Digestive and Liver Disease 42 (2010) 390–400

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Mini-symposium

Update on primary sclerosing cholangitis

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ARTICLE INFO

Article history:
Received 17 December 2009
Accepted 17 January 2010
Available online 20 February 2010

Keywords:
Cholangiocarcinoma
HLA genes
Inflammatory bowel disease
Primary sclerosing cholangitis

ABSTRACT

Early studies in primary sclerosing cholangitis (PSC) were concerned with disease characterization, and were followed by epidemiological studies of PSC and clinical subsets of PSC as well as a large number of treatment trials. Recently, the molecular pathogenesis and the practical handling of the patients have received increasing attention. In the present review we aim to give an update on the pathogenesis of PSC and cholangiocarcinoma in PSC, as well as to discuss the current opinion on diagnosis and treatment of PSC in light of the recent European Association for the Study of the Liver and the American Association for the Study of Liver Diseases practice guidelines.

1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic inflammatory condition leading to fibrotic strictures and dilatations of the bile ducts and in most cases liver cirrhosis [1,2]. Any part of the biliary tract including the gallbladder may be affected. However, the distribution of the affection is typically not uniform, leading to sampling variability on liver histology due to regional inflammation and cholestasis [3]. Dominant strictures of the common or main hepatic ducts develop in approximately half of the patients and predispose for recurrent episodes of bacterial cholangitis [4–6]. PSC should be considered a progressive condition [7], but disease course is highly variable from patient to patient and predicting outcome at the individual level is not possible [8]. The role of medical treatment in PSC is unclear and most patients reach the combined endpoint of death or liver transplantation over a period of 12–17 years following diagnosis [9–11].

Epidemiological studies have found prevalence rates of PSC in Northern European descendants of approximately 10/100.000 [12–14]. In Southern Europe and Asia, the reported numbers are 10–100-fold lower [15,16]. Most PSC patients are relatively young, with a median age at onset of 30–40 years, ranging from children below the age of 10 to elderly individuals 70–80 years old. In contrast to most autoimmune conditions, approximately 2/3 of the PSC patients are male.

An important feature of PSC is the variable presence of comorbidities. Most common is inflammatory bowel disease (IBD), which is reported in the range of 62–83% in Northern European descendants [13]. In Southern Europe and India the IBD frequency is approximately 50% [15,17,18], and in Singapore and Japan even lower (20–37%) [16,19,20]. According to standard criteria, the IBD in PSC in about 80–90% of the cases is compatible with ulcerative colitis (UC) whereas the remainder of the cases are diagnosed with Crohn's disease or IBD unclassified [21]. A variety of other autoimmune diseases have also been reported at an increased frequency in PSC [22], and approximately 6–9% of adult PSC patients have features of autoimmune hepatitis [23–25]. In the range of 3.3–36.4% of the PSC patients will develop cholangiocarcinoma [17,19,26–28], with numbers varying based on geography (lower frequencies in Southern Europe and Asia) and the population studied (higher frequencies in liver transplant center series). Importantly, there is also an increased risk of colonic cancer and gallbladder cancer among the patients [29,30]. It is presently not known whether this heterogeneity means that PSC is a "mixed bag" of multiple conditions still to be defined, or only represents variable disease behaviour of an otherwise homogeneous condition.

As evident from Table 1, years separate landmark discoveries in PSC. In the present review we aim to give an update on the literature on the pathogenesis of PSC and cholangiocarcinoma in PSC, as well as the current opinion on diagnosis and handling of PSC that has been put forward by the practice guidelines recently published by the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD).

2. Pathogenesis of PSC

The etiology and pathogenesis of PSC are not known. By the time diagnosis of PSC can be made by cholangiography, there is already extensive scarring and strictures of the biliary tree. The obstruction of bile flow leads to secondary inflammation and apoptosis

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doi:10.1016/j.dld.2010.01.011

Table 1
Literature-based history of primary sclerosing cholangitis (PSC). The list is not exhaustive and is intended to illustrate the direction of the field. Early studies were concerned with disease characterization, and were followed by epidemiological studies of PSC and clinical subsets of PSC as well as a large number of unsuccessful treatment trials. Recently, practical handling of the patients and the molecular pathogenesis have received increasing attention and will be the emphasis of this update on PSC.

Year	Landmark finding	References
1867	First description of PSC.	[208]
1965	Review of 25 case reports from 1954 to 1964 revealed a link between PSC and ulcerative colitis and other autoimmune diseases.	[209]
1966	First single-center case series (42 PSC patients) described clinical features of PSC.	[210]
1979	Autoreactivity toward biliary antigens in PSC recognized.	[211]
1980	Three case series (93 PSC patients in total) defined the clinical, biochemical, radiological and histological features of PSC.	[2,212,213]
1982	Association between HLA variants and risk of PSC recognized.	[35]
1983	Liver transplantation established as treatment for end-stage PSC.	[214]
1985	Link between PSC and cholangiocarcinoma established.	[215]
1985	Small duct PSC recognized.	[216]
1988	Recurrent PSC after liver transplantation recognized.	[217]
1991	Characteristic features of inflammatory bowel disease in PSC defined.	[21]
1991	Intestinal leakage of bacteria in rats leads to sclerosing cholangitis.	[102]
1992	PSC found to represent a risk factor for colonic dysplasia.	[218]
1992	First randomized placebo-controlled trial of ursodeoxycholic acid for PSC demonstrated improvement in biochemistry, but no significant effect on liver transplantation-free survival.	[175]
1992	Features of autoimmune hepatitis in a subset of patients with PSC recognized.	[135,137]
1993	Bile acid toxicity in *mdr2* knockout mice leads to sclerosing cholangitis.	[77]
1998	First epidemiological study of PSC documented a prevalence of approximately 1/10,000 in Norway.	[12]
2001	Aberrant homing of intestinally activated lymphocytes to liver recognized.	[66]
2005	Increased risk of PSC among relatives demonstrated, underscoring the importance of genetic risk factors.	[219]
2006	Elevated levels of IgG4 in a subset of patients with PSC recognized.	[130]
2009	Treatment of PSC with high-dose ursodeoxycholic increased risk of death or liver transplantation.	[178]
2009	European Association for the Study of the Liver practice guidelines.	[123]
2009	Genome-wide association study determined the genetic architecture of PSC.	[34]
2010	American Association for the Study of Liver Diseases guidelines.	[124]

[31], and it is thus impossible to determine whether observations at the cellular and molecular level are of primary importance in PSC pathogenesis or only secondary to the ongoing disease processes. Since the biliary tract exhibits a limited repertoire for reacting to any insult, a variety of pathogenetic mechanisms may give rise to a clinical presentation of sclerosing cholangitis [32]. A relevant question is thus whether a single pathogenetic mechanism could be expected in the remaining patients when patients with known causes for sclerosing cholangitis have been excluded. The heterogeneity of the PSC population makes this unlikely. This also means that rather than considering the various hypotheses that have been put forward on the pathogenesis of PSC as "true" or "false" (Table 2), each of the hypotheses could be considered potentially relevant, in some patients, at various stages of PSC.

Table 2
Leading hypotheses on the pathogenesis of primary sclerosing cholangitis (PSC). Rather than concluding each hypothesis as "true" or "false", they should be considered descriptive of possible components of the disease process in PSC (MAdCAM-1; mucosal addressin cellular adhesion molecule 1, CCL25; chemokine ligand 25, CCR9; chemokine receptor 9, ABCB4; ATP-binding cassette sub-family B member 4, SXR; steroid and xenobiotic receptor, PXR; pregnane X receptor).

Pathogenetic mechanism	Experimental and epidemiological support
The "aberrant homing" hypothesis	MAdCAM-1expression on sinusoidal endothelium during PSC [65,66]. Production of CCL25 in PSC and increased numbers of T-cell expressing CCR9 [67].
The "autoimmunity" hypothesis	Presence of autoantibodies [220]. Preferential usage of particular T-cell receptor gene segments of hepatic T-cell [71]. Strong HLA associations [34]. Autoreactivity in rat model of PSC [221]. Presence of features of autoimmune hepatitis and other autoimmune diseases in some patients [22,23,25,138–144,222].
The "toxic bile" hypothesis	Sclerosing cholangitis in *abcb4* −/− mice [77,79,80]. Cholestatic liver disease with portal fibrosis, in adults with *ABCB4* mutations [84,85]. Modifier effects from *ABCB4* and *SXR*/*PXR* gene polymorphisms [86,87]. Development of PSC-like changes in cystic fibrosis [223]. Improvement of hepatic biochemistries under treatment with ursodeoxycholic acid [187].
The "leaky gut" hypothesis	Bacterial translocation in rats induces PSC-like changes [99–103]. Lipopolysaccharide activates toll-like receptors on biliary epithelial cells [107]. Improvement of hepatic biochemistries under treatment with metronidazol [108]. Increased frequency of innate immune cells in PSC livers [58–60].

2.1. Genetics of PSC

The largest study of heritability in PSC has shown that siblings of patients are 9–39 times more likely to develop PSC than the overall population [33]. In the same study, siblings of PSC patients were also found to have an 8-fold increased risk of developing UC even without liver disease, meaning that shared genetic risk factors between PSC and UC are likely to exist. The outcome of a recent genome-wide association study in PSC is schematically shown in Fig. 1 [34]. The strongest associations were detected in the HLA complex on chromosome *6p21*, and weaker associations were found at three genetic loci that had previously been implicated in the susceptibility to IBD (chromosome *3p21*, chromosome *2q35* and the *GPC5*/*GPC6* region on chromosome *13q31*).

An HLA association in PSC was detected as early as 1982 (Table 1) [35], and the relative importance and PSC specificity of findings within this region clearly warrant priority in further research [34,36]. Probably both the HLA class I and HLA class II genes contribute to the associations. However, since the HLA genes are closely

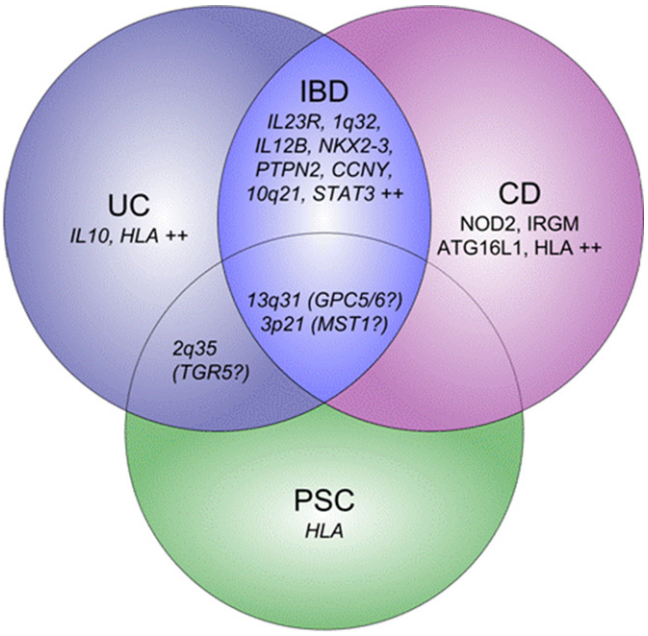

Fig. 1. The genetic architecture of primary sclerosing cholangitis (PSC). The strong HLA associations represent the only disease specific genetic finding in PSC so far. The remainder of the disease genes have also showed association in the inflammatory bowel diseases (IBD) ulcerative colitis (UC) and Crohn's disease (CD). IL10; interleukin-10, HLA; the human leukocyte antigen complex on chromosome *6p21*, TGR5; takeda G-protein coupled bile acid receptor 5, IL23R; interleukin 23 receptor, IL12B; interleukin 12B, NKX2-3, NK2 transcription factor related locus 3, PTPN2; protein tyrosine phosphatase, non-receptor type 2, CCNY; cyclin Y, STAT3; signal transducer and activator of transcription 3, GPC5/6; glypican 5 and 6, MST1; macrophage-stimulating 1, NOD2; nucleotide-binding oligomerization domain containing 2, IRGM; immunity-related GTPase family M, ATG16L1; ATG16 autophagy related 16-like 1.

linked, it has so far not been possible to conclusively dissect exactly which of the genes that are most important. For the HLA class I genes, two recent studies from Norway and Italy point to the possibility that HLA-C and possibly HLA-B variants with a particularly strong inhibitory influence on T-lymphocytes and natural killer cells via so-called killer immunoglobulin-like receptors may protect against PSC [37,38]. These HLA-C and B variants have low frequencies in Northern Europe where PSC is most prevalent [39]. Several of the HLA class II variants are linked with these HLA-C and HLA-B variants, but the increased risk associated with DRB1*1301 and the decreased risk associated with DRB1*0701 and various DRB1*04 and DRB1*11 variants seem to be due to other mechanisms [37,38,40–42]. One possible explanation is obviously the ability of these or closely linked HLA class II variants to present PSC relevant antigens to the T-lymphocytes.

The finding that only two out of 15 established susceptibility loci for UC also confer risk for PSC corroborates clinical observations that IBD in PSC may represent a distinct entity, different from UC in many aspects ("PSC-IBD") [38,43]. In most patients with IBD and PSC, inflammation is mild with a slight right-sided predominance [21,44,45]. The IBD in PSC is almost always a pancolitis, even when classified as Crohn's disease, however, often with rectal sparing and subtle inflammatory changes in the ileum ("backwash ileitis") [43,46]. What role genetic variants the two UC susceptibility loci may play in the biliary tract is not clear. At chromosome *3p21*, the problem of linked genes is a similar problem as in the HLA. One possible candidate is the macrophage-stimulating 1 (*MST1*) gene, which encodes a circulating protein which inhibits macrophages during inflammation [47]. The PSC-, CD- and UC-associated MST1 variant may impair binding of MST1 to its receptor and thus lead to deficiency of this negative feedback system [48].

At chromosome *2q35*, the bile acid receptor *TGR5* gene is the most plausible disease gene [49,50]. Like MST1, TGR5 may inhibit macrophages, and the activation of TGR5 by bile acids means that this could prevent excessive inflammation during cholestasis [49]. Furthermore, TGR5 may activate the cystic fibrosis transmembrane conductance regulator (CFTR) in the biliary epithelium [50]. CFTR plays an important role in the protection of the biliary epithelium by means of transportation of chloride ions to bile. These chloride ions are exchanged for bicarbonate by the anionic exchanger 2 (AE2) molecule, and the bicarbonate may constitute one of the mechanisms by which the biliary epithelium is protected against toxic effects from bile [51]. Interestingly, concurrent colitis and *CFTR* deficiency has been shown to induce PSC-like disease in mice [52]. So far there is no consensus as to a role for *CFTR* mutations in PSC [53–57], but the possibility should be held open that such variants may be of importance in individual patients.

2.2. Aberrant lymphocyte homing and autoreactivity in PSC

Some studies have reported an increased frequency of natural killer cells in the portal infiltrate of patients with PSC when compared with other liver diseases [58,59], and there is also an increase in Kuppfer cells and peri-sinusoidal macrophages [60]. To what extent this may be related to the genetic findings discussed above is not known. However, the majority of the mononuclear cells in the portal infiltrate in liver biopsies from patients with PSC is T-lymphocytes [61,62]. The "aberrant homing" hypothesis (Table 2) proposes that lymphocytes activated in the gut may be responsible for biliary inflammation in PSC [63]. Normal intestinal homing of T-lymphocytes is ensured by the integrin alpha 4/integrin beta 7 ($\alpha 4\beta 7$) receptor on the lymphocytes and the corresponding mucosal addressin cellular adhesion molecule 1 (MAdCAM-1) ligand on the intestinal endothelial cells [63,64]. In PSC and other inflammatory liver diseases, MAdCAM-1 is expressed on portal vein- and sinusoidal endothelium [65,66], and may thus function to recruit intestinally activated T-lymphocytes to the liver [63,64]. Supportive evidence for the phenomenon comes from the observation of an increased production of the chemokine ligand 25 (CCL25) in PSC [67], which binds the chemokine receptor 9 (CCR9) on memory T-lymphocytes. An open question of the hypothesis is whether observations are specific to PSC or merely a general feature of hepatic inflammation.

The strong HLA association in PSC detected in the genome-wide association study is typical for an autoimmune condition. The high frequency of other autoimmune diseases as well as features of autoimmune hepatitis in PSC further support the presence of an autoimmune component in the pathogenesis. Antibodies against biliary as well as colonic epithelial cells have been reported [68–70], and the preferential usage of particular T-cell receptor gene segments of hepatic T-cells also suggests that tissue-specific antigens of relevance to PSC pathogenesis may exist [71]. The most prevalent autoantibody in PSC (up to 94% of the patients) is a particular type of perinuclear anti-neutrophil cytoplasmatic antibody (pANCA) [72–74]. This antibody is also observed in UC and type 1 autoimmune hepatitis [73,75], and suggests that common pathogenetic mechanisms for these conditions are likely to exist. Recently, tubulin beta 5 (TBB-5) was identified as the main pANCA antigen [76], and antibodies against TBB-5 were found to cross-react with the bacterial FtsZ protein, meaning that an immune response against intestinal bacteria may be the cause of pANCA. Interestingly, anti-FtsZ antibodies were common among healthy controls, whereas the presence of both anti-TBB-5 and anti-FtsZ was predominantly found in autoimmune hepatitis and PSC. The pathogenetic importance of pANCA and other autoantibodies in PSC is not known and should be assessed in parallel with further studies on the HLA association in PSC.

2.3. Bile acid toxicity in PSC

Several studies have elaborated on the "toxic bile" hypothesis in PSC pathogenesis (Table 2), based on the findings of PSC-like changes in mice devoid of the phospholipid transporter "multidrug resistance protein 2" (mdr2), called MDR3 and ABCB4 in humans [77,78]. In these mice, bile acid toxicity leads to extensive fibrosis of the bile ducts mimicking intrahepatic PSC in humans [79–82]. Whereas defects in the human *ABCB4* gene leads to progressive familial intrahepatic cholestasis type 3 (PFIC3) [83], no associations between ABCB4 variants and PSC have so far been reported. However, single cases of ABCB4-related disease may be found among PSC patients without IBD, as highlighted by the findings of "mild" *ABCB4* mutations in adult patients with unexplained cholestasis and histological findings of portal fibrosis and minor ductular changes in two recent studies [84,85]. Furthermore, similar mutations may alter disease severity ("modifier effects"), as demonstrated by the findings of a more severe disease course in both PSC and primary biliary cirrhosis (PBC) patients with particular *ABCB4* variants [86,87].

Bile acids that accumulate in affected segments of the liver in PSC are toxic to the hepatocytes, and are likely to contribute to the development of liver cirrhosis in PSC [88]. The hepatocyte initiates a variety of detoxification mechanisms in cholestasis, including hydroxylation and conjugation to make bile acids more water soluble and induction of bile acid transporters on the sinusoidal membrane leading to export of metabolized bile acids to the systemic circulation for renal elimination [89]. One of the major determinants of the expression of the genes involved in these processes is the steroid and xenobiotic receptor (SXR; also called pregnane X receptor, PXR) [90,91]. PSC patients with particular genetic variants of SXR have been shown to suffer a more severe disease course, in line with the importance of the protective effects from SXR in animal models of cholestasis [89,92–96]. Since variants of SXR have recently also been shown to influence disease severity and liver damage in PBC and non-alcoholic fatty liver disease [97,98], the mechanisms involved could be of general importance for liver cell injury.

2.4. The "leaky gut" hypothesis

Studies in a rat model with intestinal bacterial overgrowth performed almost 20 years ago suggested that innate immune responses to bacterial products may initiate a PSC-like pathogenesis [99–103]. The findings warrant renewed interest for several reasons. Since the inflammation in these models was mediated by TNFα, it is of great interest to note increased levels of this pro-inflammatory cytokine also in human PSC as compared with healthy controls and other chronic cholestatic liver diseases [104–106]. Along with macrophages, both natural killer cells and T-lymphocytes can produce TNFα. Since several of the genetic studies in PSC implicate a role of innate immune responses, including macrophages and natural killer cells, the relationship between these genetic findings and translocation of bacterial components in an inflamed colon needs to be further explored.

Interestingly, toll-like receptor 4 (TLR-4) and TLR-9 expression on biliary epithelial cells may be induced by antibodies against these cells [107]. These TLRs recognize bacterial products and viral DNA and activation may aggravate ongoing biliary inflammation upon the exposure to bacterial or viral components in blood. Such components may be derived from bacterial colonization of the biliary tree, or even infections at other mucosal surfaces or flares of IBD. Whether such mechanisms could help explain the fluctuating disease course observed in many PSC patients is not known, but it is interesting to note an improvement of hepatic biochemistries in PSC patients under long-term administration of metronidazol [108]. The presence of an infectious trigger or infectious modifier effects in PSC is thus likely, but further studies are required to determine the type and importance of such factors. Possibly, a diverse spectrum of infectious agents may cause breakdown of immunological tolerance in the bile ducts in genetically susceptible individuals, leading to sustained immunological reactions towards "self-antigens" even after the infectious agents themselves have been cleared. In this regard, it is interesting to note that induction of pANCA seems to be dependent on the intestinal flora or intestinal inflammation [76].

3. Pathogenesis of cholangiocarcinoma in PSC

The mechanisms of carcinogenesis in PSC are poorly understood [109]. Regarding carcinogenic effects from bile acids, they seem to be in part mediated via DNA damage caused by reactive oxygen intermediates [110]. Defects of the DNA repair machinery have been detected in some patients with cholangiocarcinoma and may aggravate such effects [111]. A series of studies by Gores et al. have demonstrated the importance of autocrine effects from IL-6 on cholangiocarcinoma cell immortalization [112]. The effects from IL-6 are mediated via activation of the signal transducer and activator of transcription 3 (STAT3) protein which leads to the upregulation of several molecules involved in cancer cell apoptosis and proliferation [113]. Normally, the STAT3 activation is restricted via negative feedback by Suppressor of cytokine signaling 3 (SOCS3). In cholangiocarcinoma, however, this negative feedback is defective due to inactivation of the promoter region of the *SOCS3* gene by methylation of the DNA [114]. As recently reviewed elsewhere, similar mechanisms (called epigenetic alterations) may also be of more widespread importance in cholangiocarcinoma development [115].

As part of the ongoing inflammation, and in response to the altered properties of the dysplastic cholangiocytes, various immune cells play important roles in cholangiocarcinogenesis. Some of these cells may promote tumor growth and metastasis (e.g. macrophages) [116], whereas others are trying to kill abnormal cholangiocytes (e.g. natural killer cells) [117]. The importance of this balance was recently demonstrated by the finding of an association between genetic variants of the natural killer cell receptor NKG2D and cholangiocarcinoma [118]. In line with findings in other types of cancers [119], individuals who carried *NKG2D* variants that lead to less efficient killing by natural killer cells were more prone to develop cholangiocarcinoma than individuals with normal NK cells. Very characteristically, approximately 40–50% of the cholangiocarcinomas are diagnosed during the first year following the diagnosis of PSC [10,120,121]. This contrasts the situation of many other inflammation-related cancers (e.g. colonic carcinoma in UC), where the risk gradually increases over the years. In PSC, less than 10% of the patients develop cholangiocarcinoma more than 10 years after the diagnosis [120]. Based on all these observations it could be speculated that "PSC with cholangiocarcinoma" may represent a distinct clinical subset, and that the risk does not apply to all patients.

4. Diagnostic challenges in PSC

The diagnosis of PSC is made by cholangiography and the exclusion of secondary etiologies. There are no specific symptoms or clinical, biochemical or histological findings. There are important challenges regarding (1) the definition of "outlier" PSC variants (small duct PSC, autoimmune hepatitis-like PSC and IgG4-associated cholangitis), (2) PSC in children and (3) early diagnosis of biliary and colonic malignancies. Regarding the cholangiogram, the typical findings in PSC involve multifocal strictures and dilatations

Table 3
Summary points of the EASL and AASLD practice guidelines on primary sclerosing cholangitis (PSC) [123,124]. MRC; magnetic resonance cholangiography, ERC; endoscopic retrograde cholangiography, IBD; inflammatory bowel disease, UDCA; ursodeoxycholic acid.

Practice point	EASL guidelines	AASLD guidelines
Cholangiography	MRC recommended as initial investigation. ERC if indicated.	MRC recommended as initial investigation. ERC if indicated.
Liver biopsy—adults	Only in patients with normal cholangiography or disproportionally elevated serum transaminases.	Only in patients with normal cholangiography or disproportionally elevated serum transaminases.
Liver biopsy—children	Recommended.	Recommended.
Antibiotic prophylaxis during ERC	Recommended.	No recommendation point.
Long-term antibiotic treatment	No recommendation point.	Recommended in patients with recurrent attacks of acute cholangitis.
Endoscopic treatment	Balloon dilatation with or without stenting.	Balloon dilatation with or without stenting.
UDCA treatment in PSC	No specific recommendation made.	Not recommended.
UDCA chemoprevention	In patients with longstanding IBD and family history of colorectal malignancies.	Not recommended.
Treatment of PSC with features of autoimmune hepatitis	UDCA and immunosuppression recommended.	Corticosteroids and other immunosuppressive agents recommended.
Treatment of IgG4-associated sclerosing cholangitis	Corticosteroids and/or azathioprine.	No specific treatment recommendation.
Liver transplantation	Treatment of choice in cirrhotic patients and should be considered in refractory bacterial cholangitis.	Treatment of choice in cirrhotic patients and should be considered in refractory bacterial cholangitis.
Surveillance colonoscopy	Every 1–2 years in IBD.	Every 1–2 years in IBD.
Surveillance ultrasound	Annually.	Annually.
Cholangiocarcinoma surveillance	No recommendation made.	No recommendation made.

of both the intra- and the extra-hepatic bile ducts [122]. Changes of the extra-hepatic bile ducts only are rare, whereas isolated changes of the intrahepatic bile ducts have been reported at a frequency of 20–28% of the patients [4,10,27,122]. Whereas both the EASL and the AASLD guidelines now recommend MRC rather than ERC as the first investigation in patients where PSC is suspected (Table 3) [123,124], the quality of the investigation needs careful assessment and ERC should be performed in inconclusive cases. There have been concerns as to the sensitivity of MRC in detecting subtle intrahepatic changes [125], and some authors also claim that MRC is inferior to ERC in the detailed characterization of extra-hepatic biliary changes and dominant strictures [126,127].

4.1. Diagnosis of variant forms of PSC

As the etiologies of what we today denominate "primary" in relation to sclerosing cholangitis are unravelled, the list of differential diagnoses in terms of secondary sclerosing cholangitis is likely to grow. The ultimate outcome of the ongoing research on the pathogenesis of PSC could be the replacement of the PSC diagnosis by a distinct set of etiology-based diagnoses. Whether small duct PSC, PSC showing features of autoimmune hepatitis (also called "PSC-autoimmune hepatitis overlap syndrome" and "autoimmune sclerosing cholangitis") and IgG4-associated sclerosing cholangitis might represent distinct diagnoses has to be determined.

In the EASL and AASLD practice guidelines, IgG4-associated sclerosing cholangitis has now been placed on the list of etiologies for secondary sclerosing cholangitis. Interestingly, some of the IgG4-associated sclerosing cholangitis patients may have IBD, and like in regular PSC, there is a distinct male predominance [128,129]. Elevated levels of IgG4 (>135 mg/dl) are specific for the diagnosis. However, sensitivity may be lower than previously reported (71–82%) [128], and repeated measurements may be required to establish the diagnosis [129]. Whereas elevated levels of IgG4 have been reported in 7–9% of PSC patients [19,130], positive immunostaining for IgG4 was recently found in 23% of liver explant specimens from patients with PSC [128]. These data indicate that work remains in delineating IgG4-associated sclerosing cholangitis from regular PSC. The importance of establishing the diagnosis, however, is the excellent response to corticosteroid treatment.

The EASL and AASLD guidelines agree on the need for liver biopsy to exclude small duct PSC in patients with clinical and biochemical features of PSC but with a normal cholangiogram. Whereas the presence of IBD is no longer mandatory for the diagnosis of small duct PSC in either of the guidelines, liver biopsy interpretation relies on IBD status. In patients without IBD, typical changes suggestive of PSC are required. In patients with concurrent IBD, the histological changes should at least be compatible with PSC, but not necessarily typical or specific for regular PSC. As highlighted by the EASL guidelines, abandoning the IBD criterion for small duct PSC may lead to misclassification of patients with "mild" forms of hereditary cholestatic syndromes (e.g. *ABCB4*-disease) as small duct PSC [84,85,123]. In familial cases without IBD, mutational analysis may thus be advisable. Transition to large duct PSC may occur, and cholangiography should be repeated on clinical detoriation [131–134]. Typically, however, small duct PSC runs a quiescent course, and long-term survival is significantly better than for regular PSC [131,132]. Cholangiocarcinoma does not seem to occur in small duct PSC patients unless transition into regular PSC has occurred [131].

The presence of biochemical, serological and histological features of autoimmune hepatitis in a subset of PSC patients has long been recognized [135–137]. The nomenclature for this group of patients is not clear, but both the EASL and AASLD guidelines have adopted the term PSC-autoimmune hepatitis overlap syndrome. A liver biopsy should be considered in patients with an autoimmune hepatitis-like autoantibody profile (high levels of anti-nuclear antibodies [ANA] and anti-smooth muscle antibodies [anti-SMA]) or relatively high IgG and serum aminotransferase levels to assess features of autoimmune hepatitis [123,138]. By the application of recent scoring criteria for autoimmune hepatitis, approximately 6–9% of adult PSC patients seem to have features of autoimmune hepatitis [23–25], and in pediatric PSC patients the frequency is even higher [139–144]. The importance of detecting the presence of autoimmune hepatitis-like features in PSC are reports suggesting a more benign disease course associated with immunosuppressive therapy in this group of patients [138,145,146].

4.2. Diagnosis of PSC in children

The main challenges in the diagnosis of PSC in children is the slightly different spectrum of causes of secondary sclerosing cholangitis to be excluded and the high frequency of autoimmune hepatitis-like features. In contrast to adult PSC, where a liver

biopsy is not recommended, the AASLD guidelines therefore recommend liver biopsy to be performed in all children where PSC is suspected [124]. Some of the differential diagnoses in childhood PSC are listed in the EASL practice guidelines [123], and cover a variety of conditions (in particular cystic fibrosis, α1-antitrypsin deficiency, immunodeficiency syndromes, Langerhans cell histiocytosis, idiopathic neonatal sclerosing cholangitis, biliary atresia, congenital bile duct abnormalities and progressive familial intrahepatic cholestasis type 3). The subgroup of pediatric PSC patients with features of type 1 autoimmune hepatitis has been denominated autoimmune sclerosing cholangitis [144], but further studies are needed to clarify if this demarcation versus regular PSC is justified. A particular point regarding pediatric PSC is the low risk of cholangiocarcinoma and colorectal cancer, meaning that in patients with PSC and IBD below the age of 16 years neither surveillance for cholangiocarcinoma nor annual colonoscopy is recommended [124].

5. Diagnostic challenges in cholangiocarcinoma in PSC

An early diagnosis of cholangiocarcinoma in PSC is difficult to obtain. Metastatic disease has been reported at diagnosis in approximately half of the PSC patients with cholangiocarcinoma [121,147,148], and in approximately 30–40% of the cases the diagnosis was settled in conjunction with liver transplantation for PSC [120,149]. These problems are reflected by the lack of surveillance strategies for cholangiocarcinoma in both the EASL and the AASLD guidelines [123,124]. However, since the increased risk of biliary malignancies in PSC also pertains to the gallbladder [29], annual abdominal ultrasonography to detect gallbladder polyps is recommended. Furthermore, both the EASL and AASLD guidelines advice for colonoscopy with biopsies in all patients with PSC and IBD to allow for the early detection of colorectal cancer.

A problem in diagnosing cholangiocarcinoma in PSC is that the growth is often longitudinal with subtle perineural and perivascular invasion [150], meaning that in many of the patients the tumor cannot be detected by radiology. Contrast-enhanced magnetic resonance (MR) imaging with MRC is considered the imaging method of choice if a cholangiocarcinoma is suspected [151–153]. In case of pathological findings, CT typically supplements with information on lymph node enlargement and the liver parenchyma [152,154] and has been reported superior to MR imaging in terms of defining extra-hepatic growth and vascular encasement [155,156]. Positron emission tomography (PET) scanning is useful for detecting solid metastases [157], but has in recent studies proven unreliable for detecting peritoneal carcinomatosis or biliary lesions not visible on MRI/CT [158–160]. By cholangioscopy, a sensitivity of 92% and specificity of 93% in the diagnosis of malignant strictures in PSC were recently reported [161], as compared with 66% and 51%, respectively, for ERC alone. The application of intraductal ultrasound correspondingly increased the sensitivity from 63% to 88% and specificity from 53% to 91%, respectively, when compared to ERC alone [162]. As emphasized by both the EASL and AASLD guidelines, further studies on the utility of these two latter methods in the diagnosis of cholangiocarcinoma in PSC are needed.

An extensive evaluation of the tumor marker carbohydrate antigen (CA) 19-9, imaging and brush cytology-based techniques in cholangiocarcinoma in PSC was recently published [163]. As also shown in previous studies [164–166], digital image analysis (DIA) and fluorescent in situ hybridization (FISH) enhanced the sensitivity obtained by routine brush cytology investigations. Furthermore, the authors propose that repeated CA 19-9 measurements along with imaging may be useful for the screening and surveillance of cholangiocarcinoma in PSC. By application of the proposed guidelines, almost two-thirds of the cholangiocarcinomas were detected at an early stage where potentially curative liver transplantation protocols were still applicable. More refined methods for early cholangiocarcinoma detection in PSC are also clearly needed. Several "-omics" are presently at work to identify more specific tumor markers, that may be derived from cancer specific protein profiles (proteomics) [167], mutations (genomics), altered regulation of gene expression (epigenomics) [115,168,169], or small-molecular metabolites (metabolomics) [170]. The first results from some of these studies are encouraging [171,172], but it is not yet clear which method is most relevant and replication of the findings and evaluation as screening tools have not been performed for any of the candidates.

6. Treatment of PSC

The scarcity of PSC patients and the long time until a primary endpoint like death or liver transplantation is reached, means that achieving an adequate study population in randomized, double-blinded treatment trials in PSC is difficult. Furthermore, patients show a remarkable variability in natural history, in contrast to other liver diseases like primary biliary cirrhosis which follows a relatively predictable course [8]. This means that selection bias is a considerable source of error and that the application of surrogate markers for disease progression (e.g. prognostic indices) is likely to yield an imprecise picture of treatment effects.

While the first three studies on ursodeoxycholic acid were able to document an improvement of both hepatic biochemistries and histological parameters [173–175], no improvement in transplant-free survival was observed. Which components of the disease process that is altered by ursodeoxycholic acid in PSC (Table 2) and could explain these findings remain to be defined. The three largest studies to date were performed in the US and Scandinavia and utilized different doses of ursodeoxycholic acid (13–15 mg/(kg day) [176], 17–23 mg/(kg day) [177], and 28–30 mg/(kg day) [178]). In none of these studies significant effects on risk of liver transplantation or death were detected, as also evident from the recent meta-analysis of ursodeoxycholic acid trials in PSC [179]. Furthermore, contrary to suggestions made by pilot studies of high-dose ursodeoxycholic acid in PSC [180,181], the highest dose regimen (28–30 mg/(kg day)) was significantly associated with an increased risk of liver transplantation or death compared with placebo. The explanation for this is not clear, but one speculation made was that higher doses could result in increased colonic conversion of unabsorbed ursodeoxycholic acid into the toxic metabolite lithocholic acid [178]. Based on the sum of these trials, routine prescription of ursodeoxycholic acid in patients with PSC is not recommended in the EASL and AASLD guidelines.

Several studies have addressed the question of whether ursodeoxycholic acid could protect against the development of cholangiocarcinoma or colorectal cancer in PSC. While there are only anecdotal reports regarding a protective effect against cholangiocarcinoma [182,183], two small retrospective series and one small prospective study have suggested a decreased risk of colonic dysplasia associated with ursodeoxycholic acid use [184–186]. However, since none of the large prospective high-dose ursodeoxycholic acid treatment trials have been able to confirm similar effects [177,178], the AASLD guidelines conclude by recommending against prescription of ursodeoxycholic acid as a chemopreventive agent in PSC. The EASL guidelines do not conclude on the issue, and opens up for low-dose ursodeoxycholic acid in PSC patients when additional risk factors are present (e.g. family history of colorectal cancer, previous colorectal neoplasia or longstanding extensive colitis).

A variety of immunosuppressive drugs ranging from corticosteroids to monoclonal antibodies against tumor necrosis factor alpha have been tested in pilot studies as well as randomized double-blind placebo-controlled treatment trials in PSC [187].

None of these agents have proven beneficial and they should not be prescribed to the regular PSC patient. In PSC patients with features of autoimmune hepatitis and IgG4-associated sclerosing cholangitis, corticosteroid treatment with or without adjuvant immunosuppressive therapy is recommended (Table 3). In PSC patients with features of autoimmune hepatitis it is important to recognize that progression to cirrhosis occurs in a majority of the patients despite treatment [188], indicating that some of the pathologic processes may be relatively inert to immunosuppression. In IgG4-associated sclerosing cholangitis, prevention and handling of relapse may represent a considerable challenge [189–191].

Three retrospective studies have noted a significant increase in survival as compared with predicted 3- and 5-year survival rates (according to the Mayo risk score) following endoscopic treatment of dominant stenoses [192–194]. The presence of dominant strictures was also recently reported to associate with poor outcome in PSC [6]. According to both the EASL and AASLD practice guidelines (Table 3), dominant strictures in PSC with significant cholestasis should be treated with balloon dilatation [193,195,196]. Some patients also appear to benefit from short-term stenting [197,198]. No randomized, prospective controlled trials have been performed to assess the efficacy of endoscopic treatment in PSC, and the application is presently performed based on individual assessment of each patient.

In the Nordic countries, PSC is the most important indication for liver transplantation. In the US, PSC is among the five leading indications, and even in low-prevalence countries like Italy and Spain, PSC is among the ten most common indications. Patient survival is excellent, with recent 1 and 5-year survival rates at most centers approaching 90% and 85%, respectively. However, liver transplantation in PSC poses several particular challenges. Disease course is unpredictable, and some patients may require listing for liver transplantation before end-stage liver disease. Listing of PSC patients for liver transplantation on the basis of refractory bacterial cholangitis even in non-cirrhotic patients is now recommended in the EASL and AASLD guidelines (Table 3). The high risk of biliary and colonic malignancies means that thorough pre-transplant evaluation as to the presence of cancer must be performed [199,200].

An increased risk of acute cellular rejection in PSC has been demonstrated in several series [201–203]. Since high frequencies of acute cellular rejection have also been reported in recipients with an underlying autoimmune hepatitis and primary biliary cirrhosis, it is not clear whether PSC patients are particularly at risk or whether the risk is related to autoimmune liver disease in general. Furthermore, there is an increased risk of acute rejection in patients with pre-transplant IBD as compared with patients without IBD [202,204–206], and the risk of chronic rejection also seems to be higher in PSC patients with IBD [202]. Based on all these observations, some authorities recommend an intensified immunosuppressive regimen including life-long corticosteroids following liver transplantation for PSC [199], whereas others cautiously prefer a regular regimen based on a study showing an association between aggressive immunosuppression and recurrent PSC [207].

7. Conclusion

Despite the many important discoveries made over the last three decades (Table 1), many important questions related to PSC remain unanswered. Further characterization of the etiology and pathogenesis of PSC is required and should be performed on the basis of genetic risk factors and the pathogenetic knowledge already available (Table 2). Such studies may explain the heterogeneity of the patients and propose targets for novel therapeutics. The development of tools for early diagnosis of PSC in UC is also a priority, since the fibrotic stage at which the biliary pathology can be diagnosed by cholangiography may prove resistant to medical therapy. Furthermore, sensitive and specific markers for the prediction and diagnosis of cholangiocarcinoma are urgently needed, and novel markers to predict disease behavior in the individual patient would allow for adequate timing of liver transplantation as well as assessment of response to therapy.

Conflict of interest statement

None declared.

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