MINI REVIEW

Current consensus on the management of primary sclerosing cholangitis

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Summary Guidelines for the management of primary sclerosing cholangitis (PSC) have recently been published by both the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD). The current review focuses on the management of PSC, based on these guidelines. There is no established medical therapy for PSC. The role for UDCA in slowing the disease progression and improving survival is as yet unclear, and there are no specific recommendations for the general use of UDCA in this condition. Guidelines recommend that dominant bile duct strictures with significant cholestasis should be treated with biliary dilatation, with or without stenting. Prospective studies to define type, duration, optimal frequency and long-term effects of endoscopic therapy are needed. Liver transplantation is recommended for end stage disease and has excellent results. PSC patients with dysplasia in biliary brush cytology specimens should also be considered for transplantation. There is no evidence-based algorithm for the follow-up of PSC patients, but some regular investigations are recommended (surveillance colonoscopies in patients with IBD and ultrasound to detect gallbladder mass lesions).

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Introduction

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease characterized by inflammation and fibrosis of both intra- and extrahepatic bile ducts, leading to multifocal bile duct strictures. PSC is diagnosed at all ages, but most commonly around the age of 40 years. It is twice as common in males as in females. The clinical course and complications of PSC vary considerably, as some patients remain asymptomatic for many years while others experience alternating periods of symptoms or a more rapid progression. Overall, PSC has a progressive course with development of biliary cirrhosis and liver failure [1,2] and a median survival in the range of 11 to 18 years.

Diagnosis

Approximately 50% of PSC patients are asymptomatic at diagnosis. The most frequently reported complaints among symptomatic patients are jaundice, pruritus and right upper abdominal pain [3]. In Western countries, up to 80% of PSC...
patients have concomitant inflammatory bowel disease (IBD) [4], and the diagnosis of PSC is regularly revealed after investigation of elevated liver parameters in an IBD patient. Other autoimmune diseases, most often thyroid disease, diabetes mellitus, celiac disease and rheumatoid arthritis, are seen in up to 25% of cases [5].

PSC patients typically present with serum biochemical tests with a cholestatic profile. Alkaline phosphatase activity is often elevated two to three times [2,3]. A variety of autoantibodies have been observed in PSC, but none are disease specific [6]. Perinuclear antineutrophilic cytoplasmatic antibodies (pANCA), antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) are most commonly found. Elevated immunoglobulin (Ig) levels are also frequent.

A diagnosis of PSC is made in a patient with a cholestatic biochemical profile when cholangiography shows characteristic findings of bile duct irregularities with multiple strictures and segmental dilatations and causes of secondary sclerosing cholangitis are ruled out. Magnetic resonance cholangiography (MRC) is the method of choice, but endoscopic retrograde cholangiography (ERC) should be considered in equivocal cases [7,8].

A liver biopsy is not necessary for the diagnosis of PSC in patients with typical cholangiographic findings [7,8]. In the subpopulation of patients who presents with clinical and biochemical changes suggestive of PSC but with a normal cholangiogram, a liver biopsy is recommended to diagnose small duct PSC [9]. In patients with high serum aminotransferase activities, positive titres of autoantibodies (ANA and/or SMA) and markedly elevated IgG levels, a liver biopsy can be valuable to assess concomitant features of autoimmune hepatitis (PSC-AIH “overlap” syndrome). This condition is not a definite entity, but the recognition of this particular subset of patients may have implications on therapy [10].

IBD in PSC patients may be diagnosed both before and after the diagnosis of PSC. The majority of PSC-IBD patients are diagnosed with ulcerative colitis (UC), but 10% have Crohn’s disease (most often colitis) and another 10% have IBD unclassified. Typically, there is a total colitis that is mild with little or no symptoms. Backwash ileitis and rectal sparing are frequent. The IBD phenotype in PSC is so characteristic that the existence of a unique PSC-IBD condition has been suggested [11,12].

Risk of hepatobiliary and colorectal malignancies

Hepatobiliary malignancies

PSC patients carry a considerable risk of developing malignancies, especially localized to the bile ducts. Cholangiocarcinoma is seen in 7–15% of the patients, with a mean age at diagnosis of 45 years. It is worth recognizing that up to 50% of cholangiocarcinomas are diagnosed within one year of diagnosis of PSC and thereafter with a yearly incidence rate of 1.5% [13]. The prognosis of cholangiocarcinoma is dismal, with a median survival of only 6 months.

The diagnosis of cholangiocarcinoma in PSC remains a challenge. The best studied biomarker is the serum carbohydrate antigen19-9 (CA19-9). Median CA19-9 levels are higher in PSC patients with than without cholangiocarcinoma, but ranges are overlapping and elevated levels can also be seen in patients without biliary malignancies and in cases with bacterial cholangitis. In a study that used a cut-off value for CA19-9 of 130 U/mL, the marker had a sensitivity of 79% and specificity of 98% [14]. However, there is no study that addresses the value of CA19-9 as a screening tool in asymptomatic PSC patients. Distinction between benign and malignant biliary strictures by cholangiography in PSC is also challenging. Conventional brush cytology has variable sensitivity and specificity for the diagnosis of bile duct neoplasia. Cytological high-grade dysplasia has been reported to be associated with a sensitivity of 73% and specificity of 95% [15]. Diagnostic accuracy may be increased by the use of fluorescence in situ hybridization (FISH) [16], but techniques need to be validated and further explored. There is no evidence-based approach for surveillance of development of biliary malignancies, but ERC with brush cytology (and/or biopsy) sampling is recommended when clinically indicated [7,8].

Gallbladder cancer is seen in up to 2% of PSC patients, and gallbladder polyps are associated with a substantial risk (> 50%) of malignancy [17]. Guidelines advocate annual follow-up and removal of any gallbladder lesion. Hepatocellular carcinoma also develops in approximately 2% of PSC patients.

Colorectal malignancies

There is an increased risk of colorectal cancer in PSC patients with IBD beyond the risk seen in patients with IBD alone [18]. A meta-analysis identified an OR of 4.79 (95% CI 3.58–6.41) for development of colorectal cancer or dysplasia compared to patients with UC alone [19]. Annual colonoscopy with routine biopsies is therefore recommended to detect early dysplasia and initiate proper treatment. An initial colonoscopy with biopsies at diagnosis of PSC to diagnose subclinical IBD is also advised. If the initial colonoscopy is negative, it is not known whether colonoscopy should be repeated over time.

Recommendations for surveillance of development of hepatobiliary and colorectal malignancies are summarized in Fig. 1 [7,8].

Treatment

Medical therapy

The etiology and pathogenesis of PSC are unknown, but there is evidence of a genetic predisposition involving multiple genes that in combination with environmental factors and immunologic processes cause disease. The lacking knowledge on the pathogenesis has made it difficult to develop targeted medical therapy. Placebo-controlled, randomized trials with sufficient power have been difficult to set up due to the slow disease progression and the relative scarcity of patients. Nevertheless, a number of agents have been investigated in PSC.

Immunosuppressive and other agents

A variety of immunosuppressives (corticosteroids, budesonide, tacrolimus, cyclosporine, methotrexate, azathio-
Recommendations for follow-up of PSC patients

• In newly diagnosed PSC patients without known IBD, a full colonoscopy with biopsies is recommended.
• In PSC patients with IBD, surveillance colonoscopy with biopsies should be carried out every 1-2 years from the time of diagnosis of PSC to exclude colorectal neoplasia. IBD should be treated according to guidelines for IBD.
• Annual ultrasound is recommended to detect gallbladder mass lesions, and cholecystectomy is recommended in PSC patients with a gallbladder mass lesion of any size.
• There is currently no evidence-based screening strategy for cholangiocarcinoma in PSC, and no general recommendations for surveillance can be given. ERC with brush cytology (and/or biopsy) is recommended when clinically indicated (deterioration of clinical status and/or biochemical liver tests or recognition of a dominant stricture). In the absence of an evidence-based strategy, many clinicians use imaging modalities (ultrasound, MRI) in combination with CA19-9 at annual intervals.
• In PSC patients with liver cirrhosis, surveillance for development of hepatocellular carcinoma should follow general recommendations.

Figure 1 Recommendations for follow-up of primary sclerosing cholangitis (PSC) patients.

Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) is the most widely studied chemical agent in PSC. In the history of UDCA treatment in PSC expectations have altered due to shifting results of the trials performed. Pilot studies of UDCA in the early 1990s showed improvement in biochemical parameters and liver histology using dosages of 10—15 mg/kg per day [24]. A larger, double-blind, placebo-controlled study including 105 patients and using 13—15 mg/kg per day for 2 years, confirmed a biochemical effect, but not improvement in histological fibrosis, symptoms or disease progression [25]. Based on the discussion that even larger doses might be necessary to provide sufficient enrichment of the bile acid pool in cholestasis and that high doses might enhance a potential effect on immune regulation, new studies were performed. Pilot trials using UDCA 20—25 mg/kg per day showed encouraging improvement in histological fibrosis and cholangiographic findings [26]. In a double-blind, placebo-controlled study of 219 patients using UDCA doses of 17—23 mg/kg per day for 5 years, there was a trend towards improved survival in the UDCA treated group, but this did not reach statistical significance [27]. Finally, a recent randomized double-blind controlled trial giving 28—30 mg/kg per day UDCA to 150 patients was terminated due to the observation of an increased risk for death, liver transplantation and serious adverse events despite an overall biochemical improvement [28]. The mechanism for this unexpected negative effect is unclear.

A chemopreventive effect of UDCA on the risk of development of colon cancer in PSC patients with IBD has been suggested. In a retrospective study of 59 PSC patients with UC, a significantly reduced risk of colonic dysplasia in patients taking UDCA was observed although the rate of dysplasia in the control group was exceptionally high [29]. UDCA (13—15 mg/kg per day) was also associated with a significantly decreased risk of colorectal dysplasia or cancer in a follow-up of 52 patients who participated in a randomized, placebo-controlled trial [30]. In another study comparing 28 PSC patients with UC treated with UDCA to 92 untreated patients, a trend towards lower risk of colorectal neoplasia among UDCA treated patients was observed [31]. Prospective studies on the chemopreventive effect of UDCA on colorectal neoplasia in PSC patients with IBD are missing.

There is also limited evidence of a beneficial effect of UDCA on the risk to develop cholangiocarcinoma. A Scandinavian study of 255 PSC patients listed for liver transplantation over a period of 11 years observed that lack of UDCA treatment was an independent risk factor for developing hepatobiliary malignancies [32]. However, in the two large double-blind placebo-controlled prospective studies of UDCA in PSC, no effect on the risk of development of cholangiocarcinoma was observed [27,28].

The EASL and AASLD guidelines conclude somewhat differently in their recommendations on the use of UDCA in PSC:

• EASL guidelines:
  o the available data base shows that UDCA (15—20 mg/kg per day) improves serum liver tests and surrogate markers of prognosis, but does not reveal a proven benefit on survival. The limited data base does not yet allow a specific recommendation for the general use of UDCA in PSC,
  o currently there is suggestive but limited evidence for the use of UDCA for chemoprevention of colorectal cancer in PSC. UDCA may be particularly considered in high-risk groups such as those with a strong family history of colorectal cancer, previous colorectal neoplasmia or longstanding extensive colitis;
• AASLD guidelines:
  o in adult patients with PSC, we recommend against the use of UDCA as medical therapy,
  o we recommend against the use of UDCA as chemoprevention for colorectal cancer in patients with ulcerative colitis and PSC.

In the evaluation of the studies used as a basis for the recommendations, both guidelines conclude that the role for UDCA in slowing the progression of PSC-related liver disease is as yet unclear and that high dose UDCA may be harmful. Thus, the guidelines agree that low dose UDCA is safe, but efficacy unclear. They also agree that there is limited information available to support the use of UDCA as a chemopreventive agent. The EASL guidelines open for the use of UDCA, but do not actually recommend this therapy. The
AASLD guidelines interpret the lacking evidence for efficacy more strictly and recommend against the use of UDCA (but do not warn against deleterious effects of any other but high doses). The differences might possibly be interpreted on the background of a stronger tradition for the use of UDCA in PSC in Europe as compared with the US.

The decision to use UDCA or not as a general therapy in PSC patients remains a challenge, since a final conclusion on the potential role of UDCA at doses of 17–23 mg/kg per day has not yet been reached. The reevaluation of moderate doses of UDCA has been suggested [33], but then preferably in better-selected patients and with the support of better surrogate markers of efficacy. Other bile acids, like the 24-norUDCA, are under investigation and may prove to be therapeutic alternatives in the future.

**Endoscopic therapy**

Localized, high-grade strictures are a common finding in PSC patients. A dominant stricture has been defined as a stenosis with a diameter of less or equal to 1.5 mm in the common bile duct or less or equal to 1 mm in the hepatic duct. On follow-up, dominant strictures are seen in approximately 50% of patients [34]. Patients with dominant strictures appear to have a significantly reduced transplantation free survival compared with those without. There is indication of positive effects of endoscopic therapy (balloon dilatation and/or stenting) in observational studies showing biochemical and clinical improvement and improved survival compared to that expected by the Mayo risk model [35], however, randomized, controlled trials to evaluate the efficacy of endoscopic therapy are lacking. In opposition, it has been argued that variations in cholestasis are characteristics of the natural course of PSC, independently of dominant strictures [36].

Selection of patients for endoscopic therapy is important since disseminated intrahepatic changes can represent the main cause of cholestatic symptoms even in patients with major extrahepatic strictures. It is also important to evaluate the stricture before endoscopic therapy to exclude possible malignancy. Brush cytology or endoscopic biopsy is recommended.

Although both balloon dilatation and stent treatment, alone or in combination, have been used to treat dominant strictures in PSC patients for many years, the best method and the optimal frequency of the endoscopic approach have not been determined. In a retrospective study comparing balloon dilatation alone with dilatation followed by stent placement, stent therapy did not give additional benefit and was associated with more complications [37]. Others have reported that short-term stenting (up to 3 weeks) is both effective and safe [38]. A prospective, randomized, multicentre intervention trial to compare the efficacy of single session balloon dilatation and short-term stent placement in dominant bile duct strictures in PSC patients is planned by the International PSC Study Group.

Both EASL and AASLD recommend treatment with biliary dilatation of dominant strictures with significant cholestasis in PSC. Biliary stenting should be reserved for cases where stricture dilatation and biliary drainage are unsatisfactory [7,8]. Both guidelines recommend prophylactic antibiotic therapy in relation to endoscopic procedures.

**Liver transplantation**

The only therapy that can cure PSC is a liver transplantation, and PSC is an important indication for such treatment. In the Nordic countries, PSC is the most common indication for liver transplantation (~17%). The outcome of transplantation is very good with approximately 85% 5-year survival [39]. However, recurrence of PSC is seen in 20–25% of transplanted patients, and the effect of recurrence on graft survival is currently undetermined [40].

Liver transplantation is recommended in patients with advanced disease by both EASL- and AASLD guidelines [7,8]. Patients with recurrent bacterial cholangitis, intractable pruritus and severely impaired quality of life due to fatigue, should also be considered for transplantation. Guidelines also recommend that patients with biliary dysplasia are considered for transplantation to remove malignant development at an early stage before progression to invasive cholangiocarcinoma [15]. A small group of patients diagnosed with cholangiocarcinoma, but with very limited disease, can also benefit from transplantation. Selection of patients is crucial, and treatment includes neoadjuvant radiochemotherapy according to protocols [41].

**Treatment of other disease complications**

**Pruritus**

Pruritus can be a disabling complication of cholestasis. The exact mechanism is unclear and intensity is characteristically fluctuating. Dominant strictures available to endoscopic therapy should be diagnosed and treated. Guidelines for the management of pruritus in cholestatic liver disease should be followed in cases where endoscopic therapy is ineffective [7].

**Metabolic bone disease**

Cholestatic patients are at increased risk of metabolic bone disease. EASL and AASLD give similar guidelines for diagnosis and treatment of hepatic osteodystrophy in PSC. A bone mineral density examination is recommended at diagnosis to assess the presence of osteopenia or osteoporosis and should thereafter be carried out at regular intervals depending on degree of cholestasis and individual risk factors. Dietary supplementation with calcium and vitamin D should be considered in all patients with cholestatic liver disease although this advice is not evidence-based. Bisphosphonates are indicated/suggested in the case of osteoporosis [7,8].

**Cirrhosis and portal hypertension**

Symptoms of liver cirrhosis and portal hypertension like oesophageal varices, ascites and encephalopathy should be handled according to general practice for complications of portal hypertension. Cirrhotic patients also have an increased risk of developing hepatocellular carcinoma, and surveillance should be made according to general recommendations for the cirrhotic patient [42,43].

Recommendations for treatment of PSC and its complications are summarised in Fig. 2.
Recommendations for treatment of PSC and its complications

- Corticosteroids and other immunosuppressants are not indicated for treatment of PSC in adults except in cases with concomitant features of AIH (‘overlap’ syndrome).
- The role for ursodeoxycholic acid (UDCA) in slowing the disease progression in PSC is as yet unclear, and specific recommendations for the general use of UDCA in PSC cannot be given. There is suggestive, but limited evidence for a chemopreventive effect of UDCA regarding colorectal cancer. AASLD recommends against the use of UDCA in PSC, whereas the EASL guidelines open for its use and states that UDCA may be particularly considered as chemoprevention in patients with increased risk of colorectal cancer (family history, previous colorectal neoplasia or long-standing extensive colitis).
- Dominant bile duct strictures with significant cholestasis should be treated with biliary dilatation. Biliary stenting should be saved for cases of insufficient biliary drainage after dilatation. Prophylactic antibiotic treatment is recommended before biliary tract procedures.
- Liver transplantation is recommended in patients with late-stage PSC and may be considered in patients with biliary dysplasia and severe recurrent bacterial cholangitis.
- Bone density measurements to screen for osteopenia or osteoporosis are recommended at diagnosis and later with regular intervals (2-3 years). Calcium and vitamin D supplements should be considered in all PSC patients, although not evidence-based. Bisphosphonates are recommended for treatment of osteoporosis.
- Oesophageal varices, ascites and encephalopathy should be handled according to general practice for complications of portal hypertension.

Figure 2 Recommendations for treatment of primary sclerosing cholangitis (PSC) and its complications.

Conclusion and perspectives

It remains a major challenge to further elucidate the pathogenesis of PSC to identify potential targets of medical therapy. Endoscopic therapy with balloon dilatation with or without stent placement is widely applied, but efforts should be made to decide on the most effective approach regarding type, frequency and duration of treatment. PSC patients are good candidates for liver transplantation with favourable results, but with a risk of recurrence that currently is poorly understood. Molecular methods with high diagnostic accuracy for early stage cholangiocarcinoma should be further explored so that patients can be referred for liver transplantation before the development of invasive bile duct cancer.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References