Primary Sclerosing Cholangitis, Part 1: Epidemiology, Etiopathogenesis, Clinical Features, and Treatment

James H. Tabibian, MD, PhD, Ahmad H. Ali, MBBS, and Keith D. Lindor, MD

Abstract: Primary sclerosing cholangitis (PSC) is a chronic, idiopathic cholangiopathy that can progress to cirrhosis, end-stage liver disease, hepatobiliary cancer, and/or colorectal cancer. The course of PSC is often complicated by portal hypertension, symptoms of cholestasis, and recurrent bacterial cholangitis, among other conditions, with a consequent decrease in survival (median, approximately 20 years) and quality of life. The etiopathogenesis of PSC remains poorly understood, and, as such, pharmacotherapy has yet to be definitively established. Despite its rarity, PSC is the fifth leading indication for liver transplantation (LT) in the United States. Although the only intervention known to extend survival of patients with PSC, LT is costly and invasive, and recurrent PSC affects approximately 30% of LT recipients. Over the past several years, owing in part to progress in the understanding of PSC, novel pharmacotherapeutics have been developed, some of which are currently in the PSC clinical trial pipeline. Here, in the first of a 2-part series, we provide a review and update of the epidemiology, etiopathogenesis, clinical features, and treatment of PSC. The second part of the series will focus on cancer risk, prevention, and surveillance of PSC.

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease characterized by stricturing of the intra- and/or extrahepatic ducts. PSC represents an important cause of morbidity and mortality in Western societies, with many patients ultimately requiring liver transplantation (LT) due to end-stage liver disease or other complications. Patients with PSC are also at significantly increased risk of hepatobiliary cancer and colorectal cancer (CRC), particularly in the 70% of patients who also have inflammatory bowel disease (IBD).

Currently, there is no known pharmacotherapy for PSC that halts disease progression. Numerous agents have been tested, although none have yielded convincingly promising results. The rarity of PSC, its elusive etiopathogenesis, its long natural history, the challenges of retaining patients long enough in clinical trials to achieve sufficient endpoints, and the lack of validated surrogate biomarkers (eg, of treatment success) remain major barriers to developing effective and safe therapies for PSC.
Given the progressive nature of PSC and its associated morbidity and mortality, there is a large unmet need for effective medical therapies for this disease. Here, in the first of a 2-part series, we provide an overview and update of PSC, including its epidemiology, etiopathogenesis, clinical features, associated disorders, and potential therapies. The second part of the series will focus on cancer risk, prevention, and surveillance of PSC.

Clinical Epidemiology

PSC is most common in Northern European countries and North America, where the reported incidence and prevalence range from approximately 0.5 to 1.3 cases per 100,000 person-years and 3.85 to 16.2 cases per 100,000 person-years, respectively. A recent British study reported an incidence of 0.68 per 100,000 person-years and a prevalence of 5.58 per 100,000 person-years; these figures represent the highest incidence and prevalence reported to date in the United Kingdom. PSC appears to be much less common in Southern Europe and Southeast Asia, although in many regions (eg, much of the Eastern Hemisphere), its incidence and prevalence have not been well studied. The prevalence of PSC appears to be considerably higher in Australia than in New Zealand, although both areas have a higher prevalence than Southern Europe and Southeast Asia. Epidemiologic studies of PSC in pediatric patients are scarce; however, the incidence and prevalence of PSC appear to be lower in children than in adults.

As noted previously, approximately 70% of patients with PSC also have IBD, mainly ulcerative colitis, whereas only 2% to 8.1% of patients with IBD have PSC, although rates reach up to 14%. The exact nature of the PSC-IBD relationship is not well understood. Notably, PSC and IBD can be diagnosed simultaneously, although in many patients, there is a dissociation in the time of diagnosis of PSC and IBD (with the diagnosis of IBD typically being made first). In addition, PSC can present after proctocolectomy for IBD, and IBD can present after LT for PSC.

Perhaps the most contemporary and substantiated hypothesis regarding the etiopathogenesis of PSC, although still a work in progress, is the PSC-microbiome hypothesis. This hypothesis, which represents an

<table>
<thead>
<tr>
<th>Variant</th>
<th>Cholangiographic Features</th>
<th>Liver Histology Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic PSC</td>
<td>Multifocal intrahepatic and extrahepatic strictures and resultant upstream (ie, proximal)</td>
<td>Typical changes (ie, nonsuppurative paucicellular cholangitis, periductal fibrosis, ductular reaction, and ductopenia)</td>
</tr>
<tr>
<td>Intrahepatic PSC</td>
<td>Multifocal intrahepatic strictures and resultant upstream (ie, proximal) segmental ductal dilation</td>
<td>Typical changes (ie, nonsuppurative paucicellular cholangitis, periductal fibrosis, ductular reaction, and ductopenia)</td>
</tr>
<tr>
<td>Extrahepatic PSC</td>
<td>Extraperitoneal strictures and resultant upstream (ie, proximal) ductal dilation</td>
<td>Nondiagnostic or nonspecific features of cholestasis, particularly in early-stage disease</td>
</tr>
<tr>
<td>Small-duct PSC</td>
<td>Normal findings</td>
<td>Typical changes (ie, nonsuppurative paucicellular cholangitis, periductal fibrosis, ductular reaction, and ductopenia)</td>
</tr>
</tbody>
</table>

*All of these variants will generally have a cholestatic serum biochemical profile, although a small minority of patients can have normal serum liver test results.

PSC, primary sclerosing cholangitis.
expansion of the leaky gut hypothesis, is compatible with the aforementioned theme of environmental exposures and the notion that cholangiocytes play a central role in PSC, and is based on the association between PSC and IBD and the therapeutic benefits seen with specific antibiotics. The hypothesis posits that PSC may develop as a result of (1) increased enterohepatic circulation of microbial molecules (possibly facilitated by compromised intestinal barrier function), (2) alterations in microbial diversity and/or the repertoire of metabolites (eg, due to intestinal microbial dysbiosis), and/or (3) an aberrant or exaggerated cholangiocyte response (eg, induction of cholangiocyte senescence and senescence-associated secretory phenotype) to microbial molecules. This is supported by various observations in vitro and in animal models. Recently, several studies have explored the potential etiopathogenetic role of the microbiome in PSC. Compared to healthy controls and patients with IBD alone, patients with PSC have decreased microbial diversity and overrepresentation of Escherichia, Fusobacterium, Enterococcus, Lactobacillus, Blautia, Veillonella, Barnesiellaceae, Lachnospiraceae, Megaphera, Rothia, Ruminococcus, and Streptococcus. Conversely, patients with PSC have decreased populations of Clostridium cluster II, Prevotella, Roseburia, Adlercreutzia, and Bacteroides compared to healthy individuals and patients with IBD alone. Additionally, patients with PSC-IBD have a distinctive bile-acid profile compared to patients with IBD alone; the serum bile-acid pool is increased, but the stool bile-acid pool is decreased in patients with PSC-IBD compared to patients with IBD alone. The unique microbial signature in patients with PSC-IBD is thought to lead to changes in the stool bile-acid pool (or vice versa), which could ostensibly explain the increased risk for CRC in PSC-IBD; however, further studies are needed.

The role of genetics in the development and/or progression of PSC has long been suspected and is based on several lines of data. First, the risk of PSC is significantly increased in offspring and siblings of patients with PSC (hazard ratio, approximately 11). Second, genome-wide association studies (GWASs) suggest that the human leukocyte antigen (HLA) gene family collectively represents the strongest risk locus associated with PSC; associations have been described with both class 1 and 2 HLAs, including B8, DR3, DR2, and A1, and with select haplotypes. Moreover, variations in MICA (major histocompatibility complex class I–related MIC gene family) are associated with PSC predisposition; for example, independent of other HLA haplotypes, the MICA 002 allele appears to be associated with a significantly reduced risk of developing PSC, whereas the MICA 008 allele is associated with an increased risk. Third, non-HLA PSC susceptibilities and modifier genes have been identified, including (but not limited to) stromelysin-1 (ie, matrix metalloproteinase 3) and intracellular adhesion molecule 1. In addition, recent GWASs have identified associations between PSC and (1) the fucosyltransferase 2 gene (found to influence the microbial community composition of the bile), (2) the IL2RA gene (which regulates the number of FOXP3+ regulatory T cells in peripheral blood), (3) various other risk loci, and (4) IBD at several new risk loci, including genetic variants associated with PSC progression.

It is worth mentioning that numerous animal models have been developed to study PSC. Given the uncertainties regarding the etiopathogenesis of PSC, it is not surprising that no single model has fully recapitulated its

### Table 2. Causes of Secondary Sclerosing Cholangitis and Mimics of PSC

<table>
<thead>
<tr>
<th>Category</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious Causes</strong></td>
<td>AIDS cholangiopathy (eg, Cryptosporidium parvum, cytomegalovirus)</td>
</tr>
<tr>
<td></td>
<td>Helminthic infection (eg, Clonorchis, Opisthorchis, Ascaris)</td>
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<tr>
<td></td>
<td>Recurrent pyogenic cholangitis (also referred to as oriental cholangiohepatitis)</td>
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<tr>
<td><strong>Intrinsic or Extrinsic Causes</strong></td>
<td>Mirizzi syndrome</td>
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<tr>
<td></td>
<td>Cholangiocarcinoma</td>
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<td></td>
<td>Diffuse intrahepatic malignancy</td>
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<td></td>
<td>Compressive lymphadenopathy</td>
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<td></td>
<td>Portal hypertensive biliopathy</td>
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<td></td>
<td>Postoperative strictures</td>
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<tr>
<td></td>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td><strong>Immunologic Causes</strong></td>
<td>IgG4-associated cholangiopathy</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic cholangitis</td>
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<tr>
<td></td>
<td>Mast cell cholangiopathy</td>
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<tr>
<td></td>
<td>Histiocytosis X</td>
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<td></td>
<td>Systemic vasculitis</td>
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<tr>
<td></td>
<td>Hepatic allograft rejection</td>
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<tr>
<td></td>
<td>Primary biliary cholangitis</td>
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<tr>
<td><strong>Ischemic Causes</strong></td>
<td>Posttransplant nonanastomotic strictures</td>
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<tr>
<td></td>
<td>Postintraarterial chemotherapy</td>
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<tr>
<td></td>
<td>Postradiation therapy</td>
</tr>
<tr>
<td><strong>Congenital and/or Idiopathic Causes</strong></td>
<td>Cholestocholic cyst (eg, Caroli disease)</td>
</tr>
<tr>
<td></td>
<td>Progressive familial intrahepatic cholestasis</td>
</tr>
</tbody>
</table>

IgG4, immunoglobulin G subclass 4; PSC, primary sclerosing cholangitis.
Figure. A conceptual model of the etiopathogenesis and natural history of PSC. Biliary epithelial cells (ie, cholangiocytes) exist in an environment with multiple potential etiologic mediators of hepatobiliary injury. Approximately 95% of bile acids are reabsorbed in the terminal ileum and, together with other intestinal molecules, are transported back to the liver via the enterohepatic circulation. Portal blood flows into hepatic sinusoids, wherein hepatocytes may take up and modify these molecules and secrete them into bile, which is synthesized by hepatocytes and delivered into canaliculi by means of specialized membrane transporters. Canalicular bile drains into the biliary tree and is modified by cholangiocytes as it percolates through the biliary tree. Cholangiocytes recognize (eg, through cell surface receptors) and react to various molecules and may release chemokines/cytokines, growth factors, and morphogens, initiating both autocrine and paracrine signaling cascades. With respect to the source of hepatobiliary injury, it remains uncertain whether there is (1) increased exposure to microbial molecules (eg, through the enterohepatic circulation, potentially facilitated by compromised intestinal barrier function), (2) alteration to the repertoire of microbial and other intestinal molecules (eg, due to microbial dysbiosis, xenobiotics), and/or (3) an aberrant or exaggerated cholangiocyte (or another hepatic cell) response to these molecules (eg, increased induction of cholangiocyte senescence and the senescence-associated secretory phenotype). In addition, host immunogenetics (4) likely modulate the development and/or impact of any of these variables and thus play a role in determining whether hepatobiliary injury resolves or if it persists and results in chronic disease (ie, PSC). These variables may also determine whether PSC progresses to its associated major clinical endpoints, including CCA and cirrhosis. Further investigation of the cellular, molecular, and microbial interactions and signaling represented in this figure is underway and expected to advance understanding of the etiopathogenesis of PSC.

CCA, cholangiocarcinoma; HLA, human leukocyte antigen; NOD, nucleotide-binding oligomerization domain receptor; PSC, primary sclerosing cholangitis; TLR, toll-like receptor.

biochemical, cholangiographic, histologic, and premalignant features, as reviewed recently. For example, the most widely studied model, the mdr2 (ABCB4) knockout mouse model, exhibits biochemical, histologic, and cholangiographic features of PSC; however, there is no male predominance, disease severity appears to be greater in female mice (not corresponding to PSC), there is no association with IBD or cholangiocarcinoma (CCA), and the primary mechanism of injury is not representative of PSC. Thus, there is no consensus regarding the optimal
model, which has hindered development of new therapies. Of note, other murine models include the experimental biliary obstruction murine model (C57BL/6J), chemically induced cholangitis models using agents such as lithocholic acid and 3,5-diethoxycarbonyl-1,4-dihydrocollidine, and models involving biliary epithelial and endothelial cellular injury. Also of note, an in-vitro model of persistent cholangiocyte injury has recently been developed to facilitate the study of PSC and other cholangiopathies, and demonstrates various features seen in isolated primary PSC cholangiocytes as well as cholangiocytes in PSC liver sections. However, although this represents a useful culture-based system, a better animal model is still needed.

Management

Pharmacotherapy

As previously mentioned, there are no approved pharmacotherapies for PSC. Ursodeoxycholic acid (UDCA) is the most extensively investigated agent in PSC, but its current use in this disease is controversial. Preliminary studies of UDCA in PSC showed improvement in liver biochemistries. However, the results of the 2 largest clinical trials of UDCA in PSC were disappointing; one trial used an intermediate dose of UDCA and showed only a trend toward statistically significant benefit, and the other trial used high-dose UDCA and was terminated early due to excess adverse events in the UDCA-treated group. Currently, some experts maintain that a trial of UDCA at intermediate doses (18-21 mg/kg body weight/day) should be considered.

Recent advances in understanding the pathobiologic pathways implicated in cholestatic liver diseases have led to the development of several new experimental agents targeting these pathways. Tables 3 and 4 summarize clinical trials that have been completed and those currently underway in patients with PSC. Some of the prominent clinical trial findings are noted in the following paragraphs.

24-Norursodeoxycholic Acid 24-Norursodeoxycholic acid (norUDCA), a C(23) homolog of UDCA, has been found to exert anticholestatic, anti-inflammatory, and antifibrotic effects in murine models. In a phase 2 clinical trial, 161 patients with PSC were randomized to 1 of 3 doses of norUDCA (500, 1000, or 1500 mg per day) or placebo for 12 weeks. Compared to placebo, norUDCA reduced serum alkaline phosphatase (ALP) levels by 12.3%, 17.3%, and 26.0% in the 500-, 1000-, and 1500-mg groups, respectively. No difference was reported in the incidence of pruritus between the treatment and placebo groups. A phase 3 trial of norUDCA in PSC is underway.

Obeticholic Acid Obeticholic acid (OCA) is an analog of chenodeoxycholic acid and an endogenous ligand of the farnesoid X receptor (FXR). FXR plays a key role in bile-acid homeostasis; its activation leads to transcriptional repression of the CYP7A1 gene, which encodes cholesterol 7α-hydroxylase (critical for bile-acid biosynthesis), through fibroblast growth factor 19 (FGF19) signaling and other pathways. OCA has recently been approved by the US Food and Drug Administration (FDA) as therapy for primary biliary cholangitis (PBC). Pruritus has been the most common and expected side effect in clinical trials, occurring in approximately 60% of patients treated with OCA in a dose-dependent manner, and 4% to 12% of patients discontinued OCA. Phase 3 clinical trial data are needed.

Simtuzumab Lysyl oxidase homolog 2 catalyzes the first step in the formation of cross-links in collagen and elastin and has been shown to contribute to hepatic fibrogenesis. In a phase 2 clinical trial, 234 patients with PSC were randomized to weekly injections of simtuzumab (75 or 125 mg) or placebo for 96 weeks. Neither dose of simtuzumab led to significant reduction in ALP. However, the role of simtuzumab in delaying the progression of fibrosis in PSC merits further study.

Alteration of the Microbiome Oral vancomycin is a nonsystemic, selective antibacterial drug; it has been found to be well tolerated and associated with significant improvement in ALP and other markers in both adult and pediatric patients with PSC, and pediatric patients have additionally experienced IBD-related symptom resolution. A phase 3 clinical trial of vancomycin in PSC has been completed, and the data are awaiting analyses. Metronidazole has been shown to decrease ALP and bilirubin in PSC; however, long-term safety is a concern, and longer-term clinical trials are lacking. Fecal microbiota transplantation has been investigated in 10 patients with PSC; 3 patients had at least a 50% reduction in ALP. With interventions aiming to treat PSC through alteration of the microbiome, it would be of interest to examine intestinal microbial and metabolic changes (eg, bile acids), as such data may reveal further mechanistic and therapeutic insights.

Interruption of the Enterohepatic Circulation of Bile Acids Bile acids are secreted into the small intestine and are reabsorbed by the liver via the enterohepatic circulation. At the level of the intestine, absorption of bile acids occurs through the apical sodium-dependent bile-acid transporter (ASBT). LUM001 (an ASBT inhibitor) and NGM282 (a FGF19 analog) are currently in phase 2 clinical trials for the treatment of PSC.
Table 3. Completed Clinical Trials for the Treatment of PSC

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Sample Size, n</th>
<th>Study Design</th>
<th>Summary of Main Findings</th>
</tr>
</thead>
</table>
| Penicillamine | 39 vs 31 (drug vs placebo) | Double-blind, placebo-controlled | • No significant effect on survival  
• 21% stopped the drug due to side effects |
| Prednisone plus colchicine | 12 vs 12 (drug vs placebo) | Double-blind, placebo-controlled | • Improved serum liver biochemistries  
• No significant difference in histologic change |
| Methotrexate | 12 vs 12 (drug vs placebo) | Double-blind, placebo-controlled | • Decrease in ALP  
• No significant difference in histologic and cholangiographic progressions |
| Tacrolimus | 10 Open-label | • Decrease in ALP, bilirubin, AST, and ALT  
• 31% stopped the drug due to side effects |
| Colchicine | 44 vs 40 (drug vs placebo) | Double-blind, placebo-controlled | • No significant improvement in symptoms, histologic progression, and survival |
| UDCA plus methotrexate | 19 Open-label | • No effect on serum liver biochemistries  
• 26% stopped methotrexate due to side effects |
| UDCA | 51 vs 51 (drug vs placebo) | Double-blind, placebo-controlled | • Improved serum liver biochemistries  
• No significant clinical benefit in time to death, histologic progression, doubling of bilirubin, and need for liver transplantation |
| UDCA | 76 vs 74 (drug vs placebo) | Double-blind, placebo-controlled | • No significant clinical benefit in primary endpoints (time to death or need for liver transplantation) in the Scandinavian trial  
• Early termination of the US trial due to futility and significant advantage of placebo over UDCA with regard to primary endpoints (time to development of cirrhosis, varices, cholangiocarcinoma, liver transplantation, or death) |
| Nicotine | 8 Open-label | • No significant improvement in serum liver biochemistries  
• 38% of patients reduced the dose due to adverse effects |
| Budesonide or prednisone plus UDCA | 6 vs 6 vs 6 (budesonide 9 mg vs prednisone 3 mg vs 10 mg) | Double-blind, randomized, pilot | • Improvement in ALP and pruritus in patients treated with prednisone |
| Budesonide | 21 Open-label, pilot | • Improvement in ALP, AST, and portal inflammation  
• Increase in bilirubin  
• Marked bone loss |
| Pentoxifylline | 20 Open-label, pilot | • No significant improvement in serum liver biochemistries |
| Cladribine | 4 Open-label, pilot | • No significant improvement in symptoms or serum liver biochemistries |
| Etanercept | 10 Open-label, pilot | • Resolution of pruritus in 40%  
• Increase in bilirubin  
• No change in ALP |
| Mycophenolate mofetil plus UDCA | 12 vs 13 (drug vs placebo) | Double-blind, randomized | • No significant improvement in serum liver biochemistries, liver histology, or cholangiographic findings |
| Metronidazole plus UDCA | 39 vs 41 (drug vs placebo) | Double-blind, randomized, placebo-controlled | • Improvement in ALP and histology compared to UDCA monotherapy group |
| Mycophenolate mofetil | 30 Open-label, pilot | • Improvement in ALP  
• 23% stopped the drug due to side effects |
| Infliximab | 6 vs 4 (drug vs placebo) | Double-blind, placebo-controlled | • No significant improvement in ALP or liver histology |
| Ecologic 641 (probiotic) | 7 vs 7 (drug vs placebo) | Double-blind, placebo-controlled | • No significant improvement in serum liver biochemistries or symptoms |

(Table continues on the following page.)
### Table 3. (Continued) Completed Clinical Trials for the Treatment of PSC

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Sample Size, n</th>
<th>Study Design</th>
<th>Summary of Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin in pediatric patients(^{95,96,99,146,147})</td>
<td>19 (total of the 5 studies)</td>
<td>Open-label, pilot, and case series</td>
<td>• Improvement in GGT, ALT, C-reactive protein, symptoms, and cholangiographic findings</td>
</tr>
<tr>
<td>Vancomycin or metronidazole in adults(^{98})</td>
<td>8 vs 9 vs 9 vs 9 (low-dose vs high-dose vancomycin vs low-dose vs high-dose metronidazole)</td>
<td>Randomized, double-blind</td>
<td>• Improvement in ALP (primary endpoint) in the vancomycin groups&lt;br&gt;• Decrease in bilirubin in the low-dose metronidazole group and trend toward significant decrease in the low-dose vancomycin group ((P=.06))&lt;br&gt;• Decrease in Mayo PSC risk score in the low-dose vancomycin group and low-dose metronidazole group</td>
</tr>
<tr>
<td>Vancomycin(^{97})</td>
<td>18 vs 11 (drug vs placebo)</td>
<td>Triple-blind, randomized, placebo-controlled</td>
<td>• Improvement in ALP, GGT, and symptoms</td>
</tr>
<tr>
<td>Rifaximin(^{31})</td>
<td>16</td>
<td>Open-label, pilot</td>
<td>• No significant improvement in serum liver biochemistries or symptoms</td>
</tr>
<tr>
<td>Minocycline(^{20})</td>
<td>16</td>
<td>Open-label, pilot</td>
<td>• Improvement in ALP</td>
</tr>
<tr>
<td>Bezafibrate(^{148})</td>
<td>15</td>
<td>Open-label, pilot</td>
<td>• Improvement in ALP, GGT, ALT, and AST</td>
</tr>
<tr>
<td>All-trans retinoic acid plus UDCA(^{49})</td>
<td>15</td>
<td>Open-label, pilot</td>
<td>• Improvement in ALP and ALT</td>
</tr>
<tr>
<td>Obeticholic acid(^{50})</td>
<td>76 (total)(^{b})</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>• Preliminary data presented at the 2017 AASLD meeting&lt;br&gt;• Improvement in ALP</td>
</tr>
<tr>
<td>Simtuzumab(^{51})</td>
<td>79 vs 77 vs 78 (drug 75 mg/day vs 125 mg/day vs placebo)</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>• Preliminary data presented at the 2017 EASL meeting&lt;br&gt;• No significant change in ALP, hepatic collagen, and fibrosis stage</td>
</tr>
<tr>
<td>NorUDCA(^{20})</td>
<td>39 vs 41 vs 39 vs 40 (drug 500 mg/day vs 1000 mg/day vs 1500 mg/day vs placebo)</td>
<td>Double-blind, randomized, placebo-controlled</td>
<td>• Improvement in ALP in all 3 arms&lt;br&gt;• Pruritus was the main side effect</td>
</tr>
</tbody>
</table>

\(^{a}\)Numerous other studies of UDCA alone have also been reported.\(^{1,2}\) \(^{b}\)76 patients were randomized to placebo \((n=25)\), drug 1.5 mg \((n=25)\), and drug 5 mg \((n=26)\) once daily for 12 weeks. Patients tolerating the drug were titrated from 1.5 mg to 3 mg \((n=22)\) or from 5 mg to 10 mg \((n=16)\).

AASLD, American Association for the Study of Liver Diseases; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EASL, European Association for the Study of the Liver; GGT, gamma-glutamyl transpeptidase; norUDCA, 24-norursodeoxycholic acid; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.

### Other Agents

BTT1023 (a human monoclonal antibody that binds vascular adhesion protein-1), mitomycin-C (an antineoplastic agent), curcumin (an anti-inflammatory, antifibrotic, and antisenescent agent), and cenicriviroc (a dual C-C chemokine receptor [CCR] 2 and CCR5 antagonist) are all undergoing evaluation for use in PSC.

### Endoscopic Management

With the advent of magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiography (ERC) has largely become a therapeutic modality in PSC.\(^{102}\) Of the various potential applications of ERC in patients with PSC (eg, choledocholithiasis, acute cholangitis, palliative stenting of CCA), one of the most common and important indications is management of dominant strictures (DSs), which are loosely defined as stenoses with a diameter of no more than 1.5 mm in the common bile duct or no more than 1 mm in a hepatic duct. DSs develop in approximately 45% of patients with PSC and may present (although not always) with progressive jaundice, pruritus, right upper quadrant pain, and/or acute cholangitis. It is recommended that patients with clinical signs and symptoms attributable to a DS undergo evaluation; ERC with or without cholangioscopy is typically necessary in this scenario to further examine the biliary tree, obtain specimens (eg, intraductal brushings and/or biopsies), and perform therapeutic maneuvers (mainly balloon dilation). Short-term biliary stenting may also be performed, although the available data do not support this as a routine practice due to increased risk of treatment-related adverse events.\(^{103}\)

Satisfactory remediation of DSs may require multiple ERC sessions, following which a subset of patients will demonstrate biochemical and symptomatic improve-
Table 4. Clinical Trials in Progress for the Treatment of PSC

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Study Characteristics and Outcome</th>
</tr>
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</table>
| Cenicriviroc (inhibitor of CCR2 and CCR5) | • NCT02653625 (open-label, phase 2)  
  • Outcome: % change in ALP from baseline |
| BTT1023 (vascular adhesion protein-1 inhibitor) | • NCT02239211 (open-label, phase 2)  
  • Outcome: % change in ALP from baseline |
| Curcumin (anti-inflammatory, antifibrotic, antisenescence) | • NCT02978339 (open-label, phase 2)  
  • Outcome: % change in ALP from baseline |
| NGM282 (fibroblast growth factor 19 analog) | • NCT02704364 (randomized, placebo-controlled, phase 2)  
  • Outcome: % change in ALP from baseline |
| GS-9674 (farnesoid X receptor agonist) | • NCT02943460 (randomized, placebo-controlled, phase 2)  
  • Outcome: % change in ALP from baseline |
| UDCA in pediatric PSC | • NCT01088607 (open-label, phase 1)  
  • Outcome: % change in GGT and ALT from baseline |
| Vancomycin in pediatric PSC | • NCT01802073 (open-label, phase 3)  
  • Outcome: % change in ALT, GGT, MRCP findings, and biopsy findings from baseline |
| Mitomycin C (antineoplastic) | • NCT01688024 (randomized, placebo-controlled, phase 2)  
  • Outcome: change in Mayo risk score from baseline |
| LUM001 (apical sodium-dependent bile-acid transporter inhibitor) | • NCT02061540 (open-label, pilot, phase 2)  
  • Outcome: Safety change in fasting serum bile acid from baseline |
| Fecal microbiota transplantation | • NCT02424175 (open-label, pilot, phase 1 and 2)  
  • Outcome: change in gut microbial profile, ALP, AST, ALT, and bilirubin from baseline |

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCR, C-C chemokine receptor; GGT, gamma-glutamyl transpeptidase; MRCP, magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.

ments.104,105 Therefore, it is thought that endoscopic therapy for DSSs may offer long-term benefit (at least in some patients) in addition to short-term benefit. However, it remains unclear which patients with PSC are most likely to experience long-term benefit from endoscopic intervention.106 Therefore, further research is needed.

**Surgical Management**

PSC is a common indication for LT globally and is the leading indication in Northern European countries. LT is the only potentially curative treatment currently available for PSC. Compared to PBC, for which the rate of LT has declined, the trend for LT for PSC has persisted. Specific indications for LT relatively unique to patients with PSC include recurrent acute cholangitis and refractory PSC-related symptoms (specifically fatigue and pruritus).107 In select, highly specialized centers, patients with PSC complicated by CCA meeting specific criteria are also candidates for LT.108

Recurrent PSC (rPSC) is an enduring clinical dilemma. It occurs in 1.8% to 36.8% of LT recipients and is associated with a greater need for repeat LT, a 4-fold increased risk of death, and decreased overall survival compared to patients who remain rPSC-free.109 Potential risk factors include the presence of IBD, use of a living related donor, young age, sex, and colectomy prior to LT.110-113

**Associated Disorders and Complications**

**Symptoms**

Data from referral centers have found that 45% to 55% of patients with PSC are symptomatic at the time of PSC diagnosis,114 and up to 22% of asymptomatic patients will develop symptoms of PSC, mainly fatigue and pruritus, within 5 years.114 Patients with PSC who have symptoms at the time of diagnosis have significantly worse survival and impaired health-related quality of life (HRQOL) than those who are asymptomatic at the time of PSC diagnosis.114 Significant reduction in HRQOL in terms of physical and social functioning, general and mental health, and bodily pain have been well described in PSC.115

**Inflammatory Bowel Disease**

The robust association between PSC and IBD has been known for decades, but the mechanism(s) by which these
2 diseases are related remains elusive. Several theories have been proposed, many of which involve crosstalk between the inflamed colon and the liver in susceptible individuals, or a connection to the enteric microbiome, as discussed earlier.

It is worth mentioning that even in the absence of concomitant PSC, abnormalities of serum liver biochemistries are frequently encountered in patients with IBD; 29% to 55% of patients with IBD have been reported to have concomitant serum liver test abnormalities. This is clinically important, as this subset of patients has a 4.8-fold higher risk of death compared to patients with IBD who have normal serum liver test results.

Portal Hypertension
Portal hypertension is a frequent complication of PSC. For example, esophageal varices develop at a rate of 5% every year in patients with PSC, including paraesophageal varices in patients with ileostomy (or other stomas). The management of portal hypertension and its related complications in patients with PSC is no different than in non-PSC patients, as outlined in societal guidelines.

Hepatic Osteodystrophy
Bone loss is a common complication of PSC and other cholestatic liver diseases. Severe osteoporosis has been found to be 6.1 times more prevalent in patients with PSC than in matched healthy controls. Age at least 54 years, body mass index no more than 24, and presence and duration of IBD have all been found to correlate with the presence of osteoporosis in patients with PSC. Moreover, patients with PSC (especially middle-aged patients) have been found to have a high rate of nonvertebral fracture, which in turn has a negative impact on physical and mental aspects of HRQOL. Patients with PSC should be screened at the time of diagnosis and then at regular intervals (every 1-5 years per the European Association for the Study of the Liver and every 2-3 years per the American Association for the Study of Liver Diseases (AASLD)). Calcium and vitamin D supplements (for osteopenia) and bisphosphonates (for osteoporosis) are also recommended.

Cancer Risk
Compared to the general population, there is a 2-fold increased risk of any cancer and a 40-fold increased risk in the risk of liver cancer in patients with PSC. Moreover, PSC confers a 400-fold increased risk of CCA, and nearly one-third of all-cause mortality in patients with PSC is from CCA. The risk of CRC in PSC is nearly an order of magnitude higher compared to that of the general population and even higher (nearly 30-fold) in patients with PSC-IBD.

Surrogate Endpoints
Serum, imaging, and other biomarkers that could potentially be used in clinical trials as surrogate endpoints in PSC represent an area of need and active study. ALP has perhaps been the most commonly investigated biomarker and appears to be promising for prognostic purposes as well as a surrogate endpoint for therapeutic response in PSC. A joint workshop (AASLD-FDA) in March 2016 recommended the use of a bilirubin-specific blood test (ALP) and measurement of hepatic stiffness and fibrosis by transient elastography or, ideally, histology when designing clinical trials in PSC.

Several prognostic models have been proposed for predicting major outcomes of PSC using parameters such as age, sex, hepatomegaly, splenomegaly, albumin, bilirubin, cholangiography, and histology. More recently, a spleen length of more than 120 mm has been found to be predictive of adverse outcomes (hepatic decompensation, liver-related death, and need for LT).

Summary
PSC is an important global cause of morbidity and mortality. Currently, there is no effective pharmacotherapy for PSC that prevents major adverse outcomes (eg, progression to cirrhosis, carcinogenesis, or need for LT). The rarity of PSC, limited understanding of its etiopathogenesis, paucity of validated surrogate markers, and long natural history are barriers to developing effective medical therapies. LT, the only treatment shown to extend the survival of patients with PSC, is reserved for highly select patients, and even then, rPSC can be problematic. There are several experimental agents in the pharmacologic pipeline, some of which have demonstrated encouraging results and are currently being evaluated in phase 2 (or higher) trials. Overall, there continues to be progress in the understanding and management of this disease, with potential on the horizon.

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References


