Clinical management of autoimmune biliary diseases

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Review

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1. Introduction

The clinical management of autoimmune biliary diseases can be challenging. This is, in part, due to the complex pathogenesis involved with these disease entities, the lack of effective medical therapy in some cases, and the wide array of associated complications affecting susceptible individuals. For patients with conditions where effective medical therapy exists, there can be dilemmas in management based on incomplete or ineffective treatment responses and continued progression of the disease despite timely intervention. As novel studies help clarify the pathogenesis underlying these multifaceted disorders, the emergence of new paradigms for medical management is predicted.

In this review, we will provide an update on the clinical epidemiology and management of autoimmune biliary disorders. In addition, we will suggest a general approach for diagnosing these autoimmune diseases and address current pitfalls in clinical management.

A B S T R A C T

Autoimmune biliary disease is an umbrella term that encompasses several distinct entities such as primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis and overlap syndromes. The general approach to the diagnosis of these disorders involves investigating symptomatic patients presenting with a cholestatic biochemical profile. Asymptomatic patients are often diagnosed during investigation of other accompanying or discrete diseases. The distinction between the various entities is necessary for directing clinical management in this group of patients with an underlying autoimmune pathophysiology. Goals of management comprise treating symptoms, preventing complications and suppressing the underlying pathogenetic processes. Liver transplantation plays a vital role in the management of this group of patients and has shown a dramatic improvement in outcomes. Medical therapies such as ursodeoxycholic acid have shown mixed effects with excellent outcomes in primary biliary cirrhosis and less impressive results in primary sclerosing cholangitis. In this manuscript we aim to discuss in detail the management of these autoimmune biliary disorders and describe the effects of different therapies on outcomes on the different subsets of patients.

2. Epidemiology and pathogenesis of autoimmune biliary diseases

2.1. Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a chronic and progressive cholestatic liver disease predominantly diagnosed in females between their 5th and 6th decades of life [1]. The estimated incidence of PBC in the US is amongst the highest compared to other countries with an estimated incidence of 4.5 (95% confidence interval: 3.1–5.9) for women, 0.7 (95% CI, 0.1–1.3) for men, and 2.7 (95% confidence interval: 1.9–3.5) overall [2]. Histologically, PBC is characterized by the pathological destruction of small and medium bile ducts culminating in end stage liver disease and the need for liver transplantation in some individuals [2]. The proposed pathogenesis of PBC has been greatly debated, with several data sources available supporting an autoimmune component related to disease pathology. The different proposed mechanisms are shown in Table 1.

2.2. Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown etiology that is often diagnosed in the fifth
decade of life among patients with concurrent inflammatory bowel disease (IBD) [9]. The disease affects males and females at a ratio of 2:1 [10]. Hallmark features of PSC include progressive intrahepatic and extrahepatic bile duct stricturing leading to cirrhosis and end stage liver disease [10].

Current understanding of the clinical epidemiology of PSC is well illustrated by an interesting study performed in Southern Sweden which showed a three fold increase in the incidence of PSC between 1992 and 2005 [11]. This study also reported an incidence was 1.22/100,000 person years overall. The incidence in males and females was 1.78 and 0.69 per 100,000 person years respectively. Overall the point prevalence of PSC by the end of 2005 was 16.2 per 100,000. 23.7 and 8.9 per 100,000 men and women respectively had PSC at the end of 2005 in that patient population. In Olmsted County, Minnesota, the prevalence of PSC in the year 2000 was estimated at 20.9 cases and 6.3 cases per 100,000 men and women respectively. Furthermore, age adjusted incidence of PSC was estimated at 1.25 (95% CI, 0.70–2.06) and 0.54 (95% CI, 0.22–1.12) per 100,000 person years for men and women respectively and the 0.90 per 100,000 person years (95% CI, 0.56–1.36) overall. The estimated prevalence of IBD was 73% with 75% of patients having ulcerative colitis [12]. Another study by Kaplan et al. identified an age and gender adjusted annual incidence rate of 0.92 cases per 100,000 person years amongst all residents of Calgary health region in Alberta Canada between 2000 and 2005 [13]. Notably, a recent meta-analysis concluded that the incidence of PSC is estimated at 0.77 per 100,000 person years and shows an increasing occurrence of PSC over time [14].

The pathogenesis of PSC is suspected to involve several mechanisms with immune-mediated processes, bacterial infection, and genetic susceptibility being the major categories of interest. A number of observations suggest an immune-mediated pathogenesis for PSC including an increased frequency of serum autoantibodies including anti-nuclear antibodies (ANA), anti-smooth muscle autoantibodies (ASMA) and antineutrophil cytoplasmic antibodies (p-ANCA). Furthermore, PSC is strongly associated with multiple extrahepatic autoimmune diseases including celiac disease, rheumatoid arthritis, Sjögren's syndrome and thyroiditis [15–18].

In terms of genetic predisposition, human leukocyte antigen (HLA) loci are greatly associated with PSC. HLA B8 and DR3 show strong association with PSC in more than 50% of cases, whereas, HLA Dr3w22a is associated with PSC in up to 100% of patients diagnosed with PSC. Conversely, Dr2 is seen in younger patients. HLA subtypes have also been associated with prognosis where DR4 predicts worse outcomes in patients with PSC [19–22].

Genome wide association studies in PSC have shown several susceptibility loci. A novel study looking at genome wide associations in sclerosing cholangitis and UC identified that G protein-coupled receptor 35 (GPR35) conveys a risk for both PSC and UC and Transcription factor 4 (TCF4) is associated with risk for PSC but not UC [23]. Recently, a study from Cambridge assessing risk loci for PSC present in 992 patients as compared to 5162 controls concluded that a role may exist for interleukin 2 (IL2) receptor alpha (IL2Rα) IL-2/IL2RA pathway in PSC and also confirmed association of macrophage stimulating 1 (MST1) [24]. Current GWAS studies are constantly identifying new loci that preclude a risk for PSC and in the near future a better understanding of genetic predisposition of PSC and other cholestatic diseases will be possible [25].

Overproduction of tumor necrosis factor due to Kupffer cell activation by bacterial toxins which leads to portal fibrosis presents the cornerstone for the hypothesis of bacterial involvement in the pathogenesis of PSC [26]. This theory however is contradicted by the fact that development of PSC is independent of ulcerative colitis which is thought to be the major contributor to bacterial toxin production in PSC patients [27]. Similarly, an older theory on viral involvement in the pathogenesis of PSC remains weak and needs further investigation [28].

2.3 Autoimmune hepatitis

Autoimmune hepatitis (AIH) was first described in 1950 by Waldenström in young women presenting with infiltration of the liver with plasma cells, cirrhosis and elevated levels of immunoglobulin G (IgG) [29]. Reports through the 1950's helped further define features of AIH which include acne, hirsutism, amenorrhea, jaundice, hepatosplenomegaly, and the presence of disease-specific circulating autoantibodies [30].

Despite manifesting as a chronic hepatitis in most patients, AIH can sometimes develop acutely. An important feature of AIH is its responsiveness to corticosteroid therapy, reflected by the excellent outcomes achieved upon institution of proper management as compared to cirrhosis and fulminant hepatic failure with no treatment. Despite being first described in females, autoimmune hepatitis can affect both sexes and all ages. Triggers for the development of autoimmune hepatitis may include medications and infections. In 1993 the International Autoimmune Group produced a report in which criteria for diagnosis of autoimmune hepatitis were established [31].

Like many chronic liver diseases autoimmune hepatitis has both genetic predisposition and environmental triggers. Specific human leukocyte antigen haplotypes (HLA) were found to be associated with the development of AIH. Gene deletions were also described as related to disease progression in younger patients [32]. HLA haplotypes can also predict prognosis where patients with HLA DR3 or HLA DR4 may suffer a more aggressive disease course or increased extrahepatic manifestations respectively [33]. A recent study eludes to the involvement of non-classical major histocompatibility complex genes including genetic polymorphisms of CTLA-4, TNF-alpha, TBX21, TGF-beta1, Fas and VDR [34]. Moreover, antibodies to ribonucleoprotein S2 have been shown to reflect poor prognosis in patients with autoimmune hepatitis [35]. Anti-p53 has recently emerged as a helpful factor to differentiate AIH or AIH/PBC overlap from classic PBC [36].

3. General approach to diagnosis of autoimmune biliary diseases

Autoimmune liver disease often shows a cholestatic biochemical profile and is characterized by chronicity (~6 months). Cholestasis is a term used to coin disease processes affecting the formation or
flow of bile in the liver. This may manifest symptomatically as fatigue, jaundice or pruritus. The general approach to investigating and managing symptomatic patients is shown in Fig. 1. Conversely, asymptomatic patients are generally diagnosed during work-up for other diseases or on routine follow up.

The best initial investigation despite its reliance on operator experience is abdominal ultrasonography which can help distinguish between extrahepatic and intrahepatic dilation of the bile ducts in cholestasis. Advantages of ultrasound include its non-invasiveness and low cost.

The best diagnostic procedure in patients with cholestasis however is cholangiography. Magnetic resonance cholangiopancreatography has been shown to be almost as effective as endoscopic retrograde cholangiopancreatography in investigating the biliary tree. ERCP remains the gold standard due to its ability of treating extrahepatic obstructive pathology if suspected. The cost effectiveness of MRCP however makes it also a valuable option in diagnosis of cholestatic liver disease [37]. A recent study has shown that sensitivity specificity, positive and negative predictive values are high for radial endosonography and hence can be used instead of ERCP in patients with low or moderate risk of choledocholithiasis [38]. Specific diagnostic features are demonstrated in Table 2.

4. Clinical management of autoimmune biliary diseases

4.1. PBC

4.1.1. Goals of medical management

Medical management is PBC is aimed at two specific goals; first the clinician will aim to treat symptoms (jaundice, fatigue and pruritus) and complications (ascites, metabolic bone disease, hypercholesterolemia, malabsorption, anemia and vitamin deficiencies) resulting from chronic cholestasis. The second aim focuses on suppressing the underlying pathogenetic process that revolves around the destruction of intralobular bile ducts.

Major changes in the natural history of PBC have been realized, mainly resulting in decreased rates of liver transplantation and prolonged survival due to earlier diagnosis of the disease and hence timely intervention with UDCA.

4.1.2. Ursodeoxycholic acid

The first trial looking at UDCA in PBC was conducted by Poupon et al. in 1987 and demonstrated dramatic improvement in liver biochemistries in PBC patients receiving 12–15 mg/kg/day of UDCA [39]. Specific diagnostic features are demonstrated in Table 2.
Immunomodulatory properties of UDCA make it a valuable therapy for patients with primary biliary cirrhosis, through reduction of eosinophil counts and prevention of eosinophilic degranulation. Recently, UDCA has been proven as a potent option for suppressing eosinophilic inflammation not only in the gastrointestinal tract but in other body tissues. Hence, this may mean that UDCA could be a good option in patients presenting with a combination of primary biliary cirrhosis and other diseases involving eosinophilic airway inflammation such as asthma [40].

A large number of randomized controlled trials have been performed to identify the effect of UDCA on patients with PBC. UDCA was administered in these trials at a dose of 13–15 mg/kg per day for periods ranging from 2 to 6 years. It is worth noting, that due to significant improvement of liver biochemistries in patients receiving UDCA patients on placebo were switched to active drug after two years of therapy in three trials [41–43]. A randomized double blind controlled multicenter trial of 222 patients with confirmed liver biopsies and positive serum antimitochondrial antibodies demonstrated a significant reduction in biochemical parameters such as AST, ALT, ALP and bilirubin. This was also accompanied by a reduction of histological disease progression in patients receiving UDCA [43].

PBC patients with early stage disease (stage 1–2) and serum bilirubin levels <2.0 mg/dl have been shown to benefit most from UDCA therapy. This was demonstrated by a randomized controlled study of 151 patients where patients were stratified according to bilirubin level and histologic stage. However, when the study was followed up 9 years later no effect on outcomes (liver transplantation, death) was seen [42,44].

The effects of UDCA on histological progression in PBC reflect a significant reduction in the presence of florid interlobular bile duct lesions and epithelioid granuloma without any aggravation in the severity of bile duct paucity in patients treated with 4 years of UDCA (p < 0.001). Conversely, these effects were not seen in patients with piecemeal necrosis [45].

In an analysis of 367 patients with PBC in which 200 patients received UDCA and 167 received placebo, it was determined that 2 year treatment with UDCA lead to reduction of periportal necroinflammation and improvement in ductular proliferation. Moreover, UDCA delayed the progression of histologic stage in patients with early stage disease (stage 1–2) [46].

Decreased risk of death and liver transplantation in PBC patients receiving UDCA therapy (12–15 mg/kg/day) for 3 years as compared to placebo was demonstrated by a single center randomized study [47]. This was later confirmed by a randomized European study which showed a lower probability for adverse events (death, liver transplantation) in patients receiving UDCA for a median of 3.4 years as compared to placebo [41,48].

UDCA therapy also appears to delay the onset of esophageal varices in patients with PBC. The risk for developing varices in patients receiving UDCA (13–15 mg/kg/day) for 4 years is almost 4 times lower than in patients using placebo [49].

On the other hand, a Cochrane systematic review of 16 randomized trials of 1447 patients in total has concluded that UDCA has a significant effect on reducing jaundice, ascites and liver biochemistries but had no significant effect on mortality or liver transplantation [50]. It is worth noting that this review did not exclude short duration trials or trials using suboptimal doses (<13–15 mg/kg/day) of UDCA confirmed in fact the beneficial effect on transplant-free survival of UDCA (13–15 mg/kg/day) in patients with early stage PBC [51].

In conclusion, UDCA remains the only FDA approved medication for the management of PBC and should still be considered the first line of therapy in clinical practice.

4.1.3. Assessment of response and prediction of outcomes

Several studies tried to define the best way to assess if a response to UDCA therapy has occurred in patients with PBC. This is done by looking at cut-off points for biochemical improvement and linking them to clinical outcomes. The Barcelona criteria suggests that a decrease of 40% in serum ALP level in patients with PBC receiving UDCA therapy is predictive of better clinical outcomes [52].

In a study by Corpechot et al., looking at the efficiency of several combinations of threshold lab biochemistries in predicting outcomes of 292 patients with PBC concluded that patients with an ALP <3 time the upper limit of normal (ULN), AST <2 ULN, and bilirubin <\(=1 \text{mg/dl after 1 year of UDCA had a transplant-free survival rate of 90% at ten years (95% confidence interval, 81}\%–95\%\), compared to 51% (95% confidence interval, 38%–64%) for those who did not (p < 0.001) [53]. A recent study from the same group, defined the best biochemical response in early stage (histological stage 1–2) PSC as ALP and AST ≤ 1.5 × ULN, with a normal bilirubin level. Responders and non-responders were equally distributed in this study and all adverse events were observed in non-responders (p < 0.001) [54].

4.1.4. Dilemmas in management

Despite the proved usefulness of UDCA for the management of PBC patients, the dilemma exists due to the reality that not all patients respond to therapy.

Recent studies aimed at combining other agents to UDCA have shown promise. A study of nineteen patients with early stage PBC and an incomplete biochemical response to UDCA (600 mg/day), showed significant improvement in the cholestatic profile of these patients upon the addition of bezafibrate (400 mg/day) for 3 months to the UDCA therapy [55].

Moreover, long term treatment with a combination of UDCA and immunosuppressants such as colchicine or methotrexate demonstrated a sustained clinical response after 20 years in patients with primary biliary cirrhosis [56].
Novel treatment options have also been suggested for non-responders to UDCA: B cell depletion using rituximab was investigated by Tsuda et al. recently with eye opening results to the possibility of other options in non-responders [57].

Obeticholic acid, a derivative of chenodeoxycholic acid, may be used in PBC patients not responding to UDCA. The effect of obeticholic acid is realized through its action in bile acid homeostasis, acting as a potent farnesoid X receptor ligand. In a trial of 59 patients with PBC, obeticholic acid showed success in reducing alkaline phosphatase, alanine aminotransferase and gamma-glutamyl transferase when compared to placebo. It is noteworthy that the use of obeticholic acid may be limited by the development of pruritus [58]. More studies are needed to investigate the true value of obeticholic acid in PBC.

Tetrathiomolybdate was investigated in a study by Askari et al. and concluded that the agent is efficacious for the management of primary biliary cirrhosis. Reservations regarding the study design may include the utilization of biochemical endpoints only with no proof of histological improvement in patients treated with tetrathiomolybdate. Hence, as the authors suggest longer clinical trials to examine transplant-free survival and histological progression are needed [59]. Cytotoxic T lymphocyte antigen 4 (CTLA-4) a T-cell receptor acts a co-stimulatory molecule in T-cell activation which in turn leads to biliary damage. Recent evidence supports the utilization of an optimized course of therapy by means of CTLA-4 Ig to potentially aid in the therapy of PBC patients [60].

Despite improvement in some outcome measures such as serum bilirubin levels in PBC patients treated with chlorambucil, a Cochrane systemic review concluded that evidence is inadequate for the usage of chlorambucil in PBC patients. Moreover, bone marrow suppression poses an unnecessary risk for an agent with no proven efficacy in altering meaningful clinical outcomes in patients diagnosed with PBC [61].

### 4.1.5. Liver transplantation

PBC is one of the most common indications for liver transplantation in the United States [62]. Common reasons for liver transplantation in patients with PBC include refractory ascites, hepatic encephalopathy, and portal hypertension leading to hepatoportal syndrome, spontaneous bacterial peritonitis, intractable pruritus and fatigue. Liver transplantation in primary biliary cirrhosis is an effective modality in the management of PBC. Studies have demonstrated and confirmed an improvement in long term outcomes in PBC patients. A study of 161 PBC patients showed a significant improvement ($p < 0.01$) of outcomes when expected patient survival was compared to actual survival through utilization of the Mayo natural history model, 2 year survival was 74% for transplanted patients as compared to non-transplanted patients (31%) [63].

Patients with PBC may suffer several complications due to the chronicity of their disease, one of the most serious being development of hepatocellular carcinoma (HCC). The incidence of HCC amongst patients with a diagnosis of PBC is estimated at 0.36 per 100 person years. It is worth noting that a higher histological stage on liver biopsy denotes an increased risk for HCC in patients with PBC [64].

### 4.2. PSP

Primary sclerosing cholangitis is an umbrella term encompassing several entities. For instance, small duct PSC encompasses patients who lack the cholangiographic abnormalities seen with classic PSC but demonstrate typical histological features and biochemical profiles. Small duct PSC constitutes less than 10% of the entire PSC population, but is associated with better survival than classic PSC [65]. On the other hand, diagnosing patients with IgG4 sclerosing cholangitis is dependent on fulfilling criteria including an elevated IgG4 level and exclusion of IBD. Moreover, typical intraductal sonographic findings and utilization of liver biopsy are useful (especially to exclude malignancy) [66]. Endoscopic ultrasound in diagnosing early primary sclerosing cholangitis is currently under investigation. Novel methods for diagnosing PSC include peroral cholangioscopy using Spyglass direct visualization system and CT cholangiography.

#### 4.2.1. Dilemma in management

The dilemma in managing PSC exists due to absence of a medical option that has been proven to prolong survival. Liver transplantation remains the main staple for the management of patients with PSC despite the countless trials looking at different medical options for management. Improvement in biochemical profile has been witnessed in patients receiving medications such as UDCA. However, an increase in adverse events is evident at higher doses of the drug (28–30 mg/kg/day); this was specifically noted in patients with early stage disease and normal serum bilirubin levels [67,68]. Other problems associated with UDCA include an increased risk for the development of colorectal neoplasia in patients with ulcerative colitis and PSC [69]. Despite the current lack of medical treatment, promising studies tackling different aspects of the pathogenesis of PSC such as antifibrotics, antibiotics and novel bile acids are anticipated.

#### 4.2.2. PSP subsets

##### 4.2.2.1. PSC–IBD. When inflammatory bowel disease is diagnosed concurrently with PSC, the term PSC–IBD is used to underline the fact that the disease represents a separate entity. This may occur in 60–80% of patients where IBD is diagnosed in PSC patients, most of which have ulcerative colitis [14,70,71]. PSC–IBD demonstrates an increased risk of pouchitis following proctocolectomy and predominance of right sided inflammation of the colon [72]. Less severe disease activity of IBD in PSC–IBD patients is associated with increased disease progression and need for liver transplantation [73]. Worsened outcomes may also occur due to increased risk of colorectal cancer when compared to patients with IBD only [74–76].

##### 4.2.2.2. PSC without IBD. PSC lacking underlying IBD exhibit an increased frequency of symptoms at disease presentation, a lower male:female ratio and better prognosis when compared to PSC–IBD [77]. Patients may be found to have IBD later on during follow up which may require surveillance colonoscopies to identify these patients [9].

##### 4.2.2.3. Small duct PSC. When patients with suspected PSC have typical biochemical and histological features but lack cholangiographic abnormalities they are diagnosed with small duct PSC. This occurs in 5–10% of the total PSC population, of which $<25\%$ of patients may eventually develop classic PSC [78]. Small duct PSC patients have better survival than classic PSC patients [65,79]. This may be explained by the lack of development of cholangiocarcinoma and lack of need for liver transplantation [65,79,80].

##### 4.2.2.4. IgG4 sclerosing cholangitis. Patients with clinical and radiologic features compatible with PSC and an association with autoimmune hepatitis are diagnosed with Immunoglobulin G4 (IgG4) sclerosing cholangitis [81]. Specific criteria including an elevated IgG4 level, exclusion of IBD, exclusion of malignancy by bile duct biopsy, typical intraductal sonographic findings and
utilization of liver biopsy are helpful in confirming the diagnosis of IgG4 sclerosing cholangitis [82]. It is noteworthy that individuals with PSC–IBD may also have elevated serum IgG4 levels. This foreshadows an increased risk for progression to LT or death in these patients when compared to other PSC patients with normal serum IgG4 levels [83]. IgG4 sclerosing cholangitis shows a dramatic response to steroid therapy and relapses occur when steroid therapy is withdrawn [84]. Individuals with PSC and associated IBD have been shown to have elevated serum IgG4 levels which denotes worsened outcomes than PSC patients having normal serum IgG4 levels [83].

4.2.3. Current and future therapies

PSC has limited treatment options and can only be managed effectively by liver transplantation. No medical therapy has shown a significant effect on outcomes in PSC patients. UDCA shows improvement in biochemical parameters but no effect on disease progression. Conversely, UDCA is still offered as an empirical therapy for PSC patients due to lack of safe and effective medical alternatives. Recent observations suggest that sustained reductions in serum alkaline phosphatase levels to <1.5 times the upper limit of normal following UDCA therapy is significantly associated with a longer time to develop adverse clinical outcomes [85]. Ideally, the conduct of future prospective studies to verify this novel observation is study would be highly welcomed.

Medications investigated for the management of PSC include but are not limited to azathioprine, penicillamine, etanercept, methotrexate and steroids. However, no evidence exists to support any of these options for the management of PSC.

In the case of presence of a symptomatic dominant stricture, endoscopic intervention or balloon dilation could prove valuable. This of course requires ruling out cholangiocarcinoma. Liver transplantation remains the most valuable option in reducing disease progression and improving clinical outcome. Novel therapies currently being tested include vancomycin, mitomycin, metronidazole, fenofibrate and docosahexaenoic acid.

4.2.4. Prediction of outcomes

Several models have been proposed for the prediction of outcomes in patients with PSC. A study looking at 330 PSC patients from 5 European centers followed up for a period of 8.4 years concluded that time-dependent Cox regression model has the potential to estimate a more precise short-term prognosis in PSC compared with the traditional time-fixed models [86].

Kim et al. proposed a revised model to calculate the Mayo risk score in PSC patients using age, bilirubin, albumin, aspartate aminotransferase, and history of variceal bleeding. The advantages of this model include its high accuracy and elimination of the need for a liver biopsy. This model was created by using Cox proportional hazard analysis in 405 PSC patients and then validated on 124 separate patients not involved with the conception of the model [90].

Cholangiographic features have been proposed to carry a prognostic value in patients with PSC [87]. A later study by the same group in 2010 produced and validated a prognostic model dependent on cholangiographic features of PSC. Cholangiographic features are compared to a nomogram and variation in cholangiographic features may predict long term survival [88].

Broome et al. identified prognostic factors for patients with PSC by using 305 patients followed up for a median of 63 months. The study concluded a median survival of 12 years with age, serum bilirubin levels, and histological stage at baseline (time of diagnosis) were independent predictors of bad outcomes [71].

Mayo risk score (MRS) in PSC is an important factor in determining survival post liver transplant. Patients with MRS >1.56 predict reduced 5 year survival and increased mortality [89]. Child–Pugh score is also a good predictor of survival and resource allocation following liver transplantation for PSC when compared to Mayo’s PSC model [91].

4.2.5. Complications

PSC is an independent risk factor for the development of colorectal cancer (CRC) in patients with UC [92–96]. Eleven studies were included in a meta-analysis conducted in 2002, that concluded a fourfold increase in risk (OR 4.26; 95% CI 2.80–6.48) for CRC in patients with a combined PSC–UC diagnosis when compared to patients with only UC [97]. PSC does not similarly increase the risk for colorectal cancer or dysplasia in patients with Crohn’s disease [98]. Moreover, cholangiocarcinoma can complicate the disease course of about 15% of PSC patients throughout their lifetime with risk factors comprising a history of variceal bleeding, colorectal dysplasia or carcinoma and history of chronic inflammatory bowel disease [99,100].

4.2.6. Liver transplantation

Survival following liver transplantation in PSC is relatively high and is estimated at 85% at five years post surgery [101,102]. In our experience at Mayo Clinic 1, 5 and 10 year survival rates are estimated at 94, 86 and 70 percent respectively [103].

Prioritization of patients for liver transplantation is determined by using the MELD score. The MELD score is a prognostic model that incorporates serum bilirubin, international normalized ratio (INR) and serum creatinine. A study of more than 3400 patients listed for liver transplantation between 1999 and 2001, concluded that mortality on the waiting list was related to the MELD score, where patients with a MELD score <9 had 1.9% mortality as compared to 71% in patients with a MELD scores ≥40 [104]. Currently, once a patient is considered suitable to receive liver transplantation their MELD score is utilized to place the patient on the priority list for transplant. The MELD score may be lacking in terms of estimating mortality in patients with conditions such as hepatopulmonary syndrome, cystic fibrosis, portopulmonary hypertension, hilar cholangiocarcinoma and hepatocellular carcinoma.

General indications for liver transplantation include encephalopathy due to acute liver failure, cirrhosis with complications of elevated portal pressure, hepatorenal syndrome and recurrent cholangitis in PSC. Other specific indications for liver transplantation in PSC include intractable pruritus or development of hilar cholangiocarcinoma. In recent times, a number of patients with PSC have opted for living donor liver transplantation based on the development of complications not reflected by the MELD score.

Recurrence following liver transplantation may occur in 20% of patients at 10 years [105]. It appears that colectomy prior to liver transplantation is protective against recurrence of the disease post-transplantation [106].

4.2.6.1. AIH. Autoimmune hepatitis (AIH) is a chronic hepatitis characterized by immunologic and autoimmune features. It is marked with a high level of serum gamma globulin, circulating autoantibodies, and moderate to severe interface hepatitis on liver histology [107]. Untreated patients diagnosed with autoimmune hepatitis who exhibit symptoms have a high mortality reflected by an estimated survival of only 50% at 5 years [108].

4.2.6.2. Overlap syndromes. Patients with PSC or PBC can also have features of other autoimmune disease such as autoimmune hepatitis. These disorders have been referred to as “overlap syndromes”. AIH can overlap with PBC in <10% of PBC patients [109–111] and involves diagnostic features shown in Table 1. A study by Muratori et al. showed that patients with AIH–PBC overlap had a greater
likelihood of also being anti-dsDNA positive as well as AMA positive when compared to AMA positive PBC and also responds to the combination of steroids and UDCA [112]. A study of 282 patients of which 12 patients had AIH–PBC showed that this overlap may elude to worsened prognosis and rapid progression toward cirrhosis [110]. From our experience at the Mayo clinic, we identified 26 patients fulfilling the criteria for AIH–PBC diagnosis and looked at outcomes in these patients as compared to classic PSC. The overlap group showed an increased occurrence of GI bleeding, esophageal varices and ascites. They were also more likely to undergo liver transplantation and had greater mortality during follow up than classic PBC group [113].

AIH may also overlap with PSC; patients will have cholangiographic features of PSC but serologic findings of AIH [114–116]. In pediatric patients with AIH up to 50% of patients may show cholangiographic features of PSC as shown by two reports [119,120]. In patients with PSC, a high suspicion for AIH overlap should arise when findings such as elevated levels of IgG, SMA or ANA and/or features of hepatitis on histologic exam [121].

4.2.7. Treatment indications

Institution of treatment in patients with AIH requires an assessment of several factors including serum aminotransferase levels, histological findings and severity of symptoms. Studies have concluded that AIH patients with greatly elevated (>10 × ULN) have a rate of 60% at 6 months [122].

Indications for treatment as per the AASLD [122] include presence of histologic features of bridging/multilobular necrosis, elevation of serum aminotransferases to >10 × ULN or 5 × ULN with concomitant doubling of serum gamma globulin to 2 X ULN.

4.3. Selecting therapy and assessment of response

Patients with mild histologic changes or serum aminotransferases elevation and children can be started on immunosuppressive therapy (prednisone 60 mg/day or prednisone 30 mg/day plus azathioprine 50 mg/day) regardless of symptoms. The duration of treatment is dependent on normalization of lab parameters and liver histology. In patients with normalized lab values treated for at least two years, gradual tapering of steroids and azathioprine is recommended. Moreover, long term disease management should incorporate bone density assessment and adjunctive therapy should be instituted when needed.

Contraindications to immunosuppressive therapy include minimal or no disease activity, life-threatening comorbidities that can be controlled when on immunosuppressive therapy. Patients with acute liver failure should be considered for liver transplantation.

4.4. Complications and relapse

Patients with an incomplete response after 24–36 months should be treated for longer durations using prednisone and azathioprine. Conversely, patients with worsening symptoms or lab parameters despite initiation of immunosuppressive treatment should receive an increased dose of azathioprine (150 mg/day) along with 30 mg/day of prednisone. If treatment failure or intolerance to azathioprine develops, replacement with cyclosporin or mycophenolate is recommended. Complications may include the occurrence of hepatocellular carcinoma in cirrhotic patients and hence screening with ultrasound every 6 months may be warranted. If hepatocellular carcinoma is diagnosed or MELD score increases to >15 with decompenated cirrhosis then intervention with liver transplantation is needed.

5. Conclusion

Clinical management of autoimmune biliary diseases is a rapidly growing field of expertise. Increased awareness of the burden of these diseases and better understanding of their pathogenesis will further advance management. It is noteworthy that promising therapeutic modalities especially for patients with primary sclerosing cholangitis will shed a new light on its medical management and may change the clinical practice to a great extent. A wholesome approach to disease management which includes monitoring for disease and treatment complications along with optimization of therapeutic response will lead to better patient outcomes and in due course an enhanced quality of life for our patients.

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