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Recent developments in the management of idiopathic cholestatic liver disease

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Abstract

In recent years, the clinical management of patients with idiopathic cholestatic liver disease has shown significant progress. Advancement of diagnostic and therapeutic approaches and better understanding of the pathophysiology underlying these diseases have all contributed considerably to this progress. In this review, we aim to touch briefly on several developments that have occurred in this regard and to discuss novel findings and interventions valuable to clinical practice.

Keywords corticosteroids, primary biliary cirrhosis, primary sclerosing cholangitis, management, ursodeoxycholic acid

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Introduction

Idiopathic cholestatic liver diseases encompass several entities, including primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), overlap syndromes and sclerosing cholangitis associated with elevated immunoglobulin G4 (IgG4). Each entity is identified by fulfilling a spectrum of features and diagnostic criteria using several imaging modalities or the institution of liver biopsies especially in cases where the diagnosis is difficult to determine.

The management of idiopathic liver diseases involves several critical goals. These include slowing disease progression to hinder the development of end-stage liver disease and treating symptoms and complications resulting from the disease process which may affect the patient's quality of life. Proper diagnosis and histological staging is helpful in determining the most suitable therapeutic intervention for each patient. Appropriate assessment of the symptoms and complications that are inherent to each disease entity will assure that patients are managed adequately and preventative methods are instituted in a timely manner where fitting.

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Conflict of Interest: None

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Primary biliary cirrhosis

PBC is a chronic autoimmune liver disease characterized by the progressive destruction of bile ducts leading to cholestasis culminating in fibrosis and cirrhosis. It commonly affects female patients in their 5th decade and has an incidence of 2.7 per 100,000 years [1]. Understanding the underlying pathogenesis of PBC may be of critical importance in identifying effective therapeutic options. The pathogenesis in PBC appears to involve an interaction of both environmental and genetic factors, this interaction however remains obscure. Recently, genome-wide association studies (GWAS) have helped raise interest in the role of HLA antigens in the pathogenesis of PBC. It was demonstrated that the genetic architecture of PBC revolves around the HLA locus. In addition to the HLA locus, a recent GWAS study identified 12 new susceptibility loci which broadened the understanding of the genetic construction of PBC [2]. Moreover, PBC is associated with specific immunomodulatory genes and further exploration of these associations may help solidify hypotheses regarding the pathophysiology of the disease [3]. A novel study by McNally *et al* showed that the environmental component may comprise a possible constituent in the pathogenesis of PBC where seasonal variation plays a role in the diagnosis of patients with PBC [4]. It is noteworthy that social factors such as smoking contribute to increased fibrosis in patients with PBC and may hence be related to disease progression [5].

Clinically, patients with PBC typically present with positive antimitochondrial antibodies (AMA) and a cholestatic biochemical profile. The specificity of AMA for PBC is estimated at 95% [6]. Recent progress in detection of antinuclear antibodies in patients with PBC shows that beside the presence of AMA, two immunofluorescence patterns (multiple nuclear dots and membranous) may be specific for patients with PBC

[7]. In patients with suspected PBC but negative AMA a liver biopsy is required to confirm the diagnosis. A number of biochemical abnormalities may arise in patients with PBC; elevation of alkaline phosphatase (ALP) and bilirubin levels are the most common findings and can be used for patient selection in clinical trials [8].

Keynotes

- Clarifying the pathogenesis of PBC is critical in uncovering effective therapies
- Genome-wide association studies (GWAS) identified the role of HLA antigens
- Specific immunomodulatory genes, environmental and social factors may help explain the pathogenesis
- AMA status/pattern and biochemical profile are important for patient stratification

Ursodeoxycholic acid (UDCA) is the first line of therapy for PBC and shows several beneficial effects in patients with cholestasis. Usage of ursodeoxycholic acid at a dose of 13-15 mg/kg/day as the treatment of choice in patients with PBC is supported by a large pool of high quality evidence, including placebo-controlled trials and long-term case-control studies. The cornerstone of managing PBC is determining whether the patient develops a response to UDCA; this is characterized by reduction of ALP to <1.67 times the upper limit of normal (ULN), AST to <2 times the ULN and bilirubin <1.0 mg/dL [8].

The action of UDCA on PBC patients may involve the inhibition of bile acid-induced hepatocyte apoptosis and is dependent on the histological stage of the disease; in early stages of PBC, UDCA seems to exert its beneficial effects by protecting the cholangiocytes from bile acid toxicity. Conversely, in late stages of the disease the action of UDCA involves stimulation of impaired hepatocellular secretion [9]. Furthermore, UDCA delays histological progression of early stage PBC, where it ameliorates histological features of the disease and decreases liver biochemical measures such as serum bilirubin, ALP, gamma glutathione, cholesterol and immunoglobulin M levels in patients with PBC when compared to placebo [10-15]. Patients receiving UDCA may show a transplant-free survival similar to a healthy control population and also improved survival as assessed by the Mayo risk score for PBC [16-18].

When designing clinical trials to investigate novel agents for the management of PBC several key points should be addressed. Trials of new therapeutic agents should focus on patients with an incomplete response to UDCA, a combination of the new agent with UDCA is advised initially and once strong evidence arises regarding the efficacy of the novel agent then trials comparing that benefit to the standard of therapy (UDCA) should be conducted [19].

Examples of such trials include the combination of budesonide and UDCA. A study in 1999 by Leuschner *et al* showed that combining budesonide (a steroid with high receptor activity metabolized mainly by the liver) with UDCA can lead to improved liver histology [20]. This was later both supported and debated in other studies where a study by Rautiainen et al supported the benefit of this combination whereas studies by Angulo *et al* and Van Hoogstraten *et al* showed minimal benefit and worsening of osteoporosis with the use of this combination [21-23]. Other studies confirmed this finding in patients with early stage disease where significant improvement in biochemical and histological parameters was observed. Conversely, in patients with late (stage 4) disease the same combination increased the development of portal vein thrombosis and hence recommendations against its use in cirrhotic patients are compelling [24]. Although some trials may show benefit by slowing histological progression, however complications and side effects of the novel agent may hinder its usage. For example, long-term use of prednisolone is not recommended in PBC patients due to its detrimental effects on bone mineral density despite its positive effects on histological features when used alone or in combination with UDCA [24].

Various nuclear receptors are involved in bile acid homeostasis and play a role in mediating metabolic and transport functions in the liver. Recently, the farnesoid x receptor has been shown to play an important role in these processes. Obeticholic acid (6-deoxychenodeoxycholic acid) is 100 times more potent than chenodeoxycholic acid as a farnesoid receptor agonist and has shown antifibrotic properties (through inhibition of stellate cells) and possible reversal of portal hypertension in animal models [25,26].

A recent double-blind controlled trial showed that farnesoid x receptor ligands such as obeticholic acid (6-ethyl-chenodeoxycholic acid) in combination with UDCA has a therapeutic effect in patients with PBC not responding to UDCA (ALP >1.5 times upper normal limit despite UDCA therapy) through substantially improving several lab parameters including ALP, gamma-glutamyl transferase and alanine aminotransferase. The commonest side effect was pruritus which occurred in 50-80% of patients and occurred more at higher doses of the drug [27-29].

Immunosuppressive drugs (azathioprine, methotrexate, mycophenolate mofetil, chlorambucil and cyclosporin A) show mixed results in patients with PBC and are therefore not recommended. Other agents such as atorvastatin, D-penicillamine, colchicine, malotilate and silymarin are not effective in the treatment of PBC. A recent cochrane systematic review assessing the usage of bezafibrate in patients with PBC showed no effect on reducing mortality, liver-related morbidity, adverse events or pruritus when compared to placebo or UDCA [30]. Methotrexate, an antimetabolite and antifolate drug, was shown to reduce the pruritus score, serum ALP level and immunoglobulin M levels but had no significant effect on mortality in patients with PBC and hence is not recommended for management [31].

Although many patients with PBC are asymptomatic at diagnosis, some may present with symptoms such as pruritus which may affect the patient's quality of life. Hence, controlling these symptoms when present constitutes an important part

of managing patients with PBC; the management of pruritus in PBC usually follows a stepwise approach as shown in Figure 1. The progression of PBC also leads to development of complications which may require therapeutic intervention; one such complication is osteoporosis. Evidence regarding the use of bisphosphonates to manage osteoporosis in patients with PBC is controversial [32]. Hormone replacement therapy is also not recommended and appears to increase the occurrence of adverse events [33].

Hepatocellular carcinoma (HCC) can occur in patients with PBC; a study involving 725 PBC patients followed up for a period of 9 years showed an estimated risk of 0.36 per 100 patient years for the development of HCC where 3% of patients developed HCC during the period of follow-up. Advanced histologic stage and male sex were the only reported risk factors for development of HCC in patients with PBC [34].

Finally, liver transplantation is an excellent option for patients with late-stage disease as the improvement in survival is outstanding [35]. Patients are transplanted for reasons including decompensation of liver disease leading to a poor quality of life, spontaneous bacterial peritonitis or persistent ascites not responding to other treatment modalities, developing complications such as encephalopathy, HCC or recurrent bleeding esophageal varices or anticipated death within one year [36].

Keynotes

- Ursodeoxycholic acid (UDCA) 13-15 mg/kg/day is the first line of therapy for PBC
- Determining if patients are responders (to UDCA) or not can help guide management
- Novel therapeutic agents should be aimed at non-responders to UDCA
- Obeticholic acid has shown therapeutic effects in non-responders to UDCA

Primary sclerosing cholangitis

PSC is an uncommon chronic cholestatic liver disease predominantly affecting middle-aged men with underlying ulcerative colitis (UC) and characterized by progressive inflammation, fibrosis and destruction of intrahepatic and

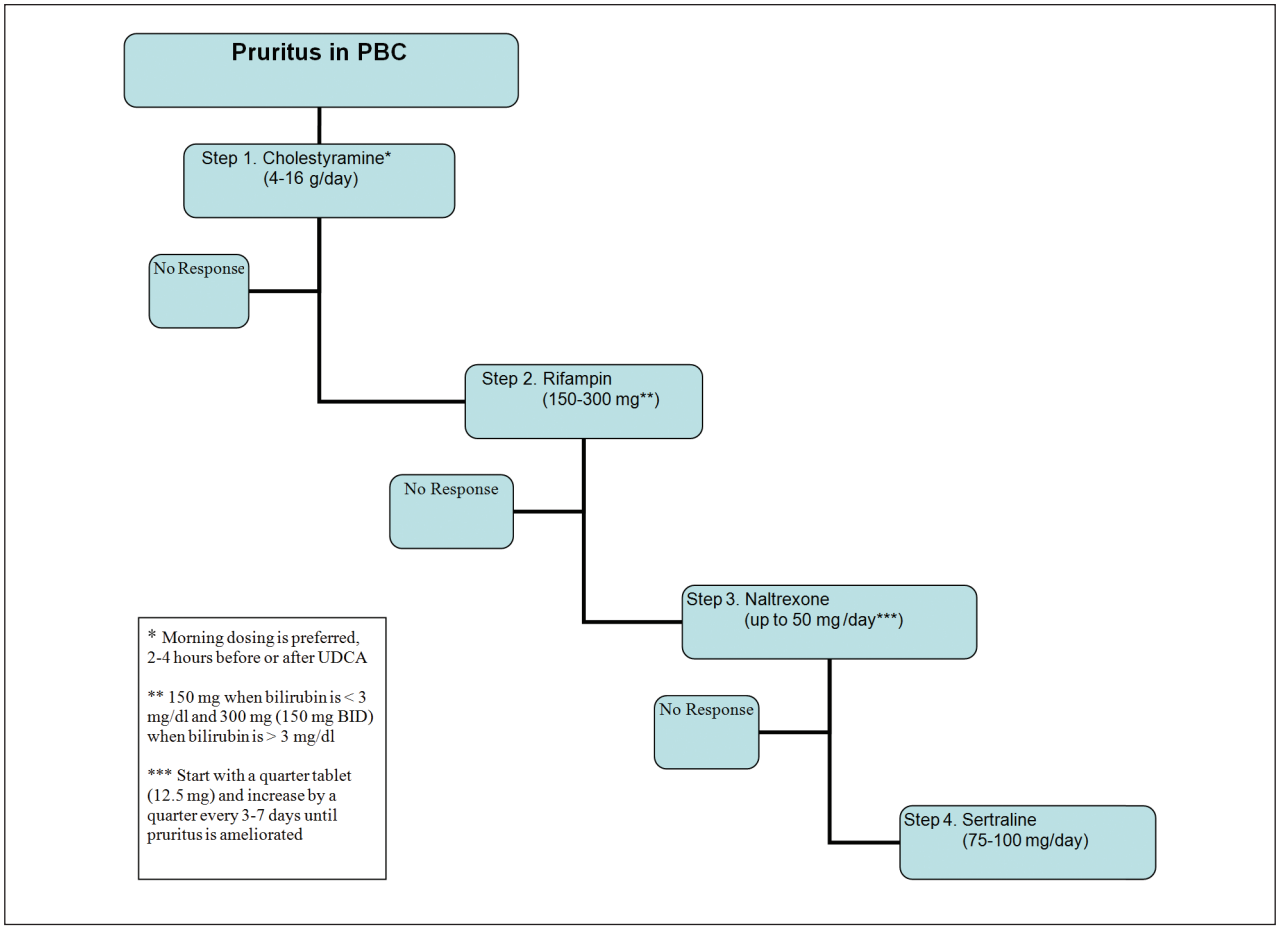

Figure 1 Management of pruritus in primary biliary cirrhosis (PBC)

Table 1 Histological findings in various stages of primary biliary cirrhosis

PBC stages	Histological findings
Stage 1	Connective tissue abnormality and/or inflammation restricted to the portal areas
Stage 2	Fibrosis and/or inflammation restricted to the portal and periportal areas
Stage 3	Bridging fibrosis
Stage 4	Cirrhosis

PBC, primary biliary cirrhosis

extrahepatic bile ducts culminating in the development of end-stage liver disease [37-40].

The best approach to diagnose patients with PSC involves finding specific features on endoscopic retrograde or magnetic resonance cholangiopancreatography (ERCP and MRCP respectively) after exclusion of secondary causes such as bacterial cholangitis, autoimmune pancreatitis, cholangiopathies and malignancy. The most important diagnostic feature on cholangiography is the presence of strictures and dilations of intra- and/or extrahepatic ducts [41]. ERCP is not a risk-free procedure and several complications may take place; a retrospective study examined the risk factors for adverse effects post-ERCP in patients with PSC. Of the symptomatic patients, 14% experienced adverse events within 30 days post-ERCP. Presence of cirrhosis, Crohn's disease, and/or autoimmune hepatitis was associated with an increased risk for adverse events post-ERCP. Other risk factors included dilation during procedure and sphincterotomy during procedure. Finally, operator experience was associated with a lower rate of adverse events [42]. For these reasons, MRCP is the preferred initial test for establishing the diagnosis of PSC and is accepted as cost-effective and accurate [43]. Staging of PSC can be done using a liver biopsy with common histologic features relating to each stage shown in Table 2.

Patients with PSC commonly present with elevated ALP levels and occasionally with symptoms such as fatigue and pruritus. Concurrent bacterial cholangitis may lead to development of fever, chills and right upper quadrant pain, whereas, advanced PSC may be marked with persistent jaundice. Normalization of lab values is frequently considered a positive response to therapeutic intervention because patients with PSC commonly present with elevated ALP, normalization of serum ALP levels may denote improved outcomes. This in fact was confirmed in a recent study by Stanich et al where PSC patients whose ALP level normalized at some point in time during follow up had a significantly lower rate of reaching an endpoint [cholangiocarcinoma (CCA), liver transplantation and death] than PSC patients with persistently elevated ALP. Patients with normalization of ALP had a lower Mayo risk score, ALP, AST and total bilirubin levels at diagnosis than those without normalization, but even after adjusting for these factors, normalization was associated with better prognosis. Overall, 40% of the patients in this study experienced normalization. UDCA treatment and/or endoscopic dilation were not found to have any effect on spontaneous normalization. The authors suggest that normalization of ALP may be a marker of disease diagnosed early and that is likely to remain quiescent. Normalization might also be used as a treatment endpoint [44].

Table 2 Histological findings in various stages of primary sclerosing cholangitis

PSC stages	Histological findings
Stage 1	Degeneration of epithelial cells in the bile ducts and inflammation of the portal triads with mononuclear infiltration and piecemeal necrosis
Stage 2	Fibrosis expanding into the parenchyma with dilation of the portal triads
Stage 3	Bridging fibrosis
Stage 4	Cirrhosis

PSC, primary sclerosing cholangitis

Keynotes

- MRCP is cost-effective and accurate for establishing the diagnosis of PSC
- Normalization of serum ALP levels in PSC may predict improved outcomes

PSC patients commonly show a concurrence of inflammatory bowel disease (IBD), specifically UC. In a recent study, several susceptibility loci identified for UC were investigated in PSC patients and controls. After correcting for multiple testing, single-nucleotide polymorphisms (SNPs) at chromosomes 2p16, 4q27, and 9q34 were found to be associated with PSC. SNPs at 4q27 and 9q34 were nominally associated in PSC patients without IBD, but this association was not statistically significant after correcting for multiple testing. For both gene relationships across implicated loci (GRAIL) and *expression quantitative trait loci* (eQTL) analysis, the three newly discovered loci were used along with six loci previously reported in the literature, including the human leukocyte antigen (HLA) locus. GRAIL showed interconnectivity between genes at six out of nine of the PSC-associated genes. GRAIL and eQTL analysis prioritized REL, IL2, and CARD9 as novel candidate genes from these loci. In sum, the authors identified three UC susceptibility loci associated with PSC, which contain the putative candidate genes REL, IL2, and CARD9. These results imply involvement of both innate and adaptive immunological factors in PSC [45]. Moreover, matrix metalloproteinases (MMP) have been suspected to contain genetic variants contributing to the development or progression of PSC because they degrade the extracellular matrix (ECM), and

are thus involved in the modulation of portal-based fibrosis. MMP3 is one such MMP. A study found an association between variants of the MMP3 gene and increased rate of progression of PSC to end-stage disease, the association was stronger in PSC patients with UC. Juran et al theorize that UC promotes liver fibrogenesis and diminished degradation of the ECM by MMP3. However, they found no connection between MMP3 variants and the risk of developing PSC and/or UC. Overall, their study suggests that the control of matrix homeostasis is important to PSC pathogenesis, and a better understanding of the genes involved in this process could lead to new treatments for and/or improved management of PSC [46].

IBD is often of clinical significance in patients with PSC and may affect the recommended management and prevention measures. In a retrospective study, it was found that patients with concomitant PSC and IBD often develop colon neoplasms (dysplasia and cancer) relatively soon after the coexistence of PSC and IBD is discovered. Specifically, the occurrence of colon neoplasms within 2 years of PSC-IBD diagnosis was similar to that of neoplasm occurrence within 8-10 years. Order of diagnosis (i.e. PSC first or IBD first) did not have an effect on the risk of dysplasia or cancer. This study supports the practice of annual colonoscopy for patients with PSC and IBD, as suggested by colon cancer surveillance guidelines. Additionally, the colon neoplasms developed in this patient cohort were spread through the colon, meaning that colonoscopy, and not sigmoidoscopy, is necessary for surveillance [47].

CCA is a dreaded complication that may occur in a significant number of patients with PSC during the course of their disease. Patients with PSC are at increased risk of CCA; the annual incidence of CCA in the setting of PSC is estimated at 0.5-1.5% and the lifetime risk is 10-15% [48,49]. Consumption of alcohol, presence of IBD, variceal bleeding, proctocolectomy, a dominant stricture, chronic UC with colorectal dysplasia or carcinoma, cirrhosis and duration of IBD are possible risk factors for the development of CCA in patients with PSC [49,50]. Diagnosis of CCA in PSC patients is often elusive and may require daunting investigation. Capillary electrophoresis mass spectrometry was recently used to identify disease-specific peptide patterns in patients with choledocholithiasis, PSC, and/or CCA. From the results of this analysis, the authors were able to develop a model to distinguish PSC alone from PSC with CCA with an area under the curve of 0.87, specificity of 78%, and sensitivity of 84%. Thus, bile proteomic analysis of bile is able to distinguish malignant bile duct disease from benign lesions. A combination of diagnostic methods could be employed to achieve higher accuracy [51]. Cytology and fluorescence *in situ* hybridization (FISH) studies are some of the common methods used to stratify risk of CCA in patients CCA in patients with PSC. In a recent study, it was found that among PSC patients with a polysomy FISH result, those with serial polysomy were at a higher risk of developing CCA than those with subsequent non-polysomy results. Specifically, 69% of patients with at least one subsequent polysomy result (i.e. serial polysomy) were eventually diagnosed with CCA, compared to 18% of those with a subsequent non-polysomy FISH result. The authors also found that there was a significant time difference in diagnosis of CCA between patients with serial polysomy and those without. In several patients with serial polysomy, CCA was not diagnosed until 1-2.7 years after the initial polysomy FISH result. Thus, FISH may detect polysomic cells a year or more before CCA can be definitively diagnosed via pathology or imaging techniques. Ultimately, the authors suggest that patients with polysomic FISH results should be carefully monitored over time [52].

Patients with PSC who develop CCA may require surgical intervention. A retrospective study investigated outcomes of PSC patients after undergoing cholecystectomy, and aimed to determine if the size of gallbladder lesions on imaging predicts the presence of neoplasia. Morbidity associated with cholecystectomy in PSC patients (both with and without cirrhosis) was high, roughly equivalent to that of patients with cirrhosis due to other causes. Postoperative complications occurred in 40% of patients, and higher Child-Pugh score was associated with early postoperative complications, via a multivariate analysis. The authors thus suggest Child-Pugh score as a means of risk-stratification for PSC patients who undergo cholecystectomy. As for gallbladder lesion size and presence of neoplasia, the authors found that polyps <0.80 cm are highly unlikely to be malignant. For detection of gallbladder neoplasia, the sensitivity and specificity of a lesion of 0.80 cm were found to be 100% and 70%, respectively. These findings suggest asymptomatic PSC patients with small polyps should perhaps be monitored, and, in the absence of other concerning features, do not necessarily need cholecystectomy [53]. A recent study showed that 37% of patients with PSC and CA 19-9 levels greater than 129 U/mL did not have CCA. For many of these patients without CCA, the elevated CA 19-9 level could be attributed to alternate causes, including normalization after endoscopic treatment (26%), persistent cholestasis (18%), recurrent bacterial cholangitis (22%), and extrahepatic malignancy (4%). However, the remaining patients (30%) had no factors that could be associated with elevated CA 19-9. There was also a large variation in CA 19-9 levels in these patients (5-73,000 U/mL) after a mean follow-up of 4 years [54].

Keynotes

- Innate and adaptive immunological factors are involved in PSC
- Control of matrix homeostasis is important to PSC pathogenesis
- IBD affects the recommended management and prevention measures in PSC
- Diagnosis of CCA in PSC patients is difficult; hence a combination of diagnostic methods can achieve higher accuracy
- Withhold surgery and employ monitoring in asymptomatic PSC with small polyps and no malignant features

UDCA is a heavily investigated therapeutic option in patients with PSC; low doses (13-15 mg/kg/d) of UDCA

failed to produce significant improvement in survival or slow histologic progression whereas higher doses (28-30 mg/kg/d) were associated with an increase of adverse clinical outcomes [55,56]. A recent study was an additional examination of the patient cohort from the high-dose UDCA study and concluded counter-intuitively that patients with early stage PSC (stage 1-2) and/or normal total bilirubin experienced increased development of endpoints (death, liver transplantation, cirrhosis, esophageal varices, and CCA) when treated with UDCA compared to placebo. This was in contrast to patients with late-stage disease and elevated serum bilirubin levels that had no effects from UDCA. Additionally, among patients who did not reach any endpoints, 31.7% had normalization of their ALP levels. Among those who did reach an endpoint, only 14.3% experienced normalization of ALP [57].

A recent study looking at patients with PSC and UC who received high-dose UDCA (28-30 mg/kg/day) as compared with those who received placebo showed that long-term use of high-dose UDCA was associated with an increased risk of colorectal neoplasia, both dysplasia and cancer, even after adjusting for UC duration and smoking history. The majority of patients receiving UDCA developed colorectal neoplasia after ≥2 years. This study strongly suggests that high-dose UDCA should not be used for chemoprevention, contrary to the results of previous studies. Nevertheless, the possible benefits of low-dose UDCA remain unclear [58].

Cystic fibrosis transmembrane conductance regulator dysfunction is associated with PSC, and leads to altered fatty acid metabolism, in particular, reduced docosahexaenoic acid (DHA). In a pilot study, DHA was administered orally at 800 mg twice per day to patients with PSC. DHA supplementation was associated with an increase in serum DHA and significant decrease in ALP. In total, 91% of patients experienced an improvement or no change in ALP: 22% with over 50% reduction in ALP levels, 35% with at least 25% reduction, and 56% with no change. No statistically significant changes in other liver function tests or fibrosis biomarkers were observed. No adverse events were observed. Additional trials and further investigation into DHA treatment are recommended [59].

The progression of sclerosing cholangitis after inhibition of the sympathetic nervous system by blockade of the β-adrenoreceptors can be examined using the $Mdr2^{-/-}$ mouse model which develops periportal fibrosis similar to human PSC. A subset of the mice was treated with the β-adrenoceptor antagonist propranolol and liver tissues were analyzed for inflammation and fibrosis progression, which were both significantly reduced after 3 months of treatment as compared to the control group. Because the propranolol treatment delayed progression of sclerosing cholangitis in this mouse model, the blockade of β-adrenoceptors may be useful in future therapeutic strategies in human PSC. The authors also speculate that such treatment could provide relief for PSC patients with portal hypertension, as the propranolol treatment repressed the expression of not only pro-fibrogenic factors (e.g. transforming growth factor-β and connective tissue growth factor) but also vasoconstricting factors (e.g. endothelin-1 and angiotensin II) [60]. These novel findings are interesting and further investigation is needed to determine if they stand in human studies.

Keynotes

- Low doses (13-15 mg/kg/d) of UDCA in PSC failed to produce significant improvement
- Higher doses (28-30 mg/kg/d) caused serious adverse outcomes especially in patients with early stage PSC (stage 1-2) and/or normal total bilirubin
- High-dose UDCA should not be used for chemoprevention due to increased risk of colon cancer
- Docosahexaenoic acid may significantly decrease ALP in PSC patients
- β-Blockers may play a role in future therapeutic strategies in PSC

Osteoporosis is one of the many complications that can affect patients with PSC. A recent study estimated the occurrence of osteoporosis in patients with PSC at 15%, and found that osteoporosis occurred 23.8-fold more frequently in the PSC group of patients than in a non-PSC population matched by age, sex, and ethnic group. Among PSC patients, factors found to correlate with the presence of osteoporosis included age ≥54 years, body mass index (BMI) ≤24, and IBD duration of ≥19 years. The rate of bone mass loss was significantly associated with duration of IBD. The authors suggest that bone density should be measured in all PSC patients upon diagnosis. For those with normal results, bone density measurements are suggested every 2-3 years for those with short term IBD, and every year or semiannually for those with bone mass in the range of osteopenia, particularly those with longer duration IBD. Interestingly, the authors found that use of corticosteroids (for treatment of IBD) was not correlated with development of osteoporosis in PSC patients. They speculate that IBD associated with PSC generally follows a more quiescent course than IBD alone, and thus PSC patients receive a lower lifetime dose of corticosteroids than IBD patients without PSC. As for treatment of osteoporosis itself, standard medication (e.g. bisphosphonates) appears to be safe for PSC patients based on the reports of other studies, but more data is needed from controlled trials [61].

Liver transplantation remains the only treatment that shows survival benefit in patients with PSC. A study that compared patients with PSC to patients with other forms of end-stage liver disease concluded that patients with PSC are less likely to die or be removed from liver transplantation waiting lists due to clinical deterioration. Moreover, among patients who died or were removed from a waiting list, MELD (Model for End-Stage Liver Disease) scores at time of listing and at time of death/removal were not significantly different in patients with and without PSC. However, among all patients included, complications of portal hypertension were found to be more frequent in patients without PSC.

Nevertheless, the reduced risk for PSC patients remained significant even after adjustments for MELD scores, complications from portal hypertension, differential rates of living donor liver transplantation, and granting of exception points. The authors suggest that the prevailing practice in certain centers of referring PSC patients for living donor liver transplantation and granting exception points should be reconsidered [62].

When CCA develops in patients with PSC, survival and other clinical outcomes may be significantly worsened. A current retrospective study was aimed at exploring factors that influence patient survival after liver transplantation for patients with CCA and how patient selection itself, and not just neoadjuvant therapy beforehand (as per the protocol at Mayo), contributed to survival. Of the patients included in this study 64% had PSC; no difference in survival between PSC and non-PSC patients was found. Among PSC patients, CCA was diagnosed prior to transplantation in only 12%, and was suspected in 35%. The 5-year survival rate post-liver transplantation was 32% for PSC patients with CCA. Among all patients with CCA, those with TNM stage ≤2 and CA 19-9 <100 U/mL had a 5-year survival rate of 58% after liver transplantation. Location of CCA (intrahepatic vs. extrahepatic) was not found to influence survival. The authors conclude that selection is indeed important when picking patients for liver transplantation. Measurement of CA 19-9 plus evaluation with computed tomography, magnetic resonance imaging, as well as a staging laparotomy could make selection better [63].

Patient, graft, and recurrence-free survival rates were 78%, 74%, and 57% at 5 years post living donor liver transplantation. Based on a multivariate analysis, MELD scores >24, first-degree related donors, cytomegalovirus antigenemia within 3 months, and biliary anastomotic complications within 1 year were found to be risk factor for recurrence. Risk factors for graft loss included MELD scores >24 and first-degree related donors. Recurrence was also found to be a risk factor for graft loss, but not for patient death. The authors suggest that first degree relative donors should be avoided. They also suggest earlier referral to transplantation centers, cytomegalovirus prophylaxis, and efforts to decrease biliary anastomotic complications [64].

Liver transplantation in chronic liver disease

Liver transplantation is valuable therapeutic option in patients with chronic liver disease especially in patients reaching end stage disease or suffering decompensation. Two scores are of crucial importance in the process of referring patients to the liver transplantation service, the MELD and the Mayo risk scores. The MELD score is of central importance and is used to prioritize patients for referral whereas the Mayo risk score aims to predict outcomes [1,65].

Other indications for referral can include quality of life issues such as intractable ascites, severe encephalopathy, intractable pruritus, severe osteoporosis, and recurrent biliary tree infections [66]. Specific indications for liver transplantation are shown in Table 3.

Keynotes

- Bone density should be measured in all PSC patients upon diagnosis
- Corticosteroids (for IBD) are not correlated with development of osteoporosis in PSC patients
- Referring PSC patients for living donor liver transplantation and granting exception points should be reconsidered
- Selection is important when choosing PSC patients to receive liver transplantation and first-degree relative donors should be avoided
- MELD score is used to prioritize patients for transplant referral whereas the Mayo risk score predicts outcomes

Overlap syndromes

PBC-autoimmune hepatitis (AIH) or overlap syndrome is a rare entity comprising patients showing features of both PBC and autoimmune hepatitis either concurrently or sequentially and this occurs in approximately 2% of PBC patients [67]. This entity possibly reflects a focal point along a continuous spectrum of autoimmune diseases occurring in patients with a certain genetic susceptibilities or merely due to simple coincidence.

A debate surrounds the diagnostic criteria for PBC-AIH

Table 3 Specific indications for liver transplantation in patients with primary biliary cirrhosis and primary sclerosing cholangitis

Disease	Specific indications for liver transplantation
PBC	Bilirubin >5 and increasing
	Albumin below 2.8 g/dL and decreasing
	Decompensation*/portal hypertension
	Recurrent, debilitating, non traumatic bone fractures
	Intractable pruritus
	MELD score (prioritize patients)
	Mayo score (predict outcomes)
PSC	Recurrent or refractory cholangitis
	Intractable pruritus
	Cholangiocarcinoma (only if part of clinical trial)
	MELD score (prioritize patients)
	Mayo risk score (predict outcomes)

**Signs of decompensation include: ascites, bleeding varices, coagulopathies and encephalopathy.*
PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; MELD, Model for End-Stage Liver Disease

overlap; a recent retrospective study evaluating 134 patients from a single center has concluded that the Paris criteria for diagnosis of PBC-AIH overlap has excellent sensitivity and specificity [68]. On the other hand, a recent study by Neuhauser *et al* with a cohort of 368 PBC patients and 43 patients with possible PBC-AIH concluded that the simplified AIH scoring system is useful for managing patients with PBC-AIH overlap and should replace the older revised AIH scoring system [69].

Due to the rarity of overlap syndromes, no long-term therapeutic trials are available to guide the management and evidence is compiled from smaller retrospective trials and studies involving primary autoimmune liver diseases.

Combination therapy of UDCA and corticosteroids has been recommended for managing patients with PBC-AIH overlap as it shows both biochemical and histological improvement [70]. Although some patients with PBC-AIH may show improvement on UDCA therapy alone, however, many patients may require corticosteroids to show a complete therapeutic response [71,72]. It is recommended that patients with PBC-AIH be tried on UDCA therapy and then if no response is detected, corticosteroids can be added. A nationwide study in Japan concluded that the need for using corticosteroids in PBC-AIH overlap can be predicted by a simplified scoring system for AIH [73]. Recently, the International Autoimmune Hepatitis Group supported the use of immunosuppressive therapy along with UDCA in patients showing features of PBC-AIH overlap [74].

Similarly, patients showing histological features of AIH and cholangiographic evidence of PSC either concurrently or sequentially are labeled as having PSC-AIH overlap. This is also seen in approximately 2% of adult patients with PSC [75]. Conversely, this ill-defined disease most commonly occurs in children and young adults and is associated with IBD and a positive P-ANCA more frequently than in patients AIH alone [76]. Patients with PSC-AIH have severe disease and show worsened prognosis than patients with PBC-AIH overlap and hence require recognition and diligent follow up [77]. Treatment of PSC-AIH overlap with UDCA and immunosuppressants is recommended although no data from controlled trials exists due to the rarity of the disease. However, documented evidence of response to immunosuppression in children with PSC-AIH overlap is present [76].

Keynotes

- No long-term therapeutic trials are available to guide the management of overlap syndromes
- Immunosuppressants and UDCA in overlap syndromes may be helpful

IgG4 sclerosing cholangitis

IgG4 sclerosing cholangitis is an idiopathic biliary disease sharing many features with PSC and hence is sometimes difficult to identify. Unlike PSC, it is characterized by its response to steroid therapy and is associated with autoimmune pancreatitis. Recently, a case report suggested that amyloid A deposits in multiple organs may help differentiate PSC from IgG4 where amyloid A appears to be more specific for PSC [78]. A recent study has suggested measuring IgG4 levels in bile to confirm the diagnosis of IgG4 sclerosing cholangitis in alleged PSC patients [51].

In a recent study, IgG4 was measured in a set of 285 PSC patients, and 12% were found to have elevated levels (>140 mg/dL). Patient age, gender, and prevalence of IBD in the patients with elevated IgG4 were similar to that of patients with PSC alone (i.e. no elevated IgG4) in other studies, suggesting that there are no clinical features that predict elevated levels of IgG4 in PSC patients. Hence, the authors suggested that IgG4 should be measured in all PSC patients upon diagnosis. Furthermore, the authors also confirmed suspicions that elevated IgG4 indicates a more pronounced disease severity. In this study, 50% of patients had liver cirrhosis despite a median duration of PSC of only 4 years.

Regarding treatment, the subset of the patients (n=33) found to have elevated IgG4 were treated with corticosteroids. The average duration of treatment was 17 months with starting dose of 40 mg prednisone for all patients. Response to steroids was good and after 2 months of treatment, IgG4 levels normalized in almost all patients. However, steroid-associated side effects and relapse were common. Specifically, 39% of patients experienced moderate or severe side effects, predominantly hyperglycemia, and 50% of patients with a response to the steroids experienced a biochemical relapse [79].

Keynotes

- Amyloid A deposits or IgG4 levels in bile may help differentiate PSC from IgG4 sclerosing cholangitis
- IgG4 sclerosing cholangitis patients should receive steroids until a response is elicited

In conclusion, patients who fulfill the criteria for IgG4 sclerosing cholangitis by having elevated serum IgG4 levels, radiological evidence of sclerosing cholangitis and a histology showing infiltration of biliary tissue by IgG4 positive plasma cells should receive steroid therapy until a response is elicited. Long-term treatment with corticosteroids or other immunosuppressants may be warranted in case of inadequate response or relapse.

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