Primary Sclerosing Cholangitis

Piotr Milkiewicz and Ewa Wunsch

Abstract

Primary sclerosing cholangitis (PSC) is a chronic liver condition which may affect both intra and extrahepatic biliary tree. Etiology of PSC remains to be fully elucidated but genetic, autoimmune, inflammatory and possibly infective factors could all contribute to its development. More than two-thirds of patients are males and the most commonly associated condition is an inflammatory bowel disease which occurs in up to 70% of affected subjects. Endoscopic cholangiopancreatography (ERCP) and magnetic resonanse cholangiopancreatography (MRCP) remain a gold standard in the diagnosis of this condition. No curative treatment of PSC exists and a proportion of patients who develop liver failure or suffer from recurrent episodes of cholangitis requires liver transplantation. PSC is associated with increased risk of malignancies, in particular cholangiocarcinoma which may arise in 12% of patients. The main aim of this chapter is to review the current knowledge on pathogenesis and clinical aspects of PSC as well as its associated malignancies.

Keywords

Primary sclerosing cholangitis · Cholangiocarcinoma · Colorectal cancer

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Contents

1 Introduction

Sclerosing cholangitis comprises a group of chronic, progressive cholestatic liver diseases which may affect both intra and extrahepatic biliary tree. Secondary and rare causes of IgG4 related sclerosing cholangitis include portal bilopathy, sclerosing cholangitis, inflammatory hepatic pseudotumours, autoimmune pancreatitis, mast cell cholangiopathy or AIDS related cholangiopathy. The main focus of this chapter is primary sclerosing cholangitis (PSC), the commonest cause of sclerosing cholangitis. PSC is one of the most fascinating and challenging conditions in the contemporary hepatology. Its aetiology remains a mystery and although underlying immunological mechanisms play an important role, for many reasons PSC can not be called a typical autoimmune condition. In terms of diagnosis and treatment neither reliable serum markers to diagnose PSC exist nor is curative medical therapy available. Liver transplantation potentially cures the disease in many patients however the disease may recur after surgery even leading to graft loss. Significantly increased risk of both biliary and extrahepatic malignancies pose a real challenge in the management of this condition.

2 Epidemiology

Incidence of PSC seems to be higher in northern Europe and United States than in southern Europe or Asia. Unfortunately, the data on the epidemiology of PSC are scanty with only a few population-based studies existing in the literature. Boberg et al. (1998) in their study on Norwegian population found the mean annual incidence to be of 1.3/100000 and the point prevalence of 8.5/100.000. Bambha et al. (2003) who studied American population living in Minnesota showed an age-adjusted incidence of PSC of 1.25/100000 in males and 0.54/100.000 in females with the prevalence of 20.9/100.000 in males and 6.3/100000 in females. In another, population-based, Canadian study, Kaplan et al. (2007) found an annual incidence to be of 0.92/100.000 and more specifically for the small-duct variant of

PSC of 0.15/100000. A more recent study from the UK where the incidence rates during the period between 1991 and 2001 were analysed showed the rate of the disease to be 0.41/100000 person-years and the prevalence in 2001 of 3.85/100000. Authors found that the incidence of PSC over the analyzed period increased by 50% (Card et al. 2008).

3 Aetiopathogenesis

Without a doubt the aetiology of PSC is multifactorial with genetic, autoimmune, inflammatory and possibly infective factors all playing their role.

An increased prevalence of PSC has been found in first degree relatives (Bergquist et al. 2005) and recent, Swedish study on 678 patients with PSC showed the risk (with the hazard ratio and 95% confidence interval) of cholangitis in off spring, siblings and parents of these patients to be 11.5; 11.1 and 2.3, respectively when compared to the relatives of the control group (Bergquist et al. 2008).

HLA haplotypes B8 and DR3 which are both associated with autoimmune conditions occur with an increased frequency in patients with PSC. MICA genes are localised between HLA-B and TNFA in the MHC class I region and MCA*008 homozygocity showed the most significant association with PSC, reaching an odds ratio of 5.01 (Norris et al. 2001). It has also been postulated that haplotypes DRB1*0701, DRB1*0401 and MICA*002 may be related to decreased risk of PSC (Spurkland et al. 1999). With regard to non-MHC genes data are conflicting and almost as a rule are not reproducible (Kitiyakara and Chapman 2008).

An autoimmune background for PSC is suggested by its common coexistence with typical autoimmune conditions and inflammatory bowel diseases, predominantly ulcerative colitis. PSC is associated with various autoantibodies, including antinuclear antibodies (ANA), smooth muscle antibodies (SMA) or perinuclear-staining antineutrophil cytoplasmic antibodies (p-ANCA). They occur with various frequencies but are unlikely to be directly involved in the pathogenesis of this condition (Angulo et al. 2000).

A potential role of infection as a possible trigger of an immune-mediated inflammation has been considered since the late 1980's. Several studies have shown a high prevalence of various microorganisms obtained from either bile or bile ducts tissues (Kahana et al. 2003; Fox et al. 1998; Olsson et al. 1998; Kulaksiz et al. 2006). However, these organisms have been found mainly in patients with immunodeficiency syndromes or PSC-like secondary cholangitis. On the other hand Olsson et al. reported a significant prevalence of hepatobiliary infection in patients with PSC caused by colonic bacteria, predominantly α-haemolytic Streptococci (1998). A potential role of infectious agents can also be suggested by the fact that combined therapy with metronidazole and ursodeoxycholic acid (UDCA) improves both liver biochemistry and histology in patients with PSC (Farkkila et al. 2004).

Well known close linkage between PSC and chronic inflammatory bowel disease (IBD) led to the hypothesis that portal bacteremia associated with increased permeability of the inflamed colon could be a potential source of biliary inflammation. This hypothesis is strengthened by the works on animal models where hepatic injury similar to PSC were observed after intraportal injection of intestinal non-pathogenic bacteria (Kono et al. 1988) or in experimental small bowel bacterial overgrowth (Lichtman et al. 1990). These findings, however, do not explain why PSC occurs more frequently in patients with ulcerative colitis than with Crohn's disease and also human studies have not confirmed portal bacteraemia or portal vein phlebitis in patients with ulcerative colitis. However, recently published studies support the idea that intestinal permeability, secondary to IBD could play a role in the pathogenesis of PSC. According to this hypothesis, colonic bacteria or bacterial antigens can trigger ANCA formation and autoimmune reaction in the genetically susceptible host by molecular mimicry in a cross-reaction with human autoantigens (O'Mahony and Vierling 2006). In this context induction of bile duct inflammation neither require a direct microbial presence in the biliary ducts nor the portal bacteraemia. However, unlike in primary biliary cirrhosis (PBC) where ubiquitous, xenobiotic-metabolising bacteria, *Novosphingobium aromaticivorans* has been suggested as a source of molecular mimicry (Selmi et al. 2003), there is no conclusive evidence which bacterial antigens might cross-react with human autoantigens and thereby play the trigger's role of autoimmunity phenomena in PSC. Recently, the bacterial cell division protein FtsZ has been proposed as a potential antigen for p-ANCA in patients with PSC and AIH (Terjung and Spengler 2009).

In patients who undergo proctocolectomy for ulcerative colitis symptoms of PSC may occur many years later. This fact led to the hypothesis that PSC can be triggered by/through long-lived memory cells, primary recruited during active inflammation of the colon (Grant et al. 2002). These T lymphocytes undergo enterohepatic circulation and can cause an organ specific immune response. The described lymphocyte tropism is a result of the unique expression of many adhesion molecules restricted to the particular locations. It has been shown that there is an overlapping expression of mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and vascular adhesion protein-1 (VAP-1) between the mucosal and hepatic endothelium, especially during episode of inflammation (Grant et al. 2001). It may suggest that mucosal memory cells may be able to enter the liver using both VAP-1 and MAdCAM-1 and, when activated by the particular stimulus or stimuli, can trigger the chronic liver inflammation even after resolution of colitis.

4 Clinical Features and Diagnosis

Up to 71% of patients are male. A significant proportion (between 21 and 44%) of affected subjects are asymptomatic at the diagnosis and their disease is diagnosed as a consequence of further investigations of accidentally found disturbance of

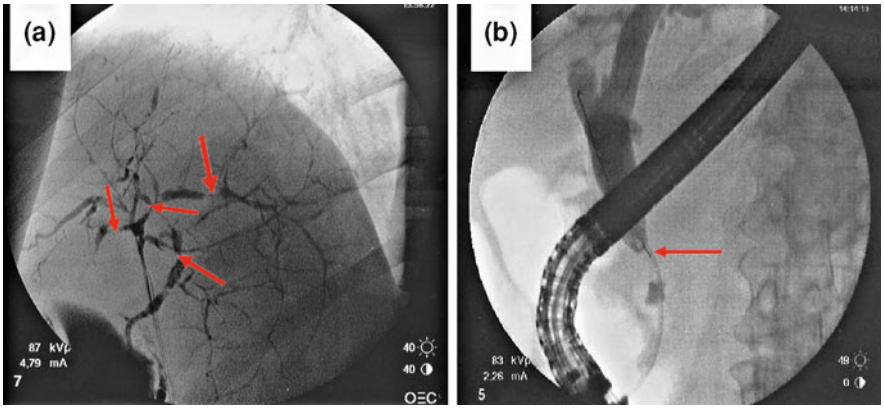

Fig. 1 **a** Primary sclerosing cholangitis with typical multiple stenoses seen in the biliary tree leading to a beaded pattern (*arrows*). **b** cholangiocarcinoma (CCA) of the common bile duct (*arrow*)

liver biochemistry. The most common complaints in those who are symptomatic are abdominal pain, icterus, skin itching and recurrent episodes of fever (Weismuller et al. 2008). The prevalence of chronic fatigue, an extremely troublesome symptom in chronic cholestasis, (Milkiewicz and Heathcote 2004) is controversial. Bjornson et al. found it to be lower than in general population (Bjornsson et al. 2004) whereas in most recent study Al-Harty et al. were able to detect it in more than 90% of patients (Al-Harthy et al. 2009).

Inflammatory bowel disease (IBD) is the most commonly associated condition which can occur in up to 73% of patients. Ulcerative colitis is diagnosed in majority of affected subjects and colonic Crohn's disease comprises between 1 and 14%. Among other associated diseases of an autoimmune background, most common are insulin dependent diabetes mellitus (IDDM), thyroid conditions and psoriasis.

Liver biochemistry demonstrates cholestasis with elevated alkaline phosphatase (ALP). Mild/moderate elevation of serum transaminases can also be commonly seen. Bilirubin levels tend to fluctuate and increase during episodes of cholangitis. In patients who developed liver cirrhosis features of impaired synthetic function with decreased levels of albumin and prolonged prothrombin time can be seen. Autoantibodies, with an exception of p-ANCA (36) play neither diagnostic nor prognostic role (Terjung and Spengler 2005).

ERCP remains a gold standard in the diagnosis of PSC. As ERCP can be associated with complications such as pancreatitis or cholangitis, MRCP is a modality of choice in an early assessment, particularly in patients without clinical and biochemical symptoms suggesting the necessity of endoscopic intervention. Except non-invasiveness of MRCP, its clear advantage is a visualisation of bile ducts localised after significant stenoses where contrast medium may not penetrate. However, interpretation of MRCP scans requires advanced radiological expertise, for sure not available in all hospitals thus ERCP with its ability of direct

diagnostic (brush cytology) and therapeutic (stenting) interventions holds its role as a gold standard. Typical ERPC image in patient with PSC is shown in Fig. 1a.

It has been recently shown that overall complications rate after ERCP in patients with PSC was comparable to these without PSC. However the risk of cholangitis was significantly higher and the duration of the procedure was significantly longer in subjects with PSC (Bangarulingam et al. 2009).

Unlike in many other liver disorders, histology plays a minor role in the diagnosis of PSC as it shows significant variability and it affects clinical management in just 1.3% of patients (Olsson et al. 1995; Burak et al. 2003). It is however useful in the assessment of the stage of fibrosis and for confirming cirrhotic. A small proportion of patients have normal ERCP/MRCP, suffer from IBD and have histology compatible with PSC. This variant is called small-duct PSC and carries significantly better prognosis in terms of progression of the disease and the risk of CCA (Bjornsson et al. 2002). It has been recently shown that unlike in PSC with typical ERCP/MRCP picture the presence of IBD exerts no significant effect on the long-term prognosis in patients with small-duct variant (Bjornsson et al. 2008).

PSC can be overlapped with AIH, more commonly in children (Gregorio et al. 2001). Also in adults it has been postulated that all patients with AIH who have elevated ALP or GGT should be screened for PSC with MRCP (Abdalian et al. 2008). This approach permits detection of PSC in 10% of adult patients with AIH (Abdalian et al. 2008).

5 Malignancies in PSC

5.1 Cholangiocarcinoma

Cholangiocarcinoma (CCA) is a tumour with extremely bad prognosis and has similar incidence and mortality rates (Khan et al. 2008). Incidence shows geographical relationship with the highest rates observed in Thailand and being 100 higher than in Europe. In East Asia CCA is associated with infestation with hepatobiliary flukes, in particular *Opisthorchis viverrini* and *Clonorchis sinensis* (Shaib and El-Serag 2004; Watanapa 1996) and in Japan and Taiwan with hepatholithiasis (Okuda et al. 2002). In Europe, PSC is the most common risk factor. Over last decades mortality rates of CCA show a significant increase of intrahepatic CCA and no increase or even fall in extrahepatic form. These data have to be interpreted with caution due to a potential error related to misclassification of hilar (Klatskin) tumour which in terms of its localisation is extrahepatic but in ICD-0-2 classification it received a code of an intrahepatic one.

In terms of pathogenesis, CCA is clearly related to processes induced by inflammation and cholestasis. Undoubtedly, like in many other tumours, interleukin-6 (IL-6) is a key signalling cytokine involved in the pathogenesis of CCA (Wise et al. 2008). Its receptor subunit gp-130 is overexpressed in CCA (Yokomuro et al. 2000) and production facilitated by other inflammatory agents

(Park et al. 1999). Increased IL-6 not only causes CCA resistance to cytotoxic treatments (Isomoto et al. 2007; Kobayashi et al. 2005) but also leads to an activation of the family of mitogen activated protein kinases (MAPK) such as p44, p42 and p38 playing a crucial role in proliferation of CCA cells (Park et al. 1999). IL-6 produced by CCA cells in an autocrine fashion upregulates anti-apoptotic molecule Mcl-1 via STAT3 and AKT cascades (Kobayashi et al. 2005).

Various other cytokines enhanced by both inflammation and cholestasis in PSC trigger the cascade of inducible nitric oxide synthase (iNOS) activation followed by reactive nitrogen oxide species (RNOS) production which leads to DNA damage and mutagenesis (Blechacz and Gores 2008). Persistent activation of epidermal growth factor receptor (EGFR) by bile salts has been observed in CCA (Werneburg et al. 2003). This phenomenon facilitates proliferation of CCA cells. EGFR phosphorylation (along with the effect of bile acids, oxysterol and iNOS) triggers MAPK leading to increased expression of cyclooxygenase-2 (COX-2) in CCA cells and inhibition of apoptosis (Endo et al. 2002; Han et al. 2004). Growth of CCA cells is also affected by various other factors such as estrogens, neuropeptides or neuroendocrine hormones. 17 beta estradiol, one of the most toxic metabolites of estradiol (Milkiewicz et al. 2001) facilitates proliferation of CCA cells, an effect clearly inhibited by tamoxifen (Sampson et al. 1997). On the other hand stimulation of alpha2 receptors, gamma-aminobutyric acid and gastrin seem all decrease proliferation of CCA cells via various mechanisms (Wise et al. 2008; Kanno et al. 2002; Fava et al. 2005). Figure 2 shows in a simplified scheme of the development of CCA.

A large study on the relationship between PSC and CCA comprising about 400 patients from 5 European centres showed that 12.2% of patients with PSC were found to have CCA (Boberg et al. 2002). In 50% of them CCA was diagnosed within first year of the diagnosis of PSC and in a further 27% CCA was found during liver transplant assessment. Typical ERCP image of CCA is shown in Fig. 1b. Interestingly, although symptoms of jaundice, pruritus or abdominal pain were more pronounced in these who developed CCA, this relation was not seen when these patients were excluded from the analysis. Also, patients who developed CCA suffered from ulcerative colitis significantly longer than these who did not (17.4 years vs. 9 years). More recently a Dutch study found the 10 and 20 year rate of CCA in patients with PSC to be of 9% and 9%, respectively (Claessen et al. 2009a). Detailed description of diagnosis, staging and treatment of CCA is not an aim of this chapter. Authors would recommend recent review on it by Blechacz and Gores (Blechacz and Gores 2008).

5.2 Other Malignancies in PSC

5.2.1 Colorectal Cancer

An increased risk of colorectal dysplasia and cancer in patients with PSC and IBD has been demonstrated in several studies with their cumulative risk being 9, 31 and 50% after 10, 20 and 25 years as compared to 2, 5 and 10%, respectively for

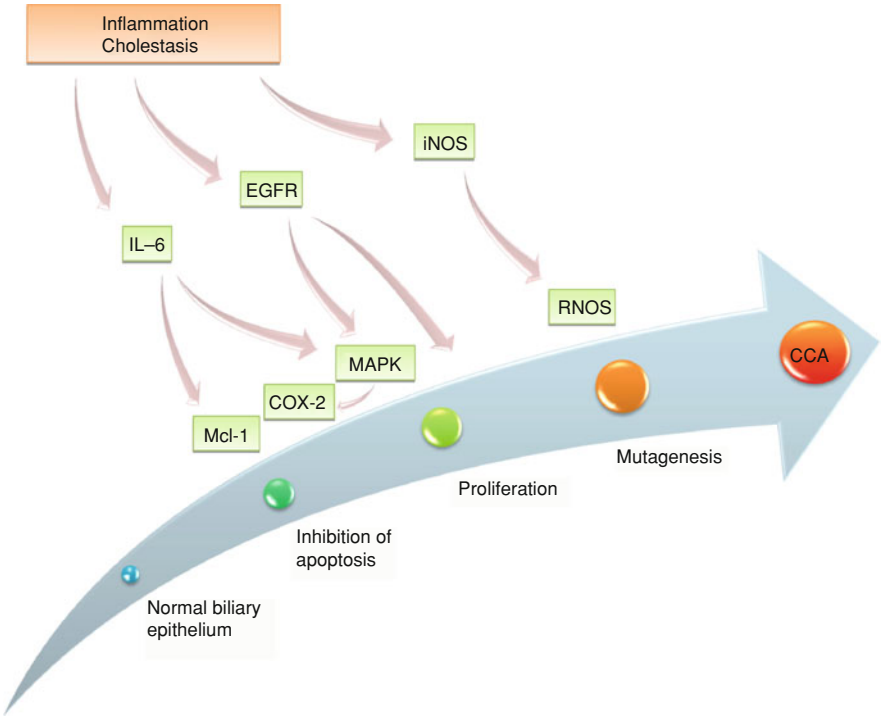

Fig. 2 Processes involved in the pathogenesis of cholangiocarcinoma in PSC (detailed description in the text). Inflammation and cholestasis with accumulation of several toxic agents lead to activation of various signaling cascades promoting inhibition of apoptosis, proliferation and mutagenesis of biliary epithelial cells. Abbreviations: interleukin-6 (IL-6), mitogen activated protein kinases (MAPK); inducible nitric oxide synthase (iNOS); reactive nitrogen oxide species (RNOS); cyclooxygenase-2 (COX-2); epidermal growth factor receptor (EGFR)

patients with UC only (Broome et al. 1995). In patients who underwent liver transplantation for PSC cumulative risk of developing colonic cancer was 14 and 17% after 5 an 10 years, respectively as compared to 0% at 10 years in these who have PSC without IBD (Vera et al. 2003). The natural history of colitis seems to be different in patients with PSC where it presents itself more frequently as pancolitis with less active course (Joo 2009). Thus the duration of colitis may be longer in these subjects, increasing the risk of colorectal carcinogenesis (Sokol et al. 2008). Also colonic cancer in patients with PSC and IBD is more frequently localised to the right colon (Claessen et al. 2009b). It is now widely recommended that patients with PSC and IBD should undergo colonoscopies on an annual basis (Kitiyakara and Chapman 2008). Those who do not have symptoms of colitis should undergo initial colonoscopy at their diagnosis of PSC but no clear guidelines exist as to the further follow-up in this subgroup of patients.

5.2.2 Gallbladder Cancer

When compared to general population, gallbladder polyps represent an increased risk of neoplastic transformation in patients with PSC, with as many as 57% of polyps found malignant in one series (Buckles et al. 2002). In another study, gallbladder adenocarcinomas were found in 14% of patients with PSC and an increased risk of gallbladder neoplasia in subjects with coexisting IBD or intrahepatic biliary cancer was also observed (Lewis et al. 2007). Thus regular examination of the gallbladder in PSC patients has been recently suggested and cholecystectomy recommended when gallbladder lesion is found, regardless of its diameter (Said et al. 2008).

5.2.3 Other Malignancies in PSC

Increased risk of two other gastrointestinal tract tumours, namely pancreatic (standard incidence ratio 9.7) and stomach cancer (standard incidence ratio 2.5) were observed in a large study from Sweden comprising more than 600 patients with PSC (Bergquist et al. 2002).

5.3 Chemoprevention

In patients with PSC and UC colonic cancer is more frequently localised to the right side of the colon suggesting a potential pathogenic role of agents to which proximal colon is exposed first. Among good candidates are secondary bile salts such as deoxycholate, a metabolite of primary bile salt (cholate), sythesised in the gut after the exposure of cholate to intestinal bacteria. Deoxycholate has a well proven toxic and cancerogenic properties (Bernstein et al. 2005; Rosignoli et al. 2008). In this context, a potential, chemopreventive role of UDCA, a hydrophyllic, secondary bile acid, commonly prescribed in PSC may be of importance. UDCA expresses several hepatoprotective properties not only by replacing toxic bile salts from a total bile acid pool but also inducing choleresis by triggering various intracellular signalling pathways (Paumgartner and Beuers 2004; Beuers et al. 2001; Milkiewicz et al. 1999, 2002; Wimmer et al. 2008). Our recent study applying gene array technique showed that UDCA is a potent modulator of genes involved in cell cycle and apoptosis (Chen et al. 2008). In terms of a potential chemopreventive effect of UDCA on the development of CCA the literature is equivocal (Olsson et al. 2005; Brandsaeter et al. 2004) but certainly it is affected by the fact that majority of CCA manifests itself shortly after the diagnosis of PSC thus the preventive effect of UDCA is difficult to prove. However, clear trends towards positive effect of UDCA have been seen by some authors with one study showing that no single case of CCA has been diagnosed in patients treated with UDCA longer than 8 years (Rudolph et al. 2007). More convincing evidence exists for chemoprevention of UDCA on colonic cancer (Wolf et al. 2005; Tung et al. 2001; Pardi et al. 2003). Additionally, these data is strengthened by the study on patients with another chronic, cholestatic liver condition, PBC where significant reduction of colonic polyps was observed in

Table 1 Studies on chemoprevention with ursodeoxycholic acid (UDCA) in primary sclerosing cholangitis (PSC)

Author/year of publication	Tumour/ lesion	Type of study	Results/conclusions
Tung et al. 2001	Colonic dysplasia	Cross-sectional	Significant decrease of colonic dysplasia in patients using UDCA
Pardi et al. 2003	Colonic dysplasia/ cancer	Prospective	Significant reduction of the risk of colonic dysplasia/cancer in patients taking UDCA
Wolf et al. 2005	Colonic dysplasia/ cancer	Retrospective	1. Not significant reduction of the incidence of colonic dysplasia/cancer in patients taking UDCA
			2. Significant reduction of overall mortality in patients taking UDCA
Brandsaeter et al. 2004	Hepatobiliary tumours	Prospective	Increased risk of hepatobiliary cancers in patients who did not take UDCA
Olsson et al. 2005	CCA	Randomised, placebo-controlled	Not significant effect of high dose of UDCA on the incidence of CCA but study did not reach an enrolment target
Rudolph et al. 2007	CCA	Prospective	Annual incidence of CCA lower than expected in patients taking UDCA

these who took UDCA (Serfaty et al. 2003). Literature data on the chemopreventive studies with UDCA in patients with PSC is summarised in Table 1.

5.4 Treatment

5.4.1 Medical

Historically, several agents have been assessed for the treatment in PSC. These include colchicine, cyclosporine A, methotrexate, *d*-penicillamine, budesonide, mycophenolate mofetil, pentoxifylline, pirfenidone, tacrolimus and prednisone (Cullen and Chapman 2006). Almost all these therapies are now considered ineffective or associated with significant side effects. The only exception is perhaps steroids. Boberg et al. (2003) have shown that a subgroup of patients with PSC may benefit from steroids in terms of long-term survival. They comprised a group of young subjects with significantly higher levels of ALT and some histological features of AIH. Nevertheless, all subjects from these study had their PSC confirmed with cholangiography.

Ursodeoxycholic acid (UDCA) has been widely used in patients with PSC however recent study has shown that long-term, high-dose therapy with this compound did not improve survival and was in fact associated with higher rates of

serious adverse events (Lindor et al. 2009). Following these findings American Association for the Study of Liver Disease (AASLD) has recommended against using UDCA in patients with PSC (Chapman et al. 2010) and most recent European Association for the Study of Liver Disease (EASL) Guidelines suggested that UDCA may be used in patients with PSC but in these who also suffer from advanced colitis (EASL Clinical Practice Guidelines 2009). Despite these controversies many experts may still consider using UDCA in a lower dose (13–15mg/ kg b.w.) recommended in patients with PBC (Chapman 2009).

A recent, pilot study showed a significant improvement of alkaline phosphatase and Mayo risk score in patients treated with minocycline (Silveira et al. 2009). This effect was attributed to anti-inflammatory and immunomodulatory rather than antimicrobial properties of minocycline. Certainly, these results have to be validated in larger cohorts of patients.

Major steps in our understanding of the pathogenesis of cholestasis and elucidation of the role of nuclear orphan receptors such as PXR, FXR, VDR, CAR or PPAR may have an important therapeutic consequences in future, however at this point the data is limited to experimental works on laboratory animals (Beuers et al. 2009).

5.4.2 Endoscopic

Endoscopic treatment plays an important role in the management of patients with PSC. Unfortunately, due to a lack of randomised studies comparing different endoscopic approaches no guidelines on applying therapeutic endoscopy in PSC exist. In principle, endoscopy is of particular use in restoring a bile flow in patients who developed a dominant stricture, especially in a common bile duct. Most commonly this can be managed with either balloon dilatation or stenting (Bjornsson et al. 2004; Bjornsson and Olsson 2004; Baluyut et al. 2001). As CCA may manifest itself as a dominant stricture material for cytology and if possible histology should be taken during the procedure (Weismuller et al. 2008). A recent, retrospective study on a large cohort of patients treated endoscopically showed that their survival at 3 and 4 years was significantly better than the one predicted by Mayo model (Gluck et al. 2008).

5.4.3 Liver Transplantation

PSC is a good indication for liver transplantation however the timing of the operation poses a significant challenge. This is mostly due to the high risk of CCA which once developed is a contraindication for the transplantation in a majority of centres. Patients with PSC usually comprise a population of relatively young and frequently clinically stable subjects thus liver transplantation on the grounds of the fact that 10–15% of them will develop CCA is not justified. As effective surveillance for CCA does not exist the decision of transplantation is difficult. There is no doubt that patients with recurrent episodes of cholangitis in whom endoscopic management is not effective are good candidates. Patients with Candida positive bile cultures may be at particular risk and should be referred for liver

transplantation early (Rudolph et al. 2009). Also those who developed liver cirrhosis with features of end stage liver disease should be considered for transplantation according to the same principles applied in other patients with cirrhosis. On occasion, intractable pruritus can be in itself an indication for surgery, but this is more common in PBC than in PSC.

A recent study, based on UNOS database obtained between 1995 and 2006 showed that despite the constant increase of the overall number of liver transplants in the US, the number of transplants for PSC showed no change over the analysed period (Lee et al. 2007). Interestingly, a clear trend towards a decrease of placing patients with PSC on the waiting list was seen. Interpretation of these phenomena is difficult as the static number of transplants performed for PSC may be related to the low MELD (Model of End Stage Liver Disease) scores of these patients and, in terms of numbers on the waiting list, it may reflect better pre-transplant treatment (UDCA, endoscopic methods). Prognosis after transplantation is favourable with 5 and 10 years survivals of 79 and 78% (European liver transplant registry 2009). PSC may recur after surgery in up to 37% of patients. Data are accumulating that the presence of intact colon poses a significant risk of the recurrence. Vera et al. (2002) have shown that cumulative, 10 years risk of PSC recurrence after grafting in patients in whom their colons were removed before or during transplantation was 0.1 as compared to 0.7 in those who had their colons intact. They also showed that in small number of patients, recurrence may lead to graft loss and re-grafting. These findings have been recently confirmed by the same group on a significantly larger cohort of patients (Alabraba et al. 2009).

As already mentioned, the presence of CCA is a clear contraindication for transplantation in PSC. However, authors from Mayo Clinic designed protocols which include meticulous staging and neoadjuvant chemoradiation which permit transplantation in carefully selected patients with PSC and CCA reaching 5 years survivals in 82% of patients as compared to 21% in these who underwent resection (Rea et al. 2005).

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