

Controversies in the management of primary sclerosing cholangitis

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Abstract

Primary sclerosing cholangitis (PSC) remains a rare but significant disease, which affects mainly young males in association with inflammatory bowel disease. There have been few advances in the understanding of the

pathogenesis of the condition and no therapeutics with proven mortality benefit aside from liver transplantation. There remain areas of controversy in the management of PSC which include the differentiation from other cholangiopathies, in particular immunoglobulin G4 related sclerosing cholangitis, the management of dominant biliary strictures, and the role of ursodeoxycholic acid. In addition, the timing of liver transplantation in PSC remains difficult to predict with standard liver severity scores. In this review, we address these controversies and highlight the latest evidence base in the management of PSC.

Key words: Immunoglobulin G4 related sclerosing cholangitis; Cholangiocarcinoma; Primary sclerosing cholangitis; Liver transplantation; Dominant strictures

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Core tip: There have been few advances in therapeutics for primary sclerosing cholangitis (PSC) and there remain areas of controversy in the management of PSC. In this review, we address these controversies, which include the differentiation of PSC from other cholangiopathies, in particular immunoglobulin G4 related sclerosing cholangitis, the management of dominant biliary strictures, the role of ursodeoxycholic acid, and the timing of liver transplantation.

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cho-

Table 1 Differential diagnosis for primary sclerosing cholangitis

Vascular	Hepatic artery thrombosis
	Portal hypertension bilopathy
	Portal cavernoma associated cholangiopathy
	Intra-arterial chemotherapy
Trauma	Sickle cell disease related cholangiopathy
	Trauma post cholecystectomy
Infections	Abdominal trauma
	AIDS related cholangiopathy
Benign	Recurrent pyogenic cholangitis
	Intraductal stone disease
Malignancy	Cholangiocarcinoma
	Autoimmune sclerosing cholangitis
Autoimmune	IgG4 related sclerosing cholangitis
	Systemic vasculitis
Other	Recurrent pancreatitis
	Sclerosing cholangitis in critically ill patient
	TPN related cholangiopathy
	Histocytosis X

IgG4: Immunoglobulin G4; TPN: Total parenteral nutrition; AIDS: Acquired immune deficiency syndrome.

lestatic disorder characterised by inflammation and fibrosis of intrahepatic and extrahepatic bile ducts, resulting in multifocal biliary strictures^[1]. The pathogenesis of PSC remains unclear but hypotheses include genetic factors^[2], lymphocyte recruitment and activation^[3], portal bacteraemia^[4] and bile salt toxicity^[5].

PSC commonly affects males^[6] with a median age at diagnosis of 35 years^[6,7]. In addition, there is a significant association with inflammatory bowel disease (IBD)^[8], hepatobiliary malignancies^[9] and colorectal cancer^[10]. A key aspect in the management of PSC is surveillance for the development of these conditions. Patients commonly present with cholestatic liver enzymes and a normal bilirubin^[8]. The demonstration of a cholangiopathy is essential for the diagnosis of PSC^[11]. Characteristic ERCP findings include diffuse multifocal strictures and irregularities, with normal or minimally dilated segments in between giving rise to the characteristic beaded pattern^[12]. The use of MRCP has been increasing, partially driven by the complication rate of 11% following ERCP^[13], and a comparable sensitivity and specificity to ERCP^[14].

PSC is strongly associated with IBD, with prevalence of 63%-81%^[8,15], most commonly ulcerative colitis (UC), in 86%-88%^[15,16]. The temporal relationship of the 2 conditions can be variable, although IBD usually precedes the diagnosis of PSC. Patients with colitis typically have mild symptoms and are sometimes asymptomatic^[17]. Endoscopic findings are very different between PSC and non-PSC groups, with more pancolitis, backwash ileitis, and rectal sparing in those with PSC^[16]. Colonoscopy with biopsies is recommended as part of the diagnostic work-up in any new diagnosis of PSC^[18]. In addition, patients with PSC and IBD have a significantly higher risk of colorectal cancer than those with IBD alone^[10] (OR = 4.79, 95%CI: 3.58-6.41).

To date, certain aspects remain controversial in the management of PSC. They include the differentiation

of PSC and from other causes of sclerosing cholangitis in particular immunoglobulin G4 related sclerosing cholangitis (IgG4-SC), the optimal management of dominant biliary strictures at endoscopy, the role of ursodeoxycholic acid (UDCA), its optimal dose and likely benefit, and the timing of liver transplantation. In this review article we will address these controversies.

SEARCH STRATEGY

We searched PubMed using the following terms: "primary sclerosing cholangitis", "secondary sclerosing cholangitis", "cholangiocarcinoma", "IgG4 related disease" and "liver transplantation". We included data from full-text articles, published in English. Further relevant articles were identified from the reference lists of review articles and guidelines from liver societies.

THE DIFFERENTIAL DIAGNOSIS OF PSC

Secondary sclerosing cholangitis (SSC), includes a heterogeneous group of conditions where different insults (*i.e.*, infections, thrombosis, iatrogenic, trauma) can give rise similar clinical characteristics to PSC^[19] (Table 1). A single-centre series of 31 patients with SSC, identified a shorter transplant free survival (median 72 mo) when compared to controls with PSC, and with no complicating cases of cholangiocarcinoma (CCA)^[20]. A more recently described entity is sclerosing cholangitis in critically ill patients. This may be related to hepatic hypoperfusion and biliary cast formation^[21], and has a particularly aggressive clinical manifestation with a reported transplant free survival of approximately 1 year^[22].

IgG4 disease was first described in 1995 in patients with pancreatitis, raised serum IgG levels and a response to corticosteroids^[23], which was termed autoimmune pancreatitis (AIP). Extra-pancreatic biliary changes that were found on ERCP, in addition to lymphoplasmocytic infiltration and fibrosis on liver biopsy, suggested an extra-pancreatic biliary component to the disease^[24]. This has now been termed IgG4-SC, and is the commonest extra-pancreatic manifestation of AIP^[25].

IgG4-SC is an important differential diagnosis for PSC, with a different natural history and treatment profile. There are some subtle differences and similarities between PSC and IgG4-SC (Table 2). Similar to PSC, IgG4-SC has a male preponderance, however it usually presents in older patients^[26]. The clinical presentation in patients with IgG4-SC is more commonly acute onset of obstructive jaundice, than is seen in classical PSC^[25], and was evident in 75% in one series^[27]. IgG4-SC can also be diagnosed in asymptomatic patients with AIP, either at initial diagnosis or during follow up. The data on rates of co-existent IBD are limited to small case series from Japan^[27] and United Kingdom^[28], which show much lower detection of IBD when compared to patients with PSC. Serum IgG4 is elevated in 76% of patients with AIP, and total IgG is elevated in 42%^[29]. An elevated

Table 2 Primary sclerosing cholangitis compared to immunoglobulin G4 related sclerosing cholangitis (adapted from Joshi 2014)

	PSC	IAC
Gender (M:F)	1.5:1	7:1
Age of onset	Young (< 40 yr)	Older (> 50 yr)
Presentation	Cholestatic liver enzymes	Obstructive jaundice
Cholangiogram	Beading, band-like strictures, peripheral pruning	Long smooth strictures, low CBD strictures
Cholangioscopy	Dilated and tortuous vessels	Scarring, pseudo diverticula
Raised serum IgG4 levels	< 20%	> 70%
Pancreatic involvement	< 5%	> 80%
Cholangiocarcinoma	9%	Rare
Association with IBD	80%	< 10%
Response to steroids	Rare (IgG4 + ve PSC)	97%

M: Male; F: Female; PSC: Primary sclerosing cholangitis; IgG4: Immunoglobulin G4; IBD: Inflammatory bowel disease.

serum IgG4 level however is not sufficient to diagnose IgG4-SC, especially as the optimal cut-off value has not been defined and may differ for subgroups of IgG4-SC^[30].

There are 4 cholangiographic patterns of disease which vary in the level of stricture location^[31]. These are usually long smooth strictures as opposed to beading and band-like strictures in PSC. Depending on the pattern of disease, hepatobiliary malignancy may form part of the differential diagnosis, hence the role for ERCP to obtain samples from dominant strictures^[26]. Brush cytology during ERCP is beneficial in detecting malignancy, however intra-ductal or ampullary biopsies are required to confirm the diagnosis of IgG4-SC. Histological features of IgG4 related disease are infiltration of plasma cells and IgG4 positive plasma cells, storiform fibrosis, and obliterative phlebitis^[32,33]. Cholangioscopy in IgG4-SC patients has demonstrated dilated and tortuous vessels in 69%, a feature that was not observed in patients with PSC^[34]. In addition, less scarring and pseudo diverticula were noted in IgG4-SC patients compared to the PSC patients. When a second procedure was carried out after steroids (32 to 93 d), a significant improvement in stenosis, dilated and tortuous vessels, and mass lesions were identified^[34].

The cholangiopathy of IgG4-SC is very responsive to corticosteroids and an improvement in bilirubin can be detected within 8 wk of therapy^[28]. We recommend 30-40 mg prednisolone o.d. for 4 wk followed by a slow wean, blood test monitoring and imaging at 6 wk^[26]. Regular clinical assessment in this period is required due to the potential risk of cholangitis and sepsis. A follow up study of IgG4 related disease patients, which included 84 with IgG4-SC, demonstrated a response to steroids in 97% but also a high relapse rate of 50%, which was not predicted by initial or on treatment serum IgG4 levels^[35]. Five percent were diagnosed with cirrhosis (histological and clinical) and one patient required liver transplantation. It has been hypothesised that unlike PSC, which presents as a more indolent disease with established fibrosclerotic changes, the biliary strictures found in IgG4-SC are at an earlier more inflammatory stage of the disease process which is more responsive

to steroids^[36]. IgG4-SC patients have not been identified to develop CCA^[37], which is in contrast to PSC which confers a significant risk of CCA^[38].

MANAGEMENT OF DOMINANT BILIARY STRICTURE

A dominant stricture is defined as a narrow biliary stricture which impedes normal bile flow, with a diameter < 15 mm in the CBD/CHD or < 10 mm in the hepatic duct^[39]. In a follow up study of 9.8 years, a new dominant stricture was found in 63% of patients^[40]. Where liver biopsies were available, those with more advanced liver disease histologically were more likely to have dominant strictures^[39,40]. The mean survival of patients with dominant strictures was significantly poorer than those without^[40] (14 years vs 23 years, $P = 0.01$). Data from long-term follow up studies (7.1 and 9.8 years), demonstrates that patients who developed CCA, almost all had pre-existing dominant strictures^[40,41].

The most concerning differential diagnosis of a dominant stricture is CCA. When a new dominant stricture is identified, a malignant aetiology needs to be excluded using the combination of axial imaging, biliary cytology and/or histology. Therapy for dominant strictures should be offered to all symptomatic patients, and current guidelines recommend endoscopic dilatation with or without stenting^[40]. A prospective study of 52 patients with dominant strictures who underwent biliary intervention (stent or dilatation) identified a significantly better survival free of transplantation at 3, 5 and 7 years, when compared to that predicted by the Mayo Risk Score^[39].

Despite an improvement in prognosis with biliary intervention, the evidence for the ideal therapeutic strategy is not clear and guidelines suggest endoscopic dilatation, but do not give definitive guidance regarding stenting^[40]. This decision is a balance between the likelihood of biochemical improvement and the risk of intervention. A large retrospective review of all biliary interventions performed for dominant strictures revealed a similar clinical and biochemical course independent

of modality of intervention, although a lower procedure related complication rate was evident in the balloon dilatation group compared to those who underwent stenting^[42]. A trial of short term temporary biliary stents (mean 11 d) demonstrated an improvement in symptoms, with only 20% requiring further intervention in 1 year and 40% in 3 years^[43]. However, within the same study a procedure related complication rate of 15% was reported^[43].

A prospective multicentre study of patients with compensated PSC without recent biliary intervention, comparing balloon dilatation to short-term plastic stenting (1-2 wk) is underway (www.clinicaltrials.gov, NCT01398917). The main endpoints of the study include re-intervention free survival time at 2 years, change in cholestatic symptoms and biochemistry at 3 mo, and adverse incidents. Data from this study may guide us towards the optimal management strategy for this group of patients.

Cholangioscopy allows for direct optical visualisation and guided biopsies of the biliary epithelium and biliary lesions. It is another diagnostic tool in the management of dominant strictures. In a multi-centre retrospective study of 52 patients with sclerosing cholangitis (48 PSC, 4 IgG4-SC) who underwent 54 procedures for suspicious biliary strictures, the sensitivity and specificity (50% and 100%, respectively) for diagnosing malignancy was comparable to a control group of patients investigated for a single biliary stricture^[44]. Failure of cannulation rate was higher in the sclerosing cholangitis group (15%), and was related to difficulty cannulating the narrowed bile duct. The adverse events rate was 17%, with 11% developing cholangitis post procedure despite prophylactic antibiotics.

A further single centre prospective study of patients with PSC referred for cholangioscopy, reported their findings in 41 consecutive patients^[45]. Cholangioscopy identified ductal stones in 56% of patients (of which 30% were not previously identified on cholangiography), and achieved complete or partial clearance in approximately three quarters of patients. One patient was diagnosed with CCA. Two of the 8 patients who proceeded to transplant were diagnosed with CCA on their explants, both of whom had undergone cholangioscopy directed biopsies which were negative. It appears that the diagnostic accuracy may be related to difficulties in deciding which parts of a stricture to biopsy, especially as it may contain both inflammation and cancer^[44]. The addition of narrow-band imaging increases the biopsy rate but does not improve the dysplasia detection rate^[46].

The use of fluorescence *in situ* hybridisation (FISH) on ERCP brushing samples has been studied in patients with PSC and suspicion of CCA. A recent meta-analysis involving 828 patients from 8 studies, identified a pooled sensitivity and specificity of 68% and 70%, respectively, and 51% and 93% respectively for the 6 studies characterising FISH polysomy^[47]. In a patient with PSC, a dominant stricture and FISH polysomy, there was a 88% specificity for CCA^[48], and where

there was serial FISH polysomy detected with no overt evidence of malignancy, 69% were diagnosed with CCA upto 2.5 years post initial test^[49]. FISH may play a role in patients with high pre-test probability of CCA, or where CCA is suspected with no clear radiological or histological evidence. However it needs to be used with caution due to the low sensitivity, and importantly the risks of repeated invasive tests and the implications of delaying or excluding patients from liver transplantation.

THE ROLE OF UDCA

UDCA is a hydrophilic bile acid which was studied in patients with PSC following the discovery of its efficacy in chronic cholestatic conditions, in particular primary biliary cirrhosis^[50].

Small prospective studies using UDCA at different doses in patients with PSC showed improvement in symptoms and liver biochemistry (8-16 mg/kg^[51], 10 mg/kg^[52]), as well as histology (13-15 mg/kg^[53]). Further studies at standard (13-15 mg/kg)^[54] and higher doses (17-23 mg/kg)^[55] did not demonstrate any survival advantage or prevention of CCA, although none were powered sufficiently to answer this hypothesis. A more recent randomised placebo controlled study at high dose (28-30 mg/kg) was terminated early due to an interim analysis demonstrating significantly higher rate of serious adverse events in the high dose UDCA group^[56]. A subsequent meta-analysis on the use of UDCA in PSC concluded that there is no significant difference in mortality, histology or risk of CCA, at both standard and higher dose^[57], and guidelines advise against its use in PSC^[18] (Table 3).

Patients with PSC and IBD have an increased risk of developing colorectal dysplasia compared to patients with IBD alone^[10]. Although the true mechanisms for this increased risk remains unclear, one proposed hypothesis is the increased exposure of the colon to toxic bile acids^[58]. Attention has therefore turned to UDCA with some data suggesting a possible chemo-preventative role for UDCA in reducing the incidence of colorectal cancer in PSC and UC patients^[59]. A meta-analysis also suggested a benefit of using low-dose UDCA (8-13 mL/kg per day) but there was significant heterogeneity of the studies^[60]. A double-blind, placebo controlled multicentre trial of 56 patients with PSC and UC given high dose UDCA (28-30 mg/kg) identified a significantly increased risk of colorectal cancer and dysplasia on both univariate, HR = 4.44 (1.30-20.1), and multivariate analysis, HR = 5.97 (1.39-41.44), in those receiving UDCA^[61]. At present based on published guidelines, the use of UDCA for chemo-prevention for colorectal dysplasia is not recommended^[18].

THE ROLE AND TIMING OF LIVER TRANSPLANTATION

Liver transplantation is an effective treatment for PSC,

Table 3 Important studies involving ursodeoxycholic acid

Ref.	Dose and study design	Number UDCA (number placebo)	Follow up	Parameter	Outcome
Chazouillères <i>et al</i> ^[51]	8-16 mg/kg UDCA alone	15	6 mo	Liver enzymes	Improved
O'Brien <i>et al</i> ^[52]	10 mg/kg UDCA alone	12	37 mo	Liver enzymes	Improved
Beuers <i>et al</i> ^[53]	13-15 mg/kg UDCA vs placebo	6 (8)	12 mo	Liver enzymes Histology	Improved Improved
Lindor <i>et al</i> ^[54]	13-15 mg/kg UDCA v placebo	51 (51)	2.2 yr	Liver enzymes Time to treatment failure Time to liver transplant	Improved No change No change
Olsson <i>et al</i> ^[55]	17-23 mg/kg UDCA vs placebo	110 (109)	5 yr	Liver enzymes Transplant free survival	No change No change
Lindor <i>et al</i> ^[56]	28-30 mg/kg UDCA vs placebo	76 (74)	Terminated	Liver enzymes Primary end-point Serious adverse events	Improved Increased Increased

UDCA: Ursodeoxycholic acid.

Table 4 Mayo risk score¹

Parameter	Weighting
Age	+ 0.03 × absolute value
Bilirubin	+ 0.54 × log
Aspartate aminotransferase	+ 0.54 × log
Variceal bleeding	+ 1.24 × yes/no
Albumin	- 0.84 × absolute value

¹The link is: <http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/revised-natural-history-model-for-primary-sclerosing-cholangitis>.

with survival post-transplant 93.7% at 1 year, 86.4% at 5 years, 69.8% at 10 years^[62]. The indications for liver transplantation are similar to other aetiologies of chronic liver disease, but also include intractable pruritus and recurrent cholangitis. Organ allocation varies according to national policy. Recurrence of PSC following liver transplantation occurs in up to 20% of patients at 5 years^[63,64]. The diagnosis of PSC recurrence post-transplant can be challenging due to the variety of causes of biliary strictures and cholangiopathy in the post-transplant setting. After exclusion of these, in combination with a concordant liver biopsy, a diagnosis of PSC recurrence can be made^[65]. In patients who develop PSC recurrence, re-transplant free survival is 85% at 1 year and 45% at 5 years^[66].

Identifying which patients will benefit from liver transplantation, and the optimal timing for this is a challenge in the management of PSC, and many predictive models have been developed to optimise this. The Mayo Risk Score was initially devised following a single centre analysis of 174 patients with PSC^[67]. Using multivariate analysis, age, log bilirubin, log haemoglobin, presence of IBD and liver biopsy stage, were identified as key parameters in predicting transplant-free survival. These parameters were incorporated into a statistical survival model which stratified patients into "low", "intermediate", and "high" risk^[67]. The Mayo Risk Score for PSC has had numerous iterations over the last 20 years^[68,69]. The latest version of the Mayo Risk Score incorporates age,

log bilirubin, log aspartate aminotransferase, variceal bleeding and albumin^[69] (Table 4). This model predicts survival over 4 years and classifies patients as "low", "medium" and "high" risk.

Cholangiograms of 129 patients with PSC identified that high-grade and diffuse strictures of the intrahepatic ducts were markers of poor prognosis^[70]. A retrospective review of 181 cholangiograms from 4 centres^[71], utilised the Amsterdam Cholangiographic Classification System for PSC^[72]. The intrahepatic and extrahepatic ducts are scored based on severity of cholangiographic changes, and combined to calculate a prognostic index, where a higher score is associated with a poorer prognosis. If a patient however has a normal cholangiogram, a score of 0 is attributed and a score cannot be calculated, thereby making this model invalid for patients with small-duct PSC. Using this classification, a validation study was able to construct a model which could predict medium and long term prognosis in individual patients with PSC^[73].

The enhanced liver fibrosis (ELF) test has recently been assessed to predict clinical outcomes in a cohort of patients with large-duct PSC^[74]. Median transplant-free survival differed significantly in the tertiles based on ELF score and a cut-off value was calculated to stratify patients into "low-score" and "high-score" groups, with a sensitivity of 67% and specificity of 83%. Patients with higher ELF score had a shorter survival, which was confirmed in a validation group of 138 patients^[74]. In a multivariate Cox regression analysis, the ELF score was associated with transplant-free survival independent of the Mayo Risk Score.

CCA remains a contraindication to liver transplantation in the majority of liver transplant centres. A protocol was developed at the Mayo Clinic (inclusion criteria: < 3 cm lesion, no metastases, no prior abdominal radiation therapy, no transperitoneal biopsy of the tumour, no prior attempt at resection with violation of the bile ducts), which included pre-transplant neo-adjuvant chemo-irradiation, and a modified post-transplant immunosuppression regimen^[75]. Using this protocol reported outcomes were comparable to other

indications for liver transplantation^[76]. Of 215 patients who received neo-adjuvant chemotherapy, 136 patients proceeded to liver transplantation (87 with PSC), with 92% 1 year and 74% 5 year survival. Twenty one percent of those who underwent operative staging were excluded from transplantation due to metastatic disease, and there was a 21% tumour recurrence post transplantation^[77]. Unfortunately these promising results have not been reproduced at other centres^[78]. There are currently several studies in progress in order to further understand the role for liver transplantation for CCA, and this data is eagerly awaited^[79].

CONCLUSION

The management of patients with PSC continues to pose a challenge to clinicians worldwide. Although guidelines are available, there are few proven therapeutic options, and there remain clinical scenarios which lack a robust evidence base with which to guide management. Many of the commonly used diagnostic tests, particularly for the detection of hepatobiliary malignancy, lack an appropriate sensitivity and specificity. Until further advances in the field take place, the mainstay of management should involve optimal biliary drainage, timely referral for liver transplantation and a low threshold for investigation for hepatobiliary or colorectal malignancy.

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