Novel Treatments in Primary Sclerosing Cholangitis

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Primary sclerosing cholangitis (PSC) is a disease of unclear cause characterized by cholestasis, fibrosis of the intrahepatic and/or extrahepatic bile ducts, leading eventually to cirrhosis of the liver, end-stage liver disease, and an increased risk for bile duct and colon cancer.¹ About 70% to 80% of patients with PSC have the inflammatory bowel disease ulcerative colitis (UC). 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.² The estimated median survival from the time of PSC diagnosis until liver transplantation or liver disease-related death is 12 to 15 years. The diagnosis of PSC is made when there is evidence of cholestasis and stricturing of the intrahepatic and/or extrahepatic bile ducts on magnetic resonance cholangiography. Small-duct PSC is characterized by cholestasis and a normal cholangiogram; in these cases, liver biopsy is required for diagnosis.³

No therapy for PSC has been proven to halt the progression of the disease. Ursodeoxycholic acid (UDCA), a naturally occurring bile acid, has been extensively studied

in PSC. The value of UDCA in PSC is questionable. In the Scandinavian clinical trial, the use of UDCA at a dose of 17 to 23 mg/kg/day was associated with improvement in liver biochemistries, but no statistically significant effect on survival or prevention of cholangiocarcinoma (CCA), although this study was underpowered to detect a significant effect on the clinical endpoints that had been sought.⁴ In the high-dose ursodiol clinical trial, the use of higher doses of UDCA (28 to 30 mg/kg/day) showed the expected improvement of liver biochemistries.⁵ However, this study was terminated at 5 years because of the higher rates of serious adverse events in the UDCA group.

In this article, we take the opportunity to briefly discuss the previously examined agents and the emerging potential treatments for PSC.

AGENTS PREVIOUSLY EXAMINED IN PSC

Table 1 summarizes the key clinical trials, along with their results, in PSC. None of the agents studied have

Abbreviations: ALP, alkaline phosphatase; ASBT, apical sodium bile acid transport system; CCA, cholangiocarcinoma; CCR, chemokine (C-C motif) receptor; CYP7a1, cholesterol 7- α hydroxylase; FXR, farnesoid X receptor; LOXL2, lysyl oxidase homolog 2; PSC, primary sclerosing cholangitis; UC, ulcerative colitis; UDCA, ursodeoxycholic acid; VAP-1, vascular adhesion protein-1.

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TABLE 1. AGENTS EXAMINED IN PSC SUBJECTS

Agent(s)	Duration of Treatment	Main Results
Penicillamine ⁶	36 months	No beneficial effect on survival
Prednisone and colchicine ⁷	24 months	Improved liver biochemistries, but no effect on survival
Methotrexate ⁸	24 months	Reduction in ALP, but no effect on survival
UDCA plus methotrexate ⁹	24 months	No significant effect on liver biochemistries or survival
Nicotine ¹⁰	12 months	No change in liver biochemistries
Budesonide or prednisone ¹¹	2 months	No change in liver biochemistries with budesonide; significant change in ALP in the prednisone group
Pentoxifylline ¹²	12 months	No significant change in liver biochemistries
Pirfenidone ¹³	12 months	No significant change in liver biochemistries; no change in liver histology after 1 year of treatment
Etanercept ¹⁴	12 months	No significant change in liver biochemistries
UDCA plus mycophenolate versus UDCA alone ¹⁵	36 months	No significant change in liver biochemistries and no difference in survival
Mycophenolate mofetil ¹⁶	12 months	Significant reduction in ALP; study agent-related adverse events in 23% of patients
UDCA (13-15 mg/kg/day) ¹⁷	6 years	Improvement of liver biochemistries including ALP; no obvious benefit on main clinical outcomes (time to death, liver transplantation, development of cirrhosis and/or CCA)
UDCA (17-23 mg/kg/day) ⁴	5 years	Significant reduction in ALP and alanine aminotransferase; no statistically significant beneficial effect on the survival or prevention of CCA between the treatment groups
Tacrolimus ¹⁸	12 months	Significant reduction in ALP and aspartate aminotransferase; study agent-related adverse events in 31% of patients
Infliximab ¹⁹	52 weeks	No significant change in liver biochemistries or histological abnormalities
UDCA (28-30 mg/kg/day) ⁵	5 years	Improved liver biochemistries in the UDCA group; increased rates of serious adverse events in the UDCA group compared with placebo
Vancomycin or metronidazole ²⁰	12 weeks	Improved ALP in the vancomycin group and bilirubin in the metronidazole group

shown a beneficial effect on clinically important endpoints and survival in PSC. It should be noted, however, that the majority of these clinical trials have been conducted in small numbers of patients, and that the duration of follow-up is short compared with the natural history of the disease. Moreover, it is difficult to retain patients in clinical trials of long duration. In addition, the lack of validated surrogate markers of clinically important endpoints in PSC poses significant challenges when designing therapeutic clinical trials in PSC.

NOVEL TREATMENTS IN PSC

Farnesoid X Receptor Ligands in PSC

The farnesoid X receptor (FXR) plays a key role in bile acid homeostasis. When bound to bile acids, FXRs repress the expression of the gene encoding for cholesterol 7- α hydroxylase (CYP7a1), the rate-limiting enzyme

in bile acid synthesis.²¹ Obeticholic acid, a first-in-class FXR agonist that has been recently reviewed by the US Food and Drug Administration for the treatment of primary biliary cholangitis, is currently being evaluated in patients with PSC.

Altering the Microbiome in PSC

Experimental evidence suggests a link between the intestinal microbiota and the hepatobiliary inflammation that occurs in PSC.²² Vancomycin use in children and adults with PSC showed improvement in liver biochemistries²³; the long-term impact of vancomycin in PSC remains to be elucidated. A study at Stanford University is evaluating the use of vancomycin in children with PSC. Fecal transplantation and probiotics are currently being investigated as a therapeutic approach in PSC subjects.

Norursodeoxycholic Acid

24-Norursodeoxycholic acid, a C(23) homolog of UDCA, alleviates inflammation and improves liver function tests in a rodent model of sclerosing cholangitis.²⁴ In a phase 2 clinical trial (results were presented at the European Association for the Study of the Liver International Liver Congress 2016, Barcelona, Spain), 159 patients with PSC were randomized to 500, 1000, and 1500 mg norursodeoxycholic acid for 12 weeks. Treatment with norursodeoxycholic acid resulted in significant reduction of serum alkaline phosphatase (ALP) in all treatment groups (by 12.3%, 17.3%, and 26%, respectively). Long-term, placebo-controlled clinical trials will determine whether norursodeoxycholic acid has a positive impact on the clinical outcomes of PSC.

BTT1023 in PSC

Vascular adhesion protein-1 (VAP-1) is an adhesion molecule expressed on the endothelial lining of blood vessels and is responsible for recruiting inflammatory cells to the site of inflammation.²⁵ BTT1023 is a human monoclonal antibody that specifically binds VAP-1. A phase 2 clinical study of BTT1023 in patients with PSC is being conducted in the United Kingdom.

Mitomycin C in PSC

Mitomycin C is an antineoplastic agent that works by inhibiting the synthesis of cellular DNA, RNA, and protein by inhibiting the synthesis of collagen by fibroblasts.²⁶ The safety and efficacy of mitomycin C is being examined in a phase 2 clinical trial in patients with PSC at Johns Hopkins University.

Cenicriviroc in PSC

Cenicriviroc, a new dual chemokine (C-C motif) receptor (CCR) 5 and CCR2 antagonist, is currently being evaluated in a clinical trial in patients with PSC. CCR5 belongs to the beta chemokine receptors family and is predominantly expressed on T cells, macrophages, and dendritic cells. Both CCR5 and CCR2 are thought to play a key role in inflammatory signaling.²⁷

Simtuzumab (GS-6624) in PSC

Lysyl oxidase homolog 2 (LOXL2) catalyzes the first step in the formation of cross-links in collagen and elastin, and has been shown to contribute to progressive liver damage.²⁸ Simtuzumab (GS-6624) is a humanized

monoclonal antibody designed to inhibit fibrosis by binding to LOXL2, and a phase 2 clinical trial of GS-6624 in subjects with PSC is currently under way.

Modulation of the Enterohepatic Circulation

Bile acids are end products of cholesterol metabolism. They are secreted from the liver into the small intestine and return to the liver via the portal circulation. The circulation of bile acids from the liver to the intestines and then back to the liver is termed the enterohepatic circulation.

NGM282 in PSC. FGF-19, a hormone secreted by the intestinal epithelial cells, plays a key role in bile acid metabolism. It reduces the biosynthesis of bile acids through repression of the expression of CYP7a1.²⁹ A phase 2 clinical trial of NGM282, an FGF-19 analog, in patients with PSC is under way.

LUM001 in PSC. Interruption of the circulation of the bile acids at the intestinal level might be of therapeutic benefit in patients with cholestatic liver diseases. The active absorption of bile acids at the intestinal level is mediated by the apical sodium bile acid transport system (ASBT).³⁰ LUM001, an engineered ASBT inhibitor, is being evaluated in patients with PSC as a therapeutic option.

CONCLUSION

PSC is an important cause of morbidity in Western society. More than two-thirds of patients with PSC have the inflammatory bowel disease UC. No therapy has been proven to halt the progression of PSC to end-stage liver disease and its consequent complications. UDCA, a naturally occurring bile acid, has been extensively studied in patients with PSC. Although it improves liver biochemistries, it does not seem to have a positive impact on the clinically important outcomes of PSC. Several newer agents are on the horizon and are currently being investigated in subjects with PSC.

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