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REVIEW

Primary sclerosing cholangitis: diagnostic and management challenges

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Abstract: Primary sclerosing cholangitis (PSC) is a chronic immune-mediated disease affecting intra- and extrahepatic bile ducts, primarily the large biliary ducts. Clinical manifestations are broad, and the spectrum encompasses asymptomatic cholestasis, icteric cholangitis with pruritis, cirrhosis, and cholangiocarcinoma. Though rare, PSC has a propensity to affect young to middle-aged males and is strongly associated with inflammatory bowel disease. There is an unmet need for effective medical treatments for PSC, and to date, the only curative therapy is liver transplantation reserved for those with end-stage liver disease. This article addresses the diagnostic and management challenges of PSC, with a succinct analysis of existing therapies, their limitations, and a glimpse into the future of the management of this multifaceted pathologic entity.

Keywords: primary sclerosing cholangitis, management, PSC

Introduction

Primary sclerosing cholangitis (PSC) is a chronic immune-mediated disease of intra-and extrahepatic bile ducts, primarily affecting large ducts. Its insidious course related to progressive fibrostenotic stricturing of the biliary tree causes important clinical sequelae, including liver cirrhosis, portal hypertension, and end-stage liver disease. Unlike primary biliary cirrhosis (PBC), which affects small bile ducts and predominantly occurs in females, PSC has a proclivity toward males, with a median age of presentation of ~40 years.[1] It is strongly associated with inflammatory bowel disease (IBD), with a unique phenotype of ulcerative colitis involving rectal sparing, right colonic disease with backwash ileitis. In such cases where IBD overlaps with PSC, there is an identified higher risk of malignancy, and therefore, such a presentation necessitates rigorous colorectal cancer surveillance per multisociety guidelines.[2] There is also an independent association of PSC with cholangiocarcinoma (CCA). CCA in the PSC patient is typically diagnosed within the first 2 years of the diagnosis of PSC, and as it is often detected at an advanced stage, it often portends a guarded prognosis. Surgery for early CCA, and even liver transplant in selected cases of hilar CCA, is associated with clear survival benefit.[3] Why CCA is diagnosed within the first 2 years of receiving a diagnosis of PSC is unknown, but is a well-described observation. It is likely that a patient with PSC who develops "early" CCA may well have has occult PSC for a much longer period but simply did not have symptoms. At present, there is insufficient evidence on CCA screening guidelines for PSC.[4,5]

There are significant diagnostic and management challenges to PSC, largely owing to its frequent subclinical presentation with normal liver tests. To date, no approved or

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proven therapy exists for PSC, with pharmacotherapy aimed at treating symptoms and managing complications.[6] Immunosuppressants, bile salts, chelators (eg, cholestyramine for pruritus), and steroids have not shown significant benefit in clinical trials. Clearly, there is an unmet need for treatment in PSC, particularly as at least a third of patients will experience liver-related death without hepatic transplantation.[7] The purpose of this review is to address the diagnostic and management challenges of PSC, with a pointed focus on new developments and avenues of clinical research.

Clinical presentation and diagnosis of PSC

PSC often has a subtle presentation, with many patients presenting with asymptomatic cholestasis on blood work. If symptoms are present, they are often nonspecific, such as fatigue and pruritus. Pruritus can range from mild to disabling, resulting in severe excoriations and a decreased quality of life. The pathophysiology of pruritus is unknown, but accumulation of bile acids in the skin and endogenous opioid production are among the hypothesized etiologies.[8]

Other signs and symptoms include right upper quadrant abdominal pain, weight loss, and episodes of fever and chills. Cirrhotic symptomatology and portal hypertension sequelae (ascites and variceal hemorrhage) occur in advanced stages of PSC, though such manifestations are typically not present at diagnosis which usually occurs much earlier in the disease course in the current era of readily available biochemistry and liver imaging.[9]

On clinical exam, patients may be unremarkable, or present with jaundice, hepatomegaly, splenomegaly, and excoriations. Of these findings, hepatomegaly and splenomegaly are the most frequent. Complications of longstanding cholestatic liver diseases like PSC include metabolic bone disease and fat malabsorption with steatorrhea. Like many autoimmune diseases, PSC is associated with a range of other autoimmune conditions, features of which may also be present on clinical exam (Table 1).[1–3]

The diagnosis of PSC is made via a showing of elevated serum markers of cholestasis (AP, γGT) in combination with imaging findings – magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) demonstrating characteristic bile duct changes with multifocal strictures and segmental dilatations, when all other possible cholestatic disorders and secondary causes are excluded.[1–6]

One of the main diagnostic challenges of PSC is the need for it to be differentiated from secondary causes of sclerosing cholangitis and immunoglobulin G4 (IgG4)-associated cholangitis/autoimmune pancreatitis.[11] In addition, PSC overlap syndromes (ie, the concurrent presence of PSC with PBC or PSC with autoimmune hepatitis) should be considered as overlap syndromes are not uncommon though underdiagnosed in PSC patients, and lack of recognition would have adverse consequences given that both PBC and autoimmune hepatitis have proven treatments.[12] Clinicians should be mindful to exclude the many secondary causes to sclerosing cholangitis, especially IgG-4 disease which is imminently treatable (unlike PSC). A list of diseases that can mimic PSC is noted in Table 2:

Biochemical tests may reveal a fluctuating pattern, owing to a transient blockage of strictured bile ducts by biliary sludge or small stones. In contrast, serum aminotransferases are not usually elevated (typically <300 IU/L) and in early disease serum albumin is normal, whereas those with active IBD may have hypoalbuminemia.[1–7] Serology in PSC may reveal other findings (Table 3).

Several other autoantibodies, including antinuclear, anti-smooth muscle, anticardiolipin, thyroperoxidase, and rheumatoid factor, may be present, but their clinical significance has not been demonstrated. Whereas PBC is typically associated with antimitochondrial antibodies, such antibodies are notably absent in PSC. One study showed that in some instances, up to 97% of patients with PSC could be positive

Table 1 Common autoimmune diseases

Rheumatoid arthritis
Autoimmune thyroiditis
Celiac disease
Inflammatory bowel disease (IBD)
Insulin-dependent diabetes mellitus
Myasthenia gravis

Note: Data from Lerner et al.[10]

Table 2 Secondary causes of sclerosing cholangitis

IgG4-associated disease
Chronic bacterial cholangitis
Infectious or ischemic cholangiopathy
Cholangiocarcinoma
Choledocholithiasis
Diffuse intrahepatic metastases
Eosinophilic cholangitis
Intra-arterial chemotherapy
Mast cell cholangiopathy
Portal hypertensive biliopathy
Recurrent pancreatitis
Recurrent pyogenic cholangitis
Surgical biliary trauma

Note: Data from Gotthardt et al.[11]
Abbreviation: IgG4, immunoglobulin G4.

Table 3 Additional serological findings possible in PSC

Serologic finding	Prevalence
Hypergammaglobulinemia	30%
Increased serum immunoglobulin M (IgM) levels	40–50%
Atypical perinuclear antineutrophil cytoplasmic antibodies (P-ANCA)	30–80%
Human leukocyte antigen DRw52a	0–100% in various reports
Increased immunoglobulin G4 (IgG4)	9%

Note: Data from Pollock et al.[13]
Abbreviation: PSC, primary sclerosing cholangitis.

for one or more than one autoantibody, while 81% were positive for ≥3 autoantibodies.[14] That study demonstrated a lack of correlation among autoantibodies and PSC disease severity, except for the presence of anticardiolipin antibodies, which correlated well with the Mayo risk score.[14]

Increased serum levels of IgG4 (typically associated with autoimmune pancreatitis) has been demonstrated in some PSC patients.[15,16] One report demonstrated that in one sample, 9% of PSC patients had IgG4 levels above the upper limit of normal.[15] Serum IgG4 concentration >135 mg/dL makes IgG4 cholangiopathy a more likely diagnosis for which treatment with corticosteroids and other immunomodulatory agents may be warranted.[17] It is vital to not miss a diagnosis of IgG4 disease given that most patients respond to treatment.

Cholangiography – via MRCP, ERCP, or percutaneous transhepatic cholangiography – is typically used to confirm a diagnosis of PSC with a showing of characteristic multifocal stricturing and dilation of intrahepatic and/or extrahepatic bile ducts. MRCP is now the mainstay modality to diagnose PSC given its safety and noninvasiveness, with far superior sensitivity and specificity over both ultrasound and computer tomography. A meta-analysis of six studies demonstrated that the sensitivity and specificity of diagnosing PSC with MRCP were 86% and 94%, respectively.[18] MRCP demonstrates the classic "beaded" appearance of the bile duct, resulting from multifocal, short, annular strictures that alternate with normal or mildly dilated segments. The presence of dominant strictures on MRCP may indicate possible underlying CCA, often necessitating ERCP. ERCP is additionally indicated in patients with cholangitis to relieve biliary obstruction, and vigilance should always be exerted to exclude CCA vs benign strictures amenable to dilatation and stent insertion.

In classic PSC, focal strictures are present in the biliary tree, with normal intervening areas. One report found a distribution of strictures in the following areas: intrahepatic and extrahepatic bile ducts – 87%; intrahepatic bile ducts alone – 11%; and extrahepatic bile ducts alone – 2%. Gallbladder and cystic duct abnormalities may also be present – one study showed gallbladder abnormalities in 41% of patients, especially the cohort with extrahepatic PSC.[19] Six percent of patients had a gallbladder mass lesion, and more than half of those were gallbladder carcinoma, highlighting the importance of cholecystectomy following detection of such lesions.[20]

Early stage disease may not present with the typical "beaded" appearance of the biliary tree, and shallow ulcerations may indeed be the only cholangiographic finding. ERCP is indicated in such patients.

Small duct PSC (or "pericholangitis") presents a diagnostic challenge in many instances owing to the fact that such patients present with normal cholangiography, attributable to the fact that only small-caliber bile ducts are affected, and this entity is undetected with cholangiographic techniques.[21] Although small ductal PSC is comparable to classic PSC on biochemical and histologic terms, extant studies show a significantly better prognosis than classic PSC,[22–24] with a potential for degeneration into classic PSC.[23,25] One case series study showed that small duct PSC degenerated to classic PSC in 4 of 27 patients studied after a median of 72 months.[22]

Continuous bile duct destruction in PSC can cause end-stage liver disease, and other sequelae include:

- Fat-soluble vitamin deficiencies (A, D, E, and K)
- Metabolic bone disease
- Dominant biliary strictures
- Cholangitis and cholelithiasis
- Cholangiocarcinoma
- Gallbladder cancer
- Hepatocellular carcinoma (in patients with cirrhosis)
- Colon cancer (in patients with concomitant ulcerative colitis)

Diagnosis

Patients with underlying IBD presenting with a cholestatic pattern on liver biochemistry (especially an elevated alkaline phosphatase) should be investigated for possible PSC. Once a high degree of clinical suspicion is achieved, a firm diagnosis can be made via a showing of cholangiographic evidence of characteristic bile duct changes (multifocal strictures, segmental dilations) and the "notable absence of secondary explanations of sclerosing cholangitis." Liver biopsy is not required in patients with typical cholangiographic findings and a suggestive biochemical profile, although it is when small duct PSC is suspected in the differential. As stated earlier, patients with autoimmune liver diseases not uncommonly

have an overlap with another condition. As such, clinicians should actively exclude concurrent autoimmune hepatitis or PBC in patients with PSC.

Liver biopsy

Although percutaneous liver biopsy may reinforce a diagnosis of PSC, it is rarely used diagnostically[26] and may not be diagnostic given the patchy nature of PSC. Liver biopsy is reserved for instances of suspected small duct disease or overlap syndrome with autoimmune hepatitis. If biopsy is indicated, prophylactic antibiotic therapy prior to biopsy minimizes the risk of subsequent cholangitis.

On biopsy, PSC presents "classically" with fibrous obliteration of small bile ducts, with concentric replacement by connective tissue in an "onion skin" pattern, although this histology is found in less than 25% of liver biopsies. More often, histologic abnormalities in PSC are nonspecific and are similar to those in PBC. PSC staging, similar to that used in PBC, is based on the degree of involvement of portal triads and/or hepatic lobules (Table 4).[27]

Imaging

Transient elastography, a noninvasive measure of hepatic fibrosis via the assessment of liver stiffness properties, can be used to estimate the degree of hepatic fibrosis in PSC.[28] A recent study showed that magnetic resonance elastography (MRE) is also able to detect cirrhosis with high specificity. Moreover, liver stiffness obtained by MRE is predictive of hepatic decompensation in PSC.[29]

Etiology

The etiology of PSC disease development and progression is largely unknown. However, multiple mechanisms, imputing both the innate and adaptive immune systems, have been hypothesized.

First and foremost, the frequent coexistence of PSC and ulcerative colitis (with a known autoimmune pathophysiologic mechanism) suggests a common autoimmune pathway.[4] However, temporal differences in copresentation or the fact that only a small percentage of ulcerative colitis patients have PSC suggests a multifactorial etiology.[30] Portal venous bacteremia has also been proposed as a mechanistic pathway in PSC pathogenesis – an extension of the idea of an infectious trigger for autoimmunity. Specifically, chronic entry of bacteria in the portal circulation can result in an inflammatory reaction in the liver and bile ducts. Alternatively (or in addition), exposure to toxic bile acids produced by infectious mediators (colonic bacteria or viruses) can reinforce immunoactivation pathways.[31–33]

An alternate pathway proposed is tied to ischemic ductal injury – support for this hypothesis stems from studies demonstrating a remarkable resemblance in clinical, biochemical, and cholangiographic profiles in bile ductal ischemic injury and PSC – also confirmed via intra-arterial infusion of floxuridine.[34] Hence, ischemic injury to peribiliary arterioles may be one of the pathophysiological processes that occurs in PSC.

The general scientific consensus is that PSC is a multifactorial disease with a similar clinical presentation. Although the precise pathophysiological process is yet to be determined, it is believed that immunologically mediated bile duct injury in PSC is the common downstream sequela resulting in its clinicopathological presentation. Further, this immunopathological process often occurs in the backdrop of patients with a favorable genetic predisposition upon exposure to environmental triggers.

Management and treatment: current practices and challenges

Management of PSC

There are two major treatment goals in PSC: slow or reverse disease progression and management of symptoms of disease progression.

This section will review the current medical, endoscopic, and surgical therapies aimed at managing progressive PSC and cancer screening in patients with PSC. Unfortunately, **no** proven treatment slows or reverses progression of the disease. However, excellent outcomes may be achieved after liver transplantation (LT) for advanced disease. Best

Table 4 Staging of PSC

Stage	Features
I	Enlargement, edema, and scarring of the portal triads, and mononuclear cell infiltration with some piecemeal necrosis and damage to isolated bile ducts. Proliferation of interlobular bile ducts with mononuclear and polymorphonuclear cells may also be present, although the inflammation is usually less dense than in primary biliary cholangitis
II	Expansion of portal triads with fibrosis extending into the surrounding parenchyma
III	Bridging fibrosis
IV	Cirrhosis

Abbreviation: PSC, primary sclerosing cholangitis.

evidence suggests fertility does not seem to be reduced in patients with PSC, who are able to deliver healthy children without an apparent increase in risk for mother or child.[35] The management guidelines here are in accordance with a 2015 guideline from the American College of Gastroenterology[2] and a 2010 guideline from the American Association for the Study of Liver diseases,[1] along with the European Association for the Study of the Liver.

Pharmacological treatments

Several immunosuppressive and anti-inflammatory agents have been studied in PSC,[5,36] a summary of which is presented in Table 5.

Inasmuch as a plethora of agents have been studied in PSC, none has been conclusively proven to alter the natural history of the disease. Some data do suggest, however, that patients with decreased alkaline phosphatase during follow-up may have improved survival.[37]

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid, and it has been the most extensively studied putative pharmacological treatments for PSC. Its role in PSC management is very controversial. UDCA is expected to exert protective effects on cholangiocytes against cytotoxic hydrophobic bile acids (at doses between 13 and 15 mg/kg per day) via the stimulation of hepatobiliary secretion, protection against bile acid-induced hepatocyte apoptosis, and induction of antioxidants.[38]

Studies have shown that high-dose UDCA may improve liver biochemistry and curb hepatic inflammation, but there is definitively no transplant-free survival benefit.[39–46] Moreover, Lindor et al demonstrated that long-term high-dose UDCA is associated with higher rates of serious adverse events, including death.[2] As such, high-dose UDCA should not be used in the management of PSC.

A management complication in PSC is that once prescribed, one study showed that withdrawal of UDCA can precipitate a worsening of pruritus and biochemical test results.[47]

Table 5 Pharmacological agents studied in PSC

Pharmacological agents studied in PSC
Ursodeoxycholic acid
Glucocorticoids
Cyclosporine
Methotrexate
Vancomycin
Azathioprine and 6-mercaptopurine
Tacrolimus
D-penicillamine

Abbreviation: PSC, primary sclerosing cholangitis.

In this study, 3 months post-UDCA treatment, study patients noted 76% increase in mean alkaline phosphatase, 118% increase in gamma-glutamyl transpeptidase, 50% increase in bilirubin, 64% increase in alanine aminotransferase, 45% increase in aspartate aminotransferase, and 0.5-point increase in Mayo risk score (from baseline). Relevant clinical symptomatology, including pruritus, worsened post-UDCA discontinuation. However, certain limitations of the study limit its application. For instance, the study assessed surrogate outcomes (ie, biochemical profiles in lieu of clinically relevant outcomes such as survival), had possible selection bias, was of short duration, and notably was unblinded.[47,48]

The American Association for the Study of Liver Diseases 2010 guideline recommends against UDCA treatment in PSC,[1] whereas a 2015 guideline from the American College of Gastroenterology does not explicitly recommend against or for make a recommendation about using UDCA other than to note that it should not be used in doses >28 mg/kg/day.[2] The guidelines acknowledge the paucity of evidence pertaining to UDCA usage in PSC, safety concerns, and the lack of proven effect on clinically relevant end points.

Some studies suggest that UDCA treatment at a dose of 13–15 mg/kg/day can be safely pursued in patients, provided that after 6 months of treatment levels of alkaline phosphatase normalize or decrease by at least 40%.[48] An animal model study has shown promising results for a derivative of UDCA (24-norursodeoxycholic acid) in the treatment of PSC.[49]

Other treatments

A summary of other treatment options and evidence of their efficacy is presented in Table 6.

Endoscopic therapy

There exists an established cohort of PSC patients with a dominant extrahepatic biliary stricture that could be compatible with endoscopic therapy.[72–74] One study of 125 PSC patients showed that the proportion of patients with disease amenable to endoscopic therapy could be as high as 45%.[75] The proportion in such a cohort is dynamic, however, since patients who do not initially have a stricture may develop one over time, eg, 40% of patients without a stricture could develop one after 5 years of follow-up.[74]

However, no controlled trial has evaluated whether endoscopic treatment of a dominant stricture improves outcomes in PSC. In fact, one study showed no significant benefit in endoscopic treatment of PSC patients and warned against routine usage until clear benefit is established.[75] Notwithstanding this study, others have shown clinical and radiographic

Table 6 Other treatment options in PSC

Treatment	Efficacy and/or associated adverse outcomes
Glucocorticoid treatment	There is no concrete evidence of long-term benefits from solitary or combination glucocorticoid treatment.[50,51] Furthermore, glucocorticoid treatment may exacerbate osteopenia often observed in PSC patients.[52]
Cyclosporine and tacrolimus	Cyclosporine in PSC treatment[53] – no observed effect on symptoms or disease progression. One case reported radiologic and biochemical amelioration post-cyclosporine treatment followed by prednisolone; however, concomitant administration of UDCA is a potential confounder. In an open-label trial of tacrolimus (FK506) in PSC, serum bilirubin and alkaline phosphatase post-1-year tacrolimus treatment declined by over 50% and the degree of relevant clinical symptoms, ie, pruritus, improved.[54] However, no significant changes were observed on ERCP or histology.
Methotrexate (MTX)	Initially promising results showing putative improvement in liver function and histologic improvement post-12-month treatment.[55,56] Follow-up studies, however, were conflicting: • Oral pulse methotrexate treatment vs placebo: reduced serum alkaline phosphatase in treatment group,[57] with no corresponding changes on ERCP, LFTs, or outcomes. • MTX +UDCA offered no marginal benefit compared to UDCA treatment alone, and was associated with pulmonary fibrosis toxicity and hair loss.[58]
Azathioprine (AZA) and 6-mercaptopurine	No RCTs. Reports show varying results.[59,60] Others have routinely used AZA in the treatment of concurrent inflammatory bowel disease and have not noted any improvement in PSC.[61]
Penicillamine	Putative benefit based on finding of increased copper in the serum, urine, and liver in PSC patients.[62] However, RCT showed more frequent side effects.[63] Subsequent studies have clarified that increased copper stores may be secondary to cholestasis.[64]
Anti-TNF agents	Hepatic injury in PSC is postulated to be mediated, in part, via tumor necrosis factor (TNF). However, etanercept had no clinical benefit,[65] and infliximab was ineffective in a placebo-controlled, double-blind study in 24 patients.[66]
Antibiotics	Antibiotic treatment for PSC based upon animal studies showed a putative link between microbial intestinal growth and a PSC-like clinical state.[67] One controlled clinical trial of 80 patients showed that metronidazole + UDCA combination treatment vs UDCA + placebo significantly improved serum alkaline phosphatase levels and the Mayo risk score.[68] Notwithstanding this effect on liver biochemistry profiles, no significant effect was observed on disease progression based on liver histology and/or ERCP.[69–71]

Abbreviations: PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; ERCP, endoscopic retrograde cholangiopancreatography; LFT, liver function tests; RCT, randomized clinical trial.

improvement in PSC patients following endoscopic dilation with or without placement of a biliary stent.[72–75] These findings suggest that short-term endoscopic dilation/stenting may be beneficial for patients with a dominant extrahepatic biliary stricture.[2] However, the quality of evidence in this domain is weak, as most studies are observational and/or retrospective in nature, and therefore susceptible to significant selection bias.

Surgical therapy

PSC may also be managed surgically, and options include biliary reconstructive procedures, proctocolectomy (in patients with ulcerative colitis), and LT.[76]

Biliary reconstruction

Studies have shown that biliary reconstruction surgery with/without intraoperative stent insertion is very effective in avoiding jaundice and cholangitis, even for several years after the procedure.[77–79] However, cirrhotic patients may experience higher morbidity and mortality, with an increased risk of postoperative infection and fibrosis of the porta hepatis, potentially complicating future LT.[77]

A retrospective study has shown that LT is superior to biliary surgical procedures.[80] Hence, much attention has since shifted away from biliary reconstruction to liver transplantation.[81]

Proctocolectomy

Extant evidence suggests lack of a significant advantage in the usage of proctocolectomy in terms of clinical outcomes in patients with concomitant PSC and chronic ulcerative colitis.[82] In a retrospective examination of 45 patients, the study reported no significant differences in new onset of hepatomegaly, splenomegaly, esophageal varices, and ascites in patients with and without proctocolectomy. Biochemically, the serial changes in bilirubin, alkaline phosphatase, aspartate aminotransferase, prothrombin time, and albumin were similar. Histologic progression on liver biopsy did not differ between groups, nor did changes on serial cholangiograms. Proctocolectomy also had no effect on survival. Hence,

current best practice is reserving proctocolectomy for situations when indicated as a result of the colitis.

Liver transplantation

Patients with advanced liver disease secondary to PSC should be referred for LT provided that the Model for End-Stage Liver Disease (MELD) score is ≥15.[1] Outcomes for LT in PSC are comparable to transplants for other indications, with 5-year survival rates approximating 85%.[83–85] Evaluation for LT is muddled by the unpredictability of the disease course and high risk of biliary tract malignancy. The Mayo risk score is a prognostic tool useful for predicting the natural history of PSC. The indications for LT in PSC are, in large part, the same as those for other categories of end-stage liver disease.[86]

Special situations, notwithstanding a low MELD score, may necessitate LT on a case-by-case basis:

- Recurrent or refractory cholangitis
- Intractable pruritus
- Peripheral or hilar CCA <3 cm in diameter

Looking forward: prospective on novel treatment approaches in PSC

There is a notable gap in effective treatment strategies to improve survival or curb and/or prevent the need for LT in PSC. Existing evidence shows a lack of transplant-free survival benefit in patients receiving UDCA treatment (notwithstanding a reported improvement in liver biochemistry and histology), as described earlier. However, current research suggests that farnesoid X receptor (FXR) agonists (eg, obeticholic acid, 6α-ethyl chenodeoxycholic acid) and 24-norursodeoxycholic acid, a side-chain-modified UDCA derivate resistant to amidation which undergoes cholehepatic shunting, may be novel treatment options. An animal model of PSC demonstrated the plausible effectiveness of the 24-norursodeoxycholic acid derivative.[87,88] Fibrates, with their global pleiotropic and anti-inflammatory properties, may be an alternative novel treatment strategy.[89,90]

Summary

As discussed, there are several challenges in the diagnosis and management of PSC. From a diagnostic standpoint, PSC patients are often asymptomatic, which can lead to difficulties in establishing a firm diagnosis. Sometimes, a PSC diagnosis is achieved in the course of abnormal laboratory biochemical findings with or without the presence of compatible clinical symptoms, ie, fatigue and pruritus. Abnormal physical examination findings include jaundice, hepatomegaly, splenomegaly, and excoriations. On biochemistry, biochemical tests demonstrate a cholestatic pattern, with elevation of the serum alkaline phosphatase predominating in most patients. Imaging, namely MRCP in the current era, confirms the diagnosis with the presence of abnormal appearing bile ducts with wall thickening, dilations, and strictures.

There are two major goals of treatment in PSC: delay or reversal of the disease process and the management of progressive disease and its complications. While several immunosuppressive and anti-inflammatory agents have been studied in patients with PSC, none has shown a consistent benefit on overall or transplant-free survival, highlighting the dire need for medical management of this rare disease. LT is currently the treatment of choice for patients with advanced liver disease secondary to PSC.

Disclosure

The authors report no conflicts of interest in this work.

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