Update on primary sclerosing cholangitis

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Summary

Primary sclerosing cholangitis (PSC) remains one of the most challenging conditions of clinical hepatology. There has been a steady growth in research to overcome this fact and the present review aims at summarizing the most recently published literature. The main emphasis will be put on the link of recent pathogenetic insights to clinical characteristics and patient management. With regard to pathogenesis, there is no consensus yet as to whether immune mediated injury or factors related to bile acid physiology are the most important. It also remains to be clarified whether PSC is a mixed bag of various secondary etiologies yet to be defined, or a disease entity predominantly represented by sclerosing cholangitis in the context of inflammatory bowel disease. Most important, there is no available medical therapy with proven influence on clinical end points, and timing of liver transplantation and patient follow-up are challenging due to the unpredictable and high risk of cholangiocarcinoma.

Introduction

To our knowledge, sclerosing cholangitis was introduced as a medical term in 1867 by Hoffman [1]. In the mid 1960s several case series were reviewed, establishing the link to inflammatory bowel disease (IBD) and describing several other clinical characteristics of a primary form of sclerosing cholangitis (PSC). The introduction of endoscopic retrograde cholangiography (ERC) throughout the 1970s greatly facilitated diagnosis, and the clinical, radiological and histopathological criteria for PSC were stated by three publications in 1980 from the US (Rochester), UK (London), and Norway (Oslo). Later, magnetic resonance cholangiography (MRC) has been recommended as the primary diagnostic modality in suspected cases of PSC (Clinical Points 1). There has been a steady growth in research activity around the many clinical challenges associated with PSC (Fig. 1), including the founding of an international PSC study group (www.ipscsg.org) in 2010. The aim of the present article is to summarize insights provided by the most recent research (published since our previous update [2]).

Clinical Points 1. Diagnosis of primary sclerosing cholangitis (PSC) [114, 117]

- In patients with a cholestatic biochemical profile not otherwise explained and where causes of secondary sclerosing cholangitis have been excluded, a diagnosis of PSC is made when magnetic resonance cholangiography (MRC) shows typical findings
- Endoscopic retrograde cholangiography (ERC) can be considered if high-quality MRC is uncertain and in patients with inflammatory bowel disease with normal high-quality MRC but high suspicion of PSC
- A liver biopsy is not necessary for the diagnosis of PSC in patients with typical cholangiographic findings
- A liver biopsy is recommended to diagnose small duct PSC if high-quality MRC (or ERC) is normal and in patients with disproportionately elevated aminotransferases to identify additional or alternative disease processes

The principle challenges in PSC all derive from the fact that etiology and pathogenesis are still largely unknown. Since the development of sclerosing cholangitis represents a “final common pathway” for multiple underlying mechanisms of bile duct injury, in vivo data in patients with established PSC do not necessarily reflect etiology. The first part of this review elaborates on recent insights into the pathogenesis of PSC, with a particular emphasis on research of relevance to novel treatment strategies currently in the testing phase. An update on aspects relevant to diagnosis of PSC will also be given, with a particular emphasis
on the recent insights into PSC associated clinical aspects, including elevated levels of serum IgG4, IBD, cholangiocarcinoma, pruritus, and concurrent autoimmune hepatitis. Finally, we will summarize the updates regarding treatment and cancer surveillance of PSC patients.

Pathogenesis of PSC – toxicity or immunology?

There is no universally accepted explanation for the bile duct injury in PSC. Mechanistic aspects of the development of similar bile duct lesions are under intense study both in human conditions and rodent models, nurturing an ongoing discussion as to whether the primary injury is caused by immune mediated mechanisms or biochemical aspects related to bile physiology and how these two aspects can potentially be integrated in one model. The definition of a subgroup of PSC patients characterized by high serum levels of IgG4 in 2006 [3] was in support of the possibility that the PSC patient population may be heterogeneous, and that one pathogenetic mechanism cannot be expected to account for all cases. Nevertheless, from a clinical perspective in Northern Europe and the US, a relatively demarcated "syndrome" of concurrent bile duct fibrosis, predominant right-sided colitis and a neoplastic propensity at both these sites, seems to comprise 70–80% of the PSC patient population. For this group of patients, it is not unreasonable to expect a relatively uniform pathogenesis.

Genetic association studies

The genetic susceptibility to PSC aligns with prototypical autoimmune diseases as much as with IBD (Fig. 2). Indeed, the hallmark of an “autoimmune” susceptibility at a genetic level; i.e., a predominant HLA association, also accounts for the overall genetic architecture of PSC (Table 1). As for most HLA associated diseases (celiac disease being a notable exception), the immunological implications of PSC associated HLA variants are unknown. Several review articles have assessed the theoretical knowledge associated with each non-HLA susceptibility locus (Table 1) [4–7]. Only speculations are possible for the potential disease mechanisms represented by these loci, since most of the functional studies that serve as the basis of these review articles were performed prior to, and independently from the knowledge of genetic associations in PSC. Furthermore, the “pool” of risk loci is incompletely defined (for reasons discussed elsewhere [8]). Importantly, in our opinion, there is also a risk of oversimplifying implications from genetic association study outcomes if too wide assumptions are formed on the basis of each individual locus (as would only be appropriate in a monogenous trait).

Despite these limitations, the largest genetic study in PSC warrants specific mentioning [9]. The study represents a major accomplishment by multiple centers within the international PSC study group. Genetic risk for PSC was assessed by means of case-control association analysis of a total of 3789 PSC cases to 25,079 controls across 130,422 single-nucleotide polymorphisms (SNPs) genotyped using the Immunochip [10]. The Immunochip is a targeted genotyping array covering 186 known disease loci from various immune-mediated diseases. Outside of these 186 loci, Immunochip also assays thousands of SNPs of intermediate significance from previous studies in these other diseases. A total of 9 novel risk loci for PSC were detected in the analysis. Furthermore, by taking a priori knowledge on genetic associations in other diseases into account (Crohn’s disease, celiac disease, psoriasis, rheumatoid arthritis, sarcoidosis, type 1 diabetes, and ulcerative colitis), there was a posteriori evidence for another 33
Table 1. Genetic susceptibility loci in primary sclerosing cholangitis. Loci are defined according to genome-wide significance threshold conservatively set at \( p < 5 \times 10^{-8} \). For each locus, overlapping associations reported in other diseases are observed. Additional risk loci may be defined by taking a priori knowledge on genetic associations reported in these other phenotypes into account (see [9] for further details).

<table>
<thead>
<tr>
<th>Locus</th>
<th>Notable gene(s) nearby</th>
<th>Shared associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p36</td>
<td>MMEL1, TNFRSF14</td>
<td>CeD, PBC, RA, UC</td>
</tr>
<tr>
<td>2q13</td>
<td>BCL2L11</td>
<td>CLL</td>
</tr>
<tr>
<td>2q33</td>
<td>CD28</td>
<td>AA, CeD, CHD, GD, Ht, MI, RA, T1D</td>
</tr>
<tr>
<td>2q37</td>
<td>GPR35</td>
<td>UC</td>
</tr>
<tr>
<td>3p21</td>
<td>MST1</td>
<td>CD UC</td>
</tr>
<tr>
<td>4q27</td>
<td>IL2, IL21</td>
<td>AA, CD, CeD, RA, T1D, UC</td>
</tr>
<tr>
<td>6p21</td>
<td>HLA class I and II, other genes</td>
<td>Multiple diseases</td>
</tr>
<tr>
<td>6q15</td>
<td>BACH2</td>
<td>CD, CeD, MS, T1D, Vi</td>
</tr>
<tr>
<td>10p15</td>
<td>IL2RA</td>
<td>AA, MS, RA, T1D, Vi</td>
</tr>
<tr>
<td>11q23</td>
<td>SIK2</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>12q13</td>
<td>HDAC7</td>
<td>CD, UC</td>
</tr>
<tr>
<td>12q24</td>
<td>SH2B3, ATXN2</td>
<td>BP, CeD, Ch, CKD, EC, Ht, Ht, MI, PBC, RVC, T1D</td>
</tr>
<tr>
<td>18q21</td>
<td>TCF4</td>
<td>Sch, FCD</td>
</tr>
<tr>
<td>18q22</td>
<td>CD226</td>
<td>T1D</td>
</tr>
<tr>
<td>19q13</td>
<td>PRKD2, STRN4</td>
<td>CLL, T1D</td>
</tr>
<tr>
<td>21q22</td>
<td>PSMD1</td>
<td>AS, CD, UC</td>
</tr>
</tbody>
</table>

AA, alopecia areata; AS, ankylosing spondylitis; BP, blood pressure; CD, Crohn's disease; CeD, celiac disease; CHD, coronary heart disease; CKD, chronic kidney disease; CLL, chronic lymphocytic leukemia; EC, eosinophil counts; FCD, Fuchs's corneal dystrophy; GD, Grave's disease; He, haemocytotic; Hg, haemoglobin; Ht, hypothyroidism; MI, myocardial infarction; MS, multiple sclerosis; PBC, primary biliary cirrhosis; RA, rheumatoid arthritis; RVC, retinal vascular calibre; Sch, schizophrenia; T1D, type 1 diabetes; UC, ulcerative colitis; Vi, vitiligo.

For gene name abbreviations, see http://www.ncbi.nlm.nih.gov/gene. For risk loci (including previously reported loci at 2q35 [encompassing several genes including TGR5 and interleukin 8 receptor IL8RA and IL8RB] and 19q13 [fucosyltransferase 2; FUT2]). The most notable novel pathway relates to the functionality connected PRKD2, HDAC7, and SIK2, but whether these associations represent aberrations of T-cell activation or bile acid homeostasis [11, 12], or other biological aspects, can only be speculated.

**Bile acid toxicity**

The concept of sclerosing cholangitis in the context of “bile toxicity” has evolved during the years following the description of the Abcb4−/− mouse and the characterization of nuclear receptor regulation of bile acid homeostasis. Extensive research on the potentially beneficial effects of ursodeoxycholic acid (UDCA) in cholestatic liver diseases has also contributed to the concept [13]. In 2010, previous notions could be unified by the launching of the hypothesis that deficiencies of a biliary bicarbonate “umbrella” (i.e., loss of alkalization of cholangiocyte apical membrane proximity) may increase membrane permeation of protonated (and thus hydrophobic) bile acids leading to bile duct injury [14]. The integrity of the cholangiocyte apical glycocalyx also appears critical for the maintenance of cholangiocyte protection [15]. The “umbrella” hypothesis further involves the interplay between the Na+–independent Cl−/HCO3− anion exchanger (AE2) and active Cl−–transporters, most notably the ATP-driven cystic fibrosis transmembrane conductance regulator (CFTR), but also the more recently defined Ca2+–driven anoctamin 1 channel [16]. The bile acid receptor TGR5 is most likely expressed at the cilia on the biliary epithelium [17], and may be involved in the regulation of these systems [18].

Sclerosing cholangitis in the context of deficient Cl−–secretion in cystic fibrosis occurs in up to 1/3 of the patients. Cystic fibrosis-related cholangiopathy has been linked to innate immune regulation, partly based on the fact that Cfr−/− mice only develop biliary lesions in the context of induced colitis [19]. The mechanism in this model seems to involve altered regulation of toll-like receptor 4 (TLR4) signaling in these mice [20]. Intriguingly, the cholangiopathy in Cfr−/− mice was resistant to treatment with non-ursodeoxycholic acid (nor-UDCA), but responded to treatment with oral neomycin and polymyxin B, suggesting a potential role of the gut microbiota in driving the increased NF-κB signaling [20]. These aspects add to the prevailing hypothesis of CFTR dysfunction leading to dehydrated mucosal surfaces and impaired mucociliary clearance. In PSC, a possible role of alterations in mucus secretion from peribiliary glands has not been studied [21, 22], but warrants incorporation in future CFTR-centered assessments.

Regulatory aspects of the enterohepatic circulation of bile acids and bile acid detoxification systems may be relevant to human PSC. Several recent review articles summarize the principles of these mechanisms [23, 24]. Key updates include the important role of farnesoid X receptor (FXR) activation in ameliorating cholangitis development in the Abcb4−/− model [25, 26], as well as the regulatory function of fibroblast growth factor 19 (FGF19) in bile homeostasis [27–29]. Genetic associations in ulcerative colitis and to a lesser extent PSC at 2q35 encompass several genes [30, 31], including TGR5 and IL8RA and IL8RB genes [30, 31]. Mechanistically, direct evidence so far available on TGR5 on PSC related aspects seems to concern immunosuppressive effects of receptor activation [32–36], more than aspects of bile homeostasis [17, 18, 37, 38]. Interpretation of the genetic findings at 2q35 in PSC is difficult, since I18 has also been implicated in cholestatic [39, 40]. Likely there are interactions and synergism between several of the regulatory pathways in the context of cholestasis (e.g., FXR and TGR5 [41]) and other receptors may also be involved, e.g., pregnane X receptor (PXR) and G-protein coupled receptor 35 (GPR35) [42, 43]. Importantly, bile homeostasis closely integrates with regulation of lipid metabolism, as also reflected by studies in the Abcb4−/− model [44].

**The gut-liver axis**

The earliest theories of PSC development derive from the potential relationship between IBD and inflammatory affection in the portal tracts (“the leaky gut”). At present, there is renewed enthusiasm and great expectations concerning the opportunities associated with characterization of gut microbiota with genomic technologies [45–47]. The gut microbiota is shaped by host gender [48], genetics [49], immune function [50], as well as environmental factors (e.g., diet and xenobiotics [51]), and is likely to represent one component of the pathogenesis of several metabolic and inflammatory conditions. One example illustrating...
how the specific genetic constitution of an individual influences the gut microbial environment is given by the FUT2 association in PSC (and Crohn’s disease) [52,53]. Even in healthy individuals, homozgyous state for the disease associated variant is associated with substantial alterations in gut microbial community composition [53,54]. The impact of dietary fat on IBD susceptibility represents another example of gene-environment interactions. The interleukin 10 gene (Il10) is an established susceptibility factor for human ulcerative colitis [55]. Saturated fat enriched diet in Il10−/− mice induces specific changes in the bile acid pool (an increased fraction of taurocholic acid) that lead to alterations in the gut microbial community composition ultimately increasing susceptibility to inflammatory bowel disease in these mice from 25–30% to over 60% [56]. Ongoing research at many sites presently explores the role of similar effects in human PSC patients and established mouse models of sclerosing cholangitis.

An important aspect of immune-mediated liver diseases and liver fibrosis is the recruitment process by which immune-cells and monocytes are recruited from circulation into sites of injury and inflammation. As reviewed elsewhere [57], gut activated T-lymphocytes in the context of IBD may contribute to portal inflammation in PSC due to overlapping adhesion molecule profiles of gut and liver endothelium (i.e., mucosal vascular addressin cell adhesion molecule 1 [MadCAM-1] and vascular cell adhesion molecule 1 [VCAM-1] expression along with chemokine C-C motif ligand 25 [CCL25] secretion). Generation of the corresponding T-lymphocyte phenotype (i.e., α4β7, α4β1, and chemokine C-C motif receptor 9 [CCR9], respectively) is retinoic acid dependent [58], predominantly occurs in the gut associated lymphoid tissues [59], and only under special circumstances in the liver [60]. This “enterohepatic circulation of lymphocytes” is clearly of potential relevance to PSC pathogenesis, and the MadCAM-1 expression observed in PSC affected livers seems to be dependent on amine oxidase activity of vascular adhesion protein 1 (VAP-1) in the presence of tumor necrosis factor alpha (TNFα) [61]. Inhibitors of CCR9 (GSK1605786) and α4β7 (vedolizumab) are already in clinical trials for IBD [www.clinicaltrials.gov]. In addition to these, there may be a role in PSC for liver-specific therapeutic manipulation of lymphocyte recruitment via VAP-1 [62]. Mechanisms of the recruitment of other inflammatory cells to the liver (monocytes, Th17 cells, T regulatory cells, and B cells) have also been explored and may offer similar opportunities for manipulating inflammatory processes in PSC [63–67].

Pathogenesis or therapeutic opportunities?

To what extent these axes of most active research are representative of primary disease mechanisms in PSC can only be speculated (Fig. 3). Largely, the key mechanism of IBD associated PSC phenotype remains obscure. However, regardless of the driving forces of the disease process in this “core” predominant PSC phenotype, efforts now delineating mechanisms for disease propagation and bile duct fibrosis are likely to be useful in the definition of novel treatment modalities.

Clinical characteristics of PSC – what is primary and what is secondary?

The list of causes of secondary sclerosing cholangitis strictly speaking only pertains to defined etiologies with histopathological appearance similar to PSC (Table 2). Examples include genetic causes on the one hand, and environmental and iatrogenic causes on the other (Fig. 4). In clinical practice, it is however important to recognize that also infiltrative diseases and various types of malformations may mimic PSC on cholangiography (Table 2). As evident from the discussion on pathogenesis, it remains to be clarified whether the remaining “bag” of PSC after these causes have been excluded is a “mixed bag” or a relatively defined disease entity with a predominant representation of the IBD associated cholangitis. Given the relatively higher frequency of IBD among PSC patients in Northern Europe and the US (62–83%) than in Southern Europe (approximately 50%) and Asia (20–37%), there may be geographic differences (i.e., the IBD-associated PSC is likely represented by a smaller fraction outside of populations of Northern European descent). The term “IBD-related sclerosing cholangitis” has been proposed for this group of patients [68], but is not established.

IgG4 and sclerosing cholangitis

IgG4 associated cholangitis is a sclerosing cholangitis that has been acknowledged during the recent years. Due to the corticosteroid responsiveness, this condition is an important differential diagnosis to PSC. Etiology is not defined, but may represent an
Secondary sclerosing cholangitis (SSC) entities cluster at both ends of this spectrum (e.g., genetic causes versus infectious causes, respectively), whereas primary sclerosing cholangitis (PSC) is a complex phenotype involving multiple, interacting genetic and environmental factors. Factors involved in the development of SSC may modify or complicate disease course in SSC (summarized in Table 3). Most characteristically, affection does not follow a “distal-to-proximal” distribution. Rather, there is a right sided predominance of inflammation, with also inflammatory affections observed in the ileum, i.e., distribution seems to maximize in the vicinity of the valvula Bauhinii, also consistent with predominance of right-sided colonic carcinomas in PSC patients with IBD [81,82]. There is at present no molecular basis known to explain these features. There is an increased risk of ulcerative colitis even without PSC in siblings of PSC patients, suggesting the presence of a shared genetic predisposition between PSC and IBD [83]. However, in the most recent large-scale assessment of this genetic overlap [9], only 8 out of 163 bona fide IBD risk loci associate with PSC (Fig. 2), and for half of the PSC loci, no consistent associations could be detected in IBD. Out of the 8 loci associating with both PSC and IBD in this analysis, one preferentially associates with ulcerative colitis [9]. Concordantly, IBD in PSC represents the most common inflammatory comorbidity in PSC [76]. There is some evidence to suggest that comorbidities in PSC (e.g., IBD and other autoimmune diseases) are of prognostic importance [77–80], but there is no consensus definition of these subgroups. Although IBD is most often classified as ulcerative colitis, there are several distinct features of IBD in PSC (summarized in Table 3). Most characteristically, affection does not follow a “distal-to-proximal” distribution. Rather, there is a right sided predominance of inflammation, with also inflammatory affections observed in the ileum, i.e., distribution seems to maximize in the vicinity of the valvula Bauhinii, also consistent with predominance of right-sided colonic carcinomas in PSC patients with IBD [81,82]. There is at present no molecular basis known to explain these features. There is an increased risk of ulcerative colitis even without PSC in siblings of PSC patients, suggesting the presence of a shared genetic predisposition between PSC and IBD [83]. However, in the most recent large-scale assessment of this genetic overlap [9], only 8 out of 163 bona fide IBD risk loci associate with PSC (Fig. 2), and for half of the PSC loci, no consistent associations could be detected in IBD. Out of the 8 loci associating with both PSC and IBD in this analysis, one preferentially associates with ulcerative colitis [9] while the others associate also with both PSC and IBD [83]. However, in the most recent large-scale assessment of this genetic overlap [9], only 8 out of 163 bona fide IBD risk loci associate with PSC (Fig. 2), and for half of the PSC loci, no consistent associations could be detected in IBD. Out of the 8 loci associating with both PSC and IBD in this analysis, one preferentially associates with ulcerative colitis [9] while the others associate also with Crohn’s disease. Clinical classification of IBD in PSC as Crohn’s disease that in some cases is in line with this overlap. In our view, the overall evidence and practical implications (e.g., the increased risk of dysplasia [84]) support the notion of a distinct sub-entity of IBD (“PSC-IBD”) and it may soon be worth considering to implement this term in clinical practice [85].

**Cholangiocarcinoma in PSC**

Recently reported patient series support the notion that up to 50% of cholangiocarcinomas in PSC are diagnosed within the first year after the diagnosis of PSC [86–88] and the challenge of making the diagnosis remains unresolved [89]. In up to 1/3 of the

### Table 2. Secondary sclerosing cholangitis

Conditions listed include both sclerosing cholangitis according to defined etiologies and liver affections that may mimic primary sclerosing cholangitis (PSC) on cholangiography. According to clinical practice guidelines, IgG4 related disease is now considered in the context of secondary sclerosing cholangitis [114,117].

<table>
<thead>
<tr>
<th>Infection</th>
<th>Bacterial/parasitic cholangitis</th>
<th>Recurrent pyogenic cholangitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunodeficiency related (infections)</td>
<td>Congenital immunodeficiency</td>
<td>Acquired immunodeficiency (e.g. HIV)</td>
</tr>
<tr>
<td>Mechanic/toxic</td>
<td>Cholelithiasis/choledocholithiasis</td>
<td>Surgical bile duct trauma</td>
</tr>
<tr>
<td>Ischaemic</td>
<td>Vascular trauma</td>
<td>Hepatic allograft arterial insufficiency</td>
</tr>
<tr>
<td>Pancreatic disease</td>
<td>Chronic pancreatitis</td>
<td>IgG4 related systemic disease</td>
</tr>
<tr>
<td>Others</td>
<td>Cystic fibrosis cholangiopathy</td>
<td>ABCB4 associated cholangiopathy</td>
</tr>
</tbody>
</table>

**Fig. 4. Concept of the relationship between environmental and genetic risk factors for sclerosing cholangitis.** Secondary sclerosing cholangitis (SSC) entities cluster at both ends of this spectrum (e.g., genetic causes versus infectious causes, respectively), whereas primary sclerosing cholangitis (PSC) is a complex phenotype involving multiple, interacting genetic and environmental factors. Factors involved in the development of SSC may modify or complicate disease course in PSC (e.g., ABCB4 variants and cholangitis, respectively).
Review

Cholestatic pruritus

Cholestatic pruritus may be debilitating for patients with PSC. Treatment is difficult and reviewed elsewhere [106]. In refractory cases, plasmapheresis and albumin dialysis may be effective [107], but sometimes pruritus may represent an indication for liver transplantation. There seems to be underlying differences in the patient population biology since some patients may be highly cholestatic without pruritus, whereas other patients are severely affected even when cholestasis is modest. Genetic reasons (e.g., modifiers reflecting underlying cholestatic predisposition [108]) or differences in immune reaction profiles between the patients [109] may be involved in causing the pruritic predisposition. At some level, the mechanisms causing cholestatic pruritus seem to involve the conversion of lysophosphatidylcholine into lysophosphatidic acid (LPA) by autotaxin [110]. Autotaxin activity in cholestatic patients correlates with pruritus, which is not the case for other candidate pruritogens like bile salts, histamine, tryptase, substance P or endogenous opioids. The mechanisms behind the increased autotaxin activity remain to be established. At another level, accumulated bile acids may be directly involved in cholestatic pruritus via activation of TGR5 on sensory neurons transmitting pruritus and pain [111].

PSC with features of autoimmune hepatitis

In a position paper published by the International Autoimmune Hepatitis Group (IAIHG), the demarcations between PSC, autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC) are elaborated upon [112]. Important, it is argued for abandoning the term “overlap syndromes” and opting for a primary diagnosis of either one of the three conditions. In both PSC and PBC, there is a propensity for non-biliary autoimmunity, and it is not surprising that in some patients this may also include hepatocyte affection and features of AIH (in 7–14% and 2–19%, respectively). In cases where a primary diagnosis of PSC and PBC can be made, the IAIHG scoring systems for AIH should not be applied in the diagnosing of such features [113]. Probably, sound clinical judgment of biochemical (ALT at least 5x ULN and IgG at least 2x ULN) and histological (suspected features of AIH is the main indication for liver biopsy in PSC) parameters should form the basis of diagnosing such features. Although not evidence based, immunosuppressive therapy along standard guidelines for treatment of AIH is recommended for PSC patients with overlapping features with AIH [112,114]. Treatment response in terms of delaying cirrhosis development is likely less pronounced than in AIH without a primary diagnosis of PSC [115,116]. It is thus important to be aware of the risk of side effects and to assess treatment response. From a mechanistic perspective, it is interesting that co-occurrence of PSC and PBC features rarely occurs. There is no evident explanation, yet it is interesting to note that for a genetic risk locus where a shared effect between PSC and PBC has been reported (1p36, see Table 1), the effect (odds ratio) of the risk variant goes in the opposite direction in PSC compared with PBC.

Table 3. Selected studies from the US, Europe and Asia summarizing key features of patients with primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) [154–156]. (See below-mentioned references for further information)

<table>
<thead>
<tr>
<th>Study, [Ref.]</th>
<th>N_psc-ibd</th>
<th>Pancolitis (%)</th>
<th>Backwash ileitis (%)</th>
<th>Rectal sparing (%)</th>
<th>Neoplasia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faubion et al. [154]</td>
<td>39</td>
<td>80</td>
<td>n.a.</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>Loftus et al. [85]</td>
<td>71</td>
<td>87</td>
<td>51</td>
<td>52</td>
<td>15</td>
</tr>
<tr>
<td>Joo et al. [155]</td>
<td>40</td>
<td>85</td>
<td>36</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Jørgensen et al. [156]</td>
<td>155</td>
<td>55</td>
<td>20</td>
<td>65</td>
<td>n.a.</td>
</tr>
<tr>
<td>Ye et al. [157]</td>
<td>21</td>
<td>95</td>
<td>43</td>
<td>38</td>
<td>14</td>
</tr>
</tbody>
</table>

n.a., not available.
for the diagnosis and management of PSC patients (Clinical Points 1 and 2). In most aspects, the guidelines agree (reviewed elsewhere [2]), yet the discrepancy on principle directions for prescription of UDCA caused a still ongoing discussion on which one of the conclusions was most appropriate. The EASL guidelines concluded that limitations in available data did not yet allow a specific recommendation for the general use of UDCA in PSC. The same guidelines opened up to the use of moderate dose UDCA (15–20 mg/day) in individuals with strong family history of colorectal cancer, previous colorectal neoplasia or longstanding extensive colitis, not for the improvement of liver disease, but to prevent neoplasia. The AASLD guidelines unambiguously recommend against the use of UDCA in adult PSC patients.

Clinical Points 2. Treatment of primary sclerosing cholangitis [114, 117]

- The role for ursodeoxycholic acid (UDCA) in PSC is currently debated. There is no definite evidence that UDCA improves survival or is efficacious in the prevention of colorectal or biliary neoplasia. Practice varies, however, between centers. It has been the tradition of the current authors to be reluctant to start PSC patients on UDCA

- Although not evidence-based, PSC patients with features overlapping with those of autoimmune hepatitis should be considered for therapy with corticosteroids and/or other immunosuppressive agents. Therapy should be individualized and adjusted according to response and the risk of side effects

- In PSC patients with dominant bile duct strictures causing biochemical and/or clinical signs of cholestasis, endoscopic dilatation with or without stenting is recommended. Short-term (2-3 weeks) stenting is favored by many, including the current authors. A multicenter, prospective, randomized intervention trial to compare the efficacy of single session balloon dilatation and short-term stenting is currently ongoing. Prophylactic antimicrobial therapy is recommended during the procedure

- Liver transplantation is a curative treatment modality in PSC patients with end-stage liver disease and in selected cases with severe symptoms of cholestasis. Transplantation may also be considered in patients with evidence of biliary epithelium dysplasia

Bile acid therapy

We will not re-review the literature that led to the slightly differing conclusions on UDCA therapy in PSC [2], but rather mention some subsequent reports that have elaborated on the complexity of the problem. Serum alkaline phosphatase (ALP) level is a long established risk factor for disease progression in PSC [118]. Genetic risk factors for PSC (i.e., FUT2) overlap with genetic factors influencing serum levels of ALP in healthy individuals [119,120], but how these factors are involved in the prognostic importance of ALP has not been studied. In a retrospective analysis of 139 PSC patients [121], those receiving UDCA and achieving an improvement of ALP to <1.5x ULN had significantly longer survival without end points compared with patients without ALP normalization. In series involving patients from previous UDCA treatment trials, the association between ALP normalization and PSC behavior seemed to be independent of UDCA administration [122,123]. The interpretation of all these data requires some caution; in principle both UDCA administration and PSC behavior seem to independently influence ALP levels. At present, it cannot be claimed that ALP normalization in the context of UDCA administration is representative of drug efficacy. Accounting for FUT2 related biology, there is a strong basis for further studies to clarify these mechanisms that seem to converge on a robust representative of disease intensity in PSC, potentially also amendable by means of bile acid therapy.

The effects of high-dose UDCA (28–30 mg/kg/day) treatment on the bile acid pool warrant reflections [124]. In PSC patients receiving such treatment, there was both an expansion and compositional changes of the total bile acid pool. While only the expansion seemed to associate significantly with adverse outcomes (progression to cirrhosis, development of varices, cholangiocarcinoma, liver transplantation, and death), the increased proportion of lithocholic acid found in this trial is theoretically harmful. It needs to be noted that in another study of bile acid pool compositional effects from UDCA treatment, only UDCA itself was significantly enriched [125]. Nevertheless, given the disease distribution in PSC, predominantly affecting the “proximities of the enterohepatic circulation”, the influence of bile acid treatment, or treatment aiming at modifying the regulation of bile acid homeostasis (e.g., FXR agonists), needs further consideration. Importantly, the bile acid pool serves not only as a potential “toxic medium” to epithelial surfaces, but profoundly interacts with the metabolism and immune function via effects on the gut microbiota [56,126,127]. There is growing interest in the influence of this interaction on IBD and liver diseases [128–130], and it may be wise to advice for future clinical trials in PSC to include assessments of bile acid composition and metagenomic parameters in the basic study readout [51].

Antibiotics and beyond

Of the many approaches currently explored for treatment of PSC, antibiotics most clearly link up with the intersections between inflammation, bile acid homeostasis, and gut microbiota. Distinguishing between non-absorbable (i.e., local effects on the gut microbiota only) and absorbable (i.e., including a portal and systemic anti-microbial effect) is reasonable. Non-absorbable antibiotics like vancomycin exert effects on systemic immune function, e.g., by influencing regulatory T-cell subsets. In a trial of 14 pediatric patients with PSC [131], significant improvement in hepatic biochemistries was observed, paralleling increased levels of regulatory T-cells. Regarding absorbable antibiotics, improvements in hepatic biochemistries have also been observed for metronidazole [132], azithromycin [133] and minocycline [134], altogether suggesting that liver affection in PSC may be influenced by anti-microbial therapies. We anticipate that upon the further characterization of metagenomic components in PSC pathogenesis (Fig. 3), specific attempts to manipulate these (by antibiotics, probiotics, prebiotics or dietary means) will be made.

The paradox of immunosuppression

The strong HLA association along with multiple shared risk loci between PSC and prototypical autoimmune diseases (Table 1),
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more pronounced than for IBD, strongly suggests that PSC pathogenesis has an "autoimmune" component [2]. Antibodies against biliary as well as colonic epithelial cells have been reported, and the preferential usage of particular T-cell receptor gene segments of hepatic T-cells also suggests the existence of tissue-specific antigens in PSC pathogenesis. In spite of this, no immunosuppressive drug tested to date has shown to significantly improve clinical outcomes. Of particular interest are cyclosporine A (CsA) and tacrolimus that exert immunosuppressive actions via inhibition of calcineurin, which again is indispensable for cytokine induction, interleukin 2 (IL2) in particular, upon engagement of the T-cell receptor. Genetic associations in PSC are reported both at the IL2 and IL2 receptor alpha (IL2RA) loci (Table 1), directly suggesting an involvement of the IL2-signaling pathway in PSC pathogenesis. Treatment trials show some influence from CsA on IBD activity in PSC [135], and from tacrolimus on hepatic biochemistries [136], but no effects on clinical end points are evident and side effects preclude a broad application. Effects of CsA and tacrolimus may also differ, at least concerning IBD in the context of PSC. This was recently underscored by the finding of enhanced IBD activity after liver transplantation for PSC in patients receiving tacrolimus and mycophenolate compared with patients on CsA and azathioprine [137]. Mechanistic elucidation of the immunological consequences of PSC susceptibility loci in vivo needs to be performed before rational application of immunosuppression can be drafted on the basis of genetics.

Antifibrotic therapy

To some extent, it may be argued that present clinical trials in PSC have concerned patients in whom fibrotic lesions are already manifested and efficacy of immunosuppressive and antibiotic treatment cannot be expected. Antifibrotic treatment strategies in preparation largely build on studies on the Abcb4−/− mouse model. Some effects converge on nuclear receptor signaling pathways, including TGR5, FXR, and peroxisome proliferator activated receptor gamma (PPARγ) [26,138]. So far, no nuclear receptor has been identified as a target of nor-UDCA [139]. Other components of the Abcb4−/− fibrogenesis are currently being targeted in treatment trials, e.g., lysyl oxidase-like 2 [140] by monoclonal antibody GS6624 (http://clinicaltrials.gov/ct2/show/NCT01672853). Up to the point where a diagnosis of PSC may be made at a pre-clinical, pre-fibrotic stage, therapies derived from this model may hold promise.

Cholangiocarcinoma surveillance

The most challenging aspect of PSC follow-up remains the unpredictable occurrence of cholangiocarcinoma. Management and surveillance strategies are reviewed elsewhere [89], and novel aspects predominantly derive from proteomic and epigenetic approaches. In serum, a proteomic study report the potential diagnostic improvement achieved by including serum leucinerich α-2-glycoprotein (LRG1) and IL6 in prediction models for cholangiocarcinoma [141]. In bile, a panel of 22 peptides detected in a screening panel was shown to discriminate between cholangiocarcinoma and PSC with an area under the receiver operating characteristics curve of 87% [142], correctly detecting 8 out of 10 cases of cholangiocarcinoma complicating PSC. In urine, a similar approach led to comparable results [143], with correct classification of 10 out of 10 cases of cholangiocarcinoma arising in the context of PSC. Based on experience in other cancers and preliminary data [144,145], epigenetic markers are also potential biomarkers for early cholangiocarcinoma development. This accounts for genes affected by CpG hypermethylation [146], as well as cholangiocarcinoma-associated serum micro RNA profiles. The prospective clinical utility of all these approaches is presently under study at several sites and it is likely that some approaches will be incorporated in patient management in the near future. This will ease timing for liver transplantation and thus ultimately assist in reducing cholangiocarcinoma-related deaths in the PSC population.

Liver transplantation

Due to the lack of effective medical treatment, liver transplantation remains the principle therapeutic option in PSC. The present literature on the high risk of acute cellular rejections in PSC following liver transplantation and PSC recurrence in the allograft was recently reviewed elsewhere [147]. One key ongoing discussion relates to whether the presence of an intact colon in PSC patients with IBD influences disease recurrence, but due to the lack of reproduction so far [148], these data are only useful for pathophysiological considerations and should not prompt pre-transplantation colectomy on a general basis. In our center, biliary epithelium dysplasia by brush cytology is considered an indication for liver transplantation in PSC, but this practice has not been prospectively evaluated. Also, in highly selected cases of hilar cholangiocarcinoma, liver transplantation in conjunction with neoadjuvant chemotherapy and radiation should be considered [149,150], in particular since patients with PSC may present with favorable tumor characteristics compared with cholangiocarcinoma outside of the context of PSC [151]. Further studies are needed to clarify the utility of liver transplantation for intrahepatic cholangiocarcinoma [152], which is presently advised against. In areas where prioritizations for liver transplantsations are made on the basis of model of end-stage liver disease (MELD) assessments, issues related to malignancies in PSC add to an already ongoing discussion on exception criteria for patients with PSC [153].

Conclusions

There is a growing interest in the hepatological community to resolve the main challenges associated with PSC. Ongoing efforts to delineate pathogenesis are of key importance, since they ultimately may guide the rational management of remaining clinical challenges, i.e., early diagnosis of PSC in patients with IBD, early diagnosis of cholangiocarcinoma in PSC, determining surrogate markers for disease progression and disease activity; and finally, treatment modalities that significantly influence clinical outcome.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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