical trial.

G&H What strategies have been used to slow disease progression, and which is the most preferred?

CP UDCA has been prescribed widely for treatment of PSC, but despite 2 decades of clinical trials, no benefit with regard to halting disease progression has been shown. Its use as a therapeutic modality is not recommended by the AASLD because of findings showing its lack of effect at normal doses on slowing disease progression and because, at high doses, it has been associated with toxicities.

As for the treatment of dominant strictures, both balloon dilatation and temporary stent placement are used. Compared with the Mayo risk score for PSC, patients who have been treated with either balloon dilatation or temporary stent placement seem to have a slower progression to liver failure or death than those who have not received such treatments, but this is only a virtual comparison. Regular screening and repeated endoscopic treatment until dominant strictures are gone are performed in only a few centers around the globe.

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G&H What therapies or strategies are currently being explored?

CP Two main avenues of research that are currently being explored are antagonizing toxic bile acids and the aberrant gut homing lymphocytes hypothesis. Nor-UDCA is a C23 homologue of UDCA. Nor-UDCA is barely amidated in liver cells and is mainly excreted into bile in its unconjugated and glucuronidated form, thereby inducing a bicarbonate-rich hypercholeresis. In the MDR2 knockout mouse model, nor-UDCA was found to be much more potent in preventing periductular fibrosis than UDCA. A phase II trial of nor-UDCA in patients with PSC is currently underway.

As for the lymphocyte homing paradigm, gut-homing lymphocytes express the integrin α4β7. These lymphocytes can interact with the mucosal addressin cellular adhesion molecule 1 (MAdCAM-1), which leads to arrest of these lymphocytes so that they can extravasate through diapedesis into their target tissue. It has been shown that there is aberrant expression of both α4β7 and MAdCAM-1 in patients with PSC. This has supported the hypothesis that mature, primed T lymphocytes inadvertently home to the liver instead of the lamina propria of the colon. Several antibodies to α4β7 and MAdCAM-1 are currently being tested in IBD models with favorable results. A clinical trial in PSC is awaited.

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Suggested Reading

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