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Novel Therapies for Primary Sclerosing Cholangitis

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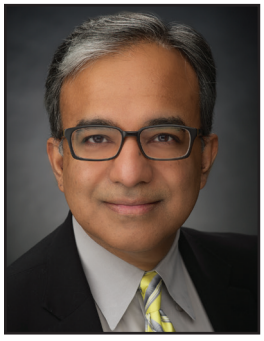

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is chronic, cholestatic liver disease that progresses to advanced liver disease and cirrhosis. It is characterized by inflammation and fibrosis of both intra and extra hepatic bile ducts leading to the formation of multiple bile duct strictures resulting into chronic cholestasis. This may eventually develop into cirrhosis with subsequent portal hypertension and hepatic decompensation.[1,2] The incidence and prevalence rates for PSC range from 0 to 1.3 per 100,000 people per year and 0 to 16.2 per 100,000 people, respectively. The estimated median survival from the time of PSC diagnosis until liver transplantation or mortality related to liver disease is 12 to 15 years.[1] Roughly 65% of PSC patients are male. PSC is strongly associated with inflammatory bowel disease (IBD), as the prevalence of IBD in PSC is 60-80%.[3] The typical PSC patient is a male in their fourth or fifth decade of life presenting with a diagnosis of ulcerative colitis (UC) or Crohn's colitis and abnormal liver biochemistries.[4,5] The IBD associated with PSC is unusual in that it is usually pancolitis with right sided predominance, backwash ileitis and rectal sparing.[6,7]

PSC is associated with an increased risk of biliary and colorectal cancer; patients with concomitant UC and PSC have a much higher risk compared with patients with UC or PSC alone.[8,9] Surveillance colonoscopy, from the time of diagnosis of PSC, cannot be stressed enough. Patients with small duct PSC disease have an improved survival and lower risk of cholangiocarcinoma as comparted to patients with large duct PSC.[8,10] Patient who demonstrate a significant reduction in serum alkaline phosphatase (ALP) in a median time of two years following diagnosis have an improved transplant-free survival and reduced risk of cholangiocarcinoma.[11] PSC is also associated with increased frequencies

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of multiple gall bladder abnormalities including cholecystitis, cholelithiasis, benign lesions and malignancies.[12] Gallbladder lesions have been found in about 5% of patients with PSC, with half of these being malignant. Gallbladder polyps are significantly associated with high risk of malignancy, so cholecystectomy is recommended even if the lesion is less than 1 cm.[13,14]

Pathogenesis

The exact pathogenesis of PSC is unknown. Multiple studies have supported an autoimmune etiology given the presence of concurrent autoimmune disease in up to 25% of PSC patients as well as strong linkage of PSC to human histocompatibility complex genes.[4] The involvement of gut microbiota has been evaluated in PSC. Several in vitro studies have demonstrated that small bowel bacterial overgrowth may cause cholangitis and liver lesions similar to those seen in PSC. Subsequent antimicrobial therapy leads to an improvement in these lesions. The strong HLA associations suggest that adaptive innate responses are also involved in the pathogenesis of PSC. IgG4 (immunoglobulin-G4) related disease is a systemic disease characterized by extensive IgG4 plasma cells and T-lymphocyte infiltration of various organs including pancreas (autoimmune pancreatitis) and bile ducts (IgG associated cholangitis, IAC). It is important to distinguish between IAC and PSC with elevated IgG4 as cholangiographic changes of IAC may resolve completely after corticosteroids treatment. PSC patients with elevated IgG4 are less responsive to corticosteroids and also multiple studies have demonstrated that these patients may progress rapidly and have more severe liver disease.[15,16]

Diagnosis

The diagnosis of PSC is made in patients with cholestatic liver test abnormalities and characteristic stricturing of the intrahepatic and/or extrahepatic bile ducts with segmental dilatation on cholangiography [e.g., magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERC) or percutaneous transhepatic cholangiography (PTC)] after excluding secondary causes of sclerosing cholangitis.[4,17] The preferable test for making a diagnosis of PSC is MRCP, which has acceptable sensitivity and specificity of 86% and 94% respectively. Small duct PSC is a disease variant characterized by cholestasis and histological features of PSC with normal bile ducts cholangiogram; liver biopsy is required for diagnosis in these cases.[17] Secondary sclerosing cholangitis is characterized by multiple biliary strictures due to recognizable causes such as infection, inflammation and long-term biliary obstruction that leads to destruction of bile ducts. PSC overlap syndromes are conditions with features of PSC and other autoimmune liver diseases such as autoimmune hepatitis (AIH) and autoimmune pancreatitis. PSC-AIH overlap syndrome is characterized by clinical, biochemical, and histological features of AIH along with cholangiographic findings similar to PSC. However, current understanding is that rather than reflecting a separate entity, the observed features of autoimmune hepatitis in PSC, including elevated transaminases and IgG, may also be due to biliary disease. Autoimmune pancreatitis (AIP) is characterized by stricturing of pancreatic duct, raised IgG4 level, a lymphocytic infiltrate and response to corticosteroid therapy. AIP in association with stricturing of bile ducts similar to PSC is termed as autoimmune pancreatitis – sclerosing cholangitis (AIP-SC). It is important to note that alkaline phosphatase levels fluctuate in PSC patients and may be normal or only mildly elevated in a significant proportion of PSC patients.[4,8,9]

Management

Managing patients with PSC is complicated, as it requires management of primary disease and also coexisting conditions and complications from end stage liver disease. Currently there is no medical therapy that will halt the progression of liver disease in PSC patients, despite numerous clinical trials over the past two decades. This is due to uncertainty regarding the pathophysiology of PSC and also lack of reliable diagnostic markers.

Ursodeoxycholic Acid

Multiple clinical trials have studied the efficacy and safety of ursodeoxycholic acid (UDCA) in PSC patients. UDCA is the most commonly

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prescribed drug for PSC, as it is effective in other cholestatic liver diseases, specifically primary biliary cholangitis (PBC). However, the role of UDCA in clinical improvement is questionable. UDCA reduces hydrophobicity of bile acid and also affects adaptive immunity by inhibiting dendritic cell response.[18,19] The initial placebo controlled clinical trials of low dose UDCA conducted in early 1990s demonstrated improvement in clinical symptoms, liver biochemistries and histological features. However, its clinical significance was limited due to small sample size.[20,21] A large, placebo-controlled clinical trial of low dose UDCA (13-15 mg/kg/day) in PSC demonstrated improvement in serum liver biochemistries but no effect on patient's clinical symptoms or time to liver transplantation. [22] A large, multicenter, randomized, placebo-controlled trial treated 219 PSC patients with moderate doses of UDCA (17-23 mg/kg/day) and followed them for five years. Improvement in liver biochemistries with UDCA treatment was seen, but there was no statistically significant effect on survival, time to liver transplantation or prevention of cholangiocarcinoma.[23] Pilot clinical trials with a higher dose of UDCA (28-30 mg/kg/day) demonstrated clinical improvement in liver biochemistries as well as Mayo risk score.[24,25] However, the largest clinical trial of high dose UDCA[26] was terminated at five years due to an increased risk of progression to liver transplantation, cirrhosis, gastric or esophageal varices and cholangiocarcinoma compared to placebo.[26] It has been demonstrated that an increased serum lithocholic acid concentration, a potent hydrophobic bile acid in patients receiving high dose of UDCA, may be responsible for these adverse outcomes.[27] A meta-analysis of nine randomized control trials (RCTs)[28] concluded that UDCA at any dose showed no significant improvement in symptoms, histological progression, mortality or cholangiocarcinoma. Similarly, a systematic review of eight RCTs [29] showed improvement in liver biochemistries but no significant reduction in the relative risk of death, varices, ascites or encephalopathy. Due to variable doses of UDCA, different treatment time course, follow up and end points, the treatment guidelines for UDCA in PSC are conflicting. The two major United States (US) societies including the AASLD (American Society for the Study of Liver Diseases)[17] and the ACG (American College of Gastroenterology)[30] do not support the use of ursodeoxycholic acid; however the EASL (European Association for the Study of the Liver)[31] recommends the use of low dose UDCA (13-15 mg / kg / day).

Novel Treatment in PSC

Farnesoid X Receptor Ligands

The Farnesoid X receptor (FXR) plays an important role in bile acid homeostasis. The natural ligands for FXR are bile salts. The key role of FXR is to down regulate the cytochrome P4507A1, the rate limiting enzymes in bile acid synthesis.[32] Obeticholic acid (OCA), a semisynthetic analogue of chenodeoxycholic acid and an FXR agonist with anti-fibrotic properties has been approved by the US Food and Drug Administration for the treatment of primary biliary cholangitis (PBC).[33] A clinical trial of obeticholic acid in patients with primary sclerosing cholangitis is underway (clinicaltrials.gov identifier, NCT02177136). The results from a phase 2 randomized, double blind, placebo controlled trial (AESOP) evaluating the safety and efficacy of OCA compared to placebo in 77 patients with PSC were presented at the annual meeting of the AASLD in 2017. Patients were randomized to placebo, OCA 1.5 – 3 mg, and OCA 5 – 10 mg (with dose titration occurring at the 12 week midpoint). By 24 weeks, ALP increased by 1% in placebo group and decreased by 22% in both OCA 1.5 – 3 and OCA 5 – 10 mg groups. In AESOP, about 46 – 48% of patients in each group were receiving UDCA at baseline. Results from a post-hoc analysis showed that improvement in serum ALP were observed with OCA regardless of treatment with UDCA. Pruritus is the common symptom of PSC and was the most common adverse event observed, occurring in 46%, 60% and 67% of patients in the placebo, OCA 1.5 – 3 mg and OCA 5 – 10 mg groups, respectively.[34]

Role of Antibiotics in PSC

Multiple in-vitro studies demonstrated a link between the intestinal microbiota and biliary inflammation in PSC. The use of vancomycin in PSC showed improvement in liver biochemistries,

however the long-term outcome is still unclear. The safety and efficacy of oral vancomycin and metronidazole were evaluated as well. Patients in the vancomycin arm achieved the primary end point (a decrease in alkaline phosphatase at 12 weeks) with less adverse effects.[35]

Simtuzumab

Lysyl oxidase homolog 2 (LOKL2) catalyzes the first step in the formation of cross links in collagen and elastin and is associated with progression of liver disease. Pre-clinical models (e.g., MDR2 knock out mice), inhibition of LOKL2 improves fibrosis. In addition, serum and tissue LOXL2 levels are elevated in PSC and correlated with fibrosis stage. A clinical trial evaluating the safety and efficacy of simtuzumab (SIM, a humanized IgG4 monoclonal antibody against LOXL2) in PSC was conducted. In a phase 2b clinical trial (results were presented at the EASL International Liver Congress 2017, Amsterdam), 234 patients with PSC were randomized to receive weekly subcutaneous injections of SIM 75 mg, SIM 125 mg or placebo for 96 weeks. The authors concluded that neither dose of SIM lead to significant reduction in mean hepatic collagen content, change in Ishak fibrosis stage, serum alkaline phosphatase concentration or progression of cirrhosis.[36]

Norursodeoxycholic Acid

24-Norursodeoxycholic acid is a synthetic bile acid and C23 homolog of ursodexoycholic acid. It reduces inflammation and improves fibrosis as well as liver function tests in rodent model of sclerosing cholangitis. Results from a phase 2 clinical trial evaluating the safety and efficacy of norursodeoxycholic in patients with PSC were presented at the EASL ILC in 2016;[37] 59 PSC patients were randomized to 500, 1000, and 1500 mg of norursodeoxycholic for 12 weeks. The authors concluded that PSC patients treated with norursodeoxycholic demonstrated significant reduction in serum ALP levels within 12 weeks of treatment in all groups (12.3%, 17.3% and 26%, respectively). A long term clinical trial will determine the effect of norursodeoxycholic acid on clinical outcomes of PSC such progression of disease to cirrhosis, time to liver transplantation and liver related mortality.[37]

ASBT Inhibitor

Interruption of intestinal bile acid circulation might have therapeutic benefit in PSC. The active absorption of bile acids in the terminal ileum is mediated by Apical Sodium Dependent Bile Acid Transporter (ASBT). ASBT inhibition reduced cholestatic liver injury and fibrosis by increasing fecal excretion of bile acids, lowering hydrophobic biliary bile acid concentrations. Lopixabat, an ASBT inhibitor is currently being evaluated in patients with PSC.[38]

Cenicriviroc

Cenicriviroc, a dual chemokine receptor (CCR) 5 and CCR2 antagonist is currently being studied for PSC. CCR5 and CCR2 are involved in the inflammatory and fibrogenic pathways that cause fibrosis and often lead to cirrhosis and liver cancer.[39]

NGM282

NGM282 is a variant of the human hormone FGF19 that reduces liver fat content, reverses fibrosis and improves liver function. Results from a phase 2 clinical trial evaluating the safety and efficacy of NGM282 in patients with PSC were recently presented at the EASL ILC 2018; 62 PSC patients with elevated ALP were randomized to receive daily subcutaneous injection of NGM282 1mg or 3 mg or placebo. The primary end point was the change in ALP from baseline to week 12. The study did not meet the primary end point.

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However, significant reductions in serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) were observed in 3 mg cohort at week 12. Also markers of fibrosis and bile acid synthesis were significantly reduced in both NGM282 cohorts at week 12 as compared to placebo group.[40]

CONCLUSION

PSC, a disease with complex pathophysiology, results in morbidity and mortality due to liver disease. No therapy thus far has been effective to slow the progression of disease and complications from cirrhosis in PSC. UDCA has been evaluated in depth in PSC, but even though it improves liver biochemistries, there is no significant improvement in clinical outcomes of PSC such as cirrhosis, time to liver transplantation and mortality from liver disease. Multiple novel therapeutic agents beyond UDCA are now targeting bile acid homeostasis and are currently being evaluated in patients with PSC. ■

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