REVIEW

Cirrhosis and autoimmune liver disease: Current understanding

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Abstract

Primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) constitute the classic autoimmune liver diseases (AILDs). While AIH target the hepatocytes, in PBC and PSC the targets of the autoimmune attack are the biliary epithelial cells. Persistent liver injury, associated with chronic AILD, leads to un-resolving inflammation, cell proliferation and the deposition of extracellular matrix proteins by hepatic stellate cells and portal myofibroblasts. Liver cirrhosis, and the resultant loss of normal liver function, inevitably ensues. Patients with cirrhosis have higher risks or morbidity and mortality, and that in the decompensated phase, complications of portal hypertension and/or liver dysfunction lead to rapid deterioration. Accurate diagnosis and monitoring of cirrhosis is, therefore of upmost importance. Liver biopsy is currently the gold standard technique, but highly promising non-invasive methodology is under development. Liver transplantation (LT) is an effective therapeutic option for the management of end-stage liver disease secondary to AIH, PBC and PSC. LT is indicated for AILD patients who have progressed to end-stage chronic liver disease or developed intractable symptoms or hepatic malignancy; in addition, LT may also be indicated for patients presenting with acute liver disease due to AIH who do not respond to steroids.

Key words: Hepatic fibrosis; Cirrhosis; Myofibroblasts; Primary biliary cirrhosis; Primary sclerosing cholangitis; Autoimmune hepatitis; Liver transplantation

Core tip: In chronic liver disease, including autoimmune liver diseases, perpetual liver injury leads to persistent inflammation, cell proliferation and the deposition of extracellular matrix proteins. If left untreated, this process eventually leads to the development of liver cirrhosis, characterised by the presence of fibrosis and nodular regeneration. Liver biopsy is currently the gold standard technique, but highly promising non-invasive methodology is under development.

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INTRODUCTION

Liver disorders with probable autoimmune aetiology include autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). Each disease complies with, to varying extents, a proposed "multiple hit hypothesis" accounting for autoimmunity development, in which interacting environmental, infectious, genetic, epigenetic and immunological factors account for the loss of tolerance to self-constituents[1]. While AIH target the hepatocytes, in PBC and PSC the targets of the autoimmune attack are the biliary epithelial cells. Each of the autoimmune liver diseases (AILDs) is associated with distinct epidemiological and clinical characteristics. However, overlap syndromes, characterised by the coexistence of features of more than one AILD, are increasingly being recognised[2].

AILDS

PBC

PBC is a cholestatic autoimmune liver disease characterised by progressive destruction of the small and intermediate-sized bile ducts[3]. The histologic picture of PBC involves non-suppurative cholangitis with destruction of the biliary epithelium and portal infiltration of inflammatory cells. PBC also presents with biochemical evidence of cholestasis. PBC has pronounced female preponderance and a strong tendency to present in middle age[3]. Epidemiological characteristics of PBC are outlined in Table 1.

High titre positivity for serum anti-mitochondrial autoantibodies (AMAs) is pathognomonic for PBC, being detected in up to 95% of patients[3-5]. Moreover, asymptomatic people with AMA-positivity eventually progress to disease development[6]. AMAs target lipoylated domains of the 2-oxoacid dehydrogenase complexes, with the immunodominant epitope belonging to the E2 components of the pyruvate dehydrogenase complex[3,4,7]. PBC-specific anti-nuclear autoantibodies (ANAs), with a characteristic "multiple nuclear dot" or "nuclear membrane" pattern, are found in 25%-40% of patients[8].

There is mounting evidence that the development of PBC can be accounted for by a proposed "multiple hit" hypothesis for the development of autoimmunity (Figure 1). The molecular mimicry hypothesis postulates that microorganisms with epitopes that are structurally similar to self-components trigger an immune response with interspecies promiscuity. Several potential infectious triggers have been proposed[9] including *Escherichia coli*[10-14] and *Nosphingobium aromaticivorans*[15-17].

Numerous lines of evidence demonstrate that genetic factors alter susceptibility to PBC development. Female relatives of patients are at increased risk of developing PBC, and there is a high concordance rate between monozygotic twins[18]. Strong genetic associations lying within the MHC, for example HLA-DR8 in Europe and North America, have consistently been reported[19,20]. Genome wide association studies (GWAS) have revealed non-*MHC* gene associations that could be related to abnormal immune activation, including *IL12A*, *IL12RB2*, *STAT-4* and *CTLA-4*[21-23].

Ursodeoxycholic acid (UDCA) is the standard treatment for PBC, improving both biochemical and histological indicators of disease activity and elongating transplant-free survival time in a significant proportion of patients[24,25].

PSC

PSC is a chronic inflammatory disease of the biliary epithelium, characterised by progressive bile duct destruction. The small, medium and large bile ducts are affected by obliterative concentric fibrosis which leads to the development of biliary strictures[26]. In contrast to the other AILDs, PSC affects males more commonly than females[27]. The median age of onset is approximately 41 years of age[27] (Table 1).

The most common biochemical abnormality in PSC patients is elevated serum alkaline phosphatase (AP)[28]. The most reliable diagnostic tool is cholangiography, which enables visualisation of characteristic multifocal strictures within the intra- and extra-hepatic bile ducts[29]. Concomitant inflammatory bowel disease (IBD), most frequently ulcerative colitis, is found in up to 80% of patients[28,30].

As with the other AILDs, the aetiology of PSC remains unknown but it is likely to follow the proposed multiple hit hypothesis (Figure 1), resulting from interplay between numerous genetic and environmental factors. The strong link with IBD has led to the emergence of the gut/lymphocyte homing hypothesis, which postulates that memory lymphocytes primed in the gut-associated lymphoid tissue, and therefore expressing the gut-homing integin $\alpha 4\beta 7$ and the chemokine receptor CCR9, migrate from the gastrointestinal tract to the liver[31,32]. Importantly, the ligand for $\alpha 4\beta 7$, MAdCAM-1, and the cognate chemokine for CCR9, CCL25, both usually restricted to the gut[32,33], are aberrantly expressed in the portal vein endothelium and sinusoidal endothelium respectively in PSC patients. Moreover, approximately 20% of liver-infiltrating T cells express $\alpha 4\beta 7$ and CCR9, and have an effector memory phenotype[34,35]. The "leaky gut hypothesis", on the other hand, involves direct translocation of intestinal flora *via* the portal vein[28]. Although direct evidence of this phenomenon is lacking[36], future studies investigating the influence of the gut microbiota on PSC development/progression are warranted.

Similarly to the other AILDs, the strongest PSC genetic associations lie within *HLA* gene. In GWAS, the strongest association signals have been found near HLA-B[37-39]. There are, however, also believed to be HLA class Ⅱ

Table 1 Epidemiological characteristics associated with the three autoimmune liver diseases

	PBC	PSC	AIH
Female/male ratio	10/1	1/2	4/1
Average age at presentation	50	41	Childhood/adolescence and approximately 40
Incidence	0.33-5.8/100000	0-1.3/100000	0.08-3/100000
Prevalence	1.91-40.2/100000	0-16.2/100000	11.6-35.9/100000
Risk within family	1st degree relative incidence 4%-6%	Unknown	Unknown
Concordance in monozygotic twins	60%	Only case reports	Only case reports
Note	AMA positivity	Frequent association with IBD Increased risk of hepatobiliary/colorectal malignancies	Positivity for ANA and or SMA (AIH type-1) or anti-LKM-1 (AIH type-2)

AIH: Autoimmune hepatitis; AMA: Anti-mitochondrial autoantibodies; ANA: Anti-nuclear autoantibody; IBD: Inflammatory bowel disease; LKM: Liver kidney microsomal; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis; SMA: Smooth muscle autoantibody.
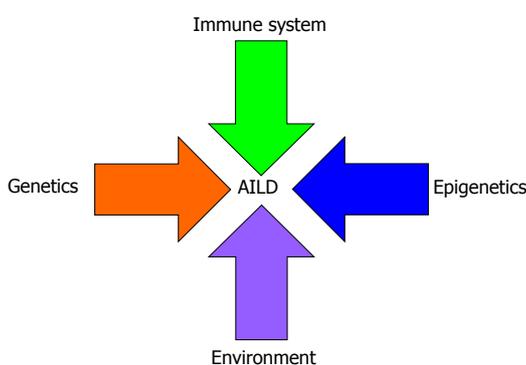
Figure 1 "Multiple hit hypothesis" accounting for the development of autoimmune disease. Interplay between immunological, genetic, epigenetic and environmental factors is thought to account for the loss of tolerance to self constituents in AILD. AILD: Autoimmune liver disease.

susceptibility genes contributing to the association signal found within in this region[38,39]. Non HLA associations identified by GWAS include *BCL2LII*, which encodes the pro-apoptotic protein *BIM*, *TNFRSF14* and *IL2RA*[37-39].

AIH
AIH is a progressive inflammatory disease which, in contrast to the two cholestatic AILDs, targets the hepatocytes themselves. AIH has marked female predilection. AIH can present at all ages, but the two peak ages of incidence are in childhood or adolescence and at around 40 years of age[40] (Table 1). Trademark biochemical/serological characteristics of AIH are elevated aminotransferase levels, positivity for autoantibodies and increased IgG. A histological picture of interface hepatitis is typical of AIH. Autoantibody positivity is an important clinical feature of AIH, facilitating diagnosis and enabling distinction between two types of the disease. Patients seropositive for ANA and/or anti-smooth muscle autoantibodies (SMA) have AIH type-1 whereas those presenting with positivity for anti-liver kidney type-1 autoantibody (anti-LKM-1) or anti-liver cytosol type-1 (anti-LC-1) have AIH type-2[41,42].

Although AIH aetiology remains to be elucidated, available evidence is strongly suggestive of interplay between genetic and environmental factors (Figure 1).

The observation that the hepatitis C virus shares high sequence homology with the auto-antigenic target of anti-LKM-1 autoantibodies, cytochrome P450-2D6, has led to the suggestion that molecular mimicry could trigger AIH development in a genetically predisposed host[43,44]. Other potential triggers for AIH include the hepatitis B virus, cytomegalovirus and the herpes simplex virus[43].

Genetic associations affecting susceptibility to disease development, response to therapy and prognosis have been reported[45]. The most significant genetic associations lie within the MHC, at the HLA-DRB1 locus. Susceptibility to AIH type-1 is linked to alleles encoding the HLA-DR3 and DR4 molecules[46], while AIH-2 susceptibility and severity have been linked to alleles encoding the HLA-DR3 and DR7 molecules[47]. Susceptibility to AIH has also been linked to polymorphisms in genes located outside the MHC, including *CTLA-4*[48], *TNF-α*[49] and *Fas*[50].

With the standard treatment regimen for AIH - prednisolone, with or without the addition of azathioprine - up to 80% of AIH patients are able to reach remission[51].

Overlap syndromes
It is not uncommon for patients to present with features characteristic of AIH and either PSC or PBC. Because standardised and validated diagnostic criteria are lacking, these "overlap syndromes" remain ill defined. PBC/AIH overlap is present in some 10% of AIH or PBC patients[52,53], and the most commonly used method for diagnosis is the presence of two of the following features of AIH in conjunction with two of the following features of PBC. The AIH features are: (1) ALT at least 5 times the upper limit of normal (ULN); (2) SMA positivity or IgG level of at least 2 times ULN; and (3) liver histology showing moderate or severe periportal or periseptal inflammation. The PBC criteria are: (1) AP at least twice ULN or gamma glutamyl transferase above 5 times ULN; (2) AMA positivity; and (3) bile duct lesions on liver biopsy[52,54,55]. AIH/PSC overlap is now believed to represent a significant proportion of patients with AILD[56,57]. The characteristics of AIH/PSC overlap are the classical features of AIH-1 - positivity for ANA and/or SMA, high IgG levels and interface hepatitis on biopsy - in addition to biochemical evidence of cholestasis, frequent
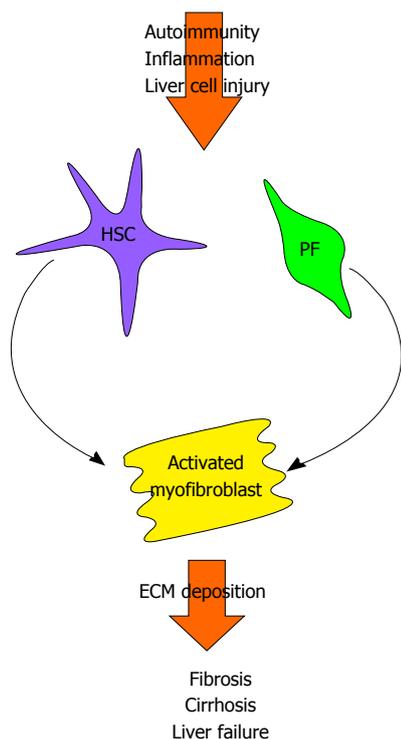
Figure 2 Development of fibrosis and cirrhosis in autoimmune liver disease. Persistent autoimmune-mediated inflammation and liver cell injury leads to the activation and differentiation of quiescent hepatic stellate cells (HSC) and portal fibroblasts (PF) into activated myofibroblasts. These proliferative, pro-inflammatory and pro-fibrogenic myofibroblasts increase collagen synthesis and deposit extracellular matrix proteins (ECM), leading to the development of fibrous scar tissue. Cirrhosis, characterised by significant fibrosis and nodular regeneration, eventually ensues, with the resultant loss of liver function and eventually liver failure.

occurrence of IBD, histological features consistent with PSC[58]. Cholangiographic evidence of intrahepatic or extrahepatic PSC also supports this diagnosis[59].

FIBROSIS: KEY PLAYERS

In chronic liver disease, including AILD, perpetual liver injury leads to persistent inflammation, cell proliferation and the deposition of extracellular matrix proteins. If left untreated, this process eventually leads to the development of liver cirrhosis, characterised by nodular regeneration diffuse nodular regeneration surrounded by fibrotic septa with consequent extinction of the parenchyma, together leading to distortion of hepatic vascular architecture[60]. Loss of normal liver function inevitably ensues (Figure 2)[61].

Hepatic stellate cells, found in the space of Dissé, have long been believed to be the main contributors to liver fibrosis. Liver damage induces hepatic stellate cells to differentiate into proliferative and contractile myofibroblasts, with a pro-inflammatory and fibrogenic phenotype[61-63]. Portal fibroblasts, located in the connective tissue of the portal triad are another source of myofibroblasts[64]. These are of particular importance in the context of the cholestatic AILDs. Liver damage leads to the myofibroblastic differentiation of quiescent

portal fibroblasts[64], a process which can be enhanced in these conditions by the cholangiocytes themselves. When cholangiocytes become "reactive", they proliferate and express co-stimulatory molecules, chemokines and pro-fibrogenic molecules, therefore further promoting fibrogenesis[65-70]. Bile acids, elevated as a consequence of cholestasis, could also perpetuate fibrogenesis indirectly by damaging hepatocytes[71], or by directly targeting myofibroblasts[72].

It has also been suggested that hepatic myofibroblasts could arise from hepatocytes or cholangiocytes *via* epithelial-mesenchymal transition, whereby polarised epithelial cells undergo phenotypic transformation in response to microenvironmental cues[73]. There are reports that hepatic epithelial cells can acquire some of the phenotypic characteristics of myofibroblastic cells *in vitro*. Co-expression of epithelial and fibroblastic cell markers has also been described in human tissue sections[74,75]. However, partly because these cell "markers" inadequately define both the epithelial and fibroblastic populations, conclusive evidence of epithelial-mesenchymal transition has been hard to come by. Furthermore, lineage tracing studies, using Cre/lox recombination, have failed to find evidence of liver epithelial cell-mesencymal transition in murine models of bile-duct ligation or hepatitis induced by carbon tetrachloride (CCL_4) or 3,5-diethoxycarbonyl-1,4-dihydrocollidine[76,77].

NATURAL HISTORY OF CIRRHOSIS

It is well known that, compared with pre-cirrhotic patients, patients with cirrhosis have higher risks or morbidity and mortality[78]. Cirrhosis can be divided into a compensated phase, free of symptoms, and a decompensated phase, in which complications of portal hypertension and/or liver dysfunction lead to rapid deterioration. The two stages can be considered separate clinical entities according to the AASLD and EASL guidelines[79]. Median survival time in the compensated phase is over 12 years, whereas survival in the decompensated phase drops to approximately 2 years. The decompensated phase is defined by the development of jaundice, ascites, variceal haemorrhage or encephalopathy[80,81]. The compensated stage has been further divided into stage 1, consisting of patients lacking varices, and stage 2, characterised by the presence of varices in the absence or variceal bleeding. The decompensated stage has been split into stage 3, associated with ascites and a lack of variceal haemorrhage, and stage 4, comprising patients with variceal haemorrhage (with or without ascites). One year mortality rates of 1%, 3%, 20% and 57% respectively have been reported[82,83]. In a recent study, however, Zipprich *et al*[84] (2012) failed to replicate entirely these reported values, finding that stage 3 and stage 4 patients had one year survival rates of approximately 20% and 18% respectively. The authors of this study cite recent advances in variceal haemorrhage therapy[85] as a potential reason for this discrepancy and proposed modifications to the system of stratification. The newly defined

stage 3 consists of patients with variceal haemorrhage but without ascites, while stage 4 is characterised by the presence of ascites (with or without variceal bleeding)[84].

The risk of progression from compensated to decompensated cirrhosis is approximately 31% in the first year of diagnosis and 5%-7% thereafter[86]. Because of the striking reduction in survival time in the decompensated state, it is important to identify patients at greatest risk of cirrhosis progression. Newly developed non-invasive techniques for fibrosis/cirrhosis assessment are currently being tested.

The Child-Pugh, and more recently developed Model of End-Stage Liver Disease (MELD) Scores are the most widely used methods by which prognosis is assessed in the context of end-stage liver disease. The Child-Pugh Score incorporates values between 1 and 3 for each of the following criteria: Degree of encephalopathy, presence of ascites, serum bilirubin and albumin levels and international normalised ratio (INR). The MELD score encompasses bilirubin, INR and creatinine levels[87]. MELD was initially developed for predicting survival following transhepatic portosystemic shunt, but is now used to accurately predict survival in the context of cirrhosis[88], list patients for transplant and allocate organs.

DIAGNOSING CIRRHOSIS

Liver biopsy is still the most accurate and widely used method by which cirrhosis can be diagnosed and staged. There are, however, notable disadvantages to this method of examination, including cost, risk of bleeding, and sampling error[89]. Non-invasive tests for both diagnosis and assessment of fibrosis/cirrhosis progression are becoming increasingly sought. Proposed tests include those using the results of routine liver-function examinations, such as the AST-to-platelet ratio index, as well as examinations to measure liver stiffness; FibroTest and transient elastography (TE; FibroScan)[90,91]. There are promising indications that non-invasive methods could be used in the context of AILD. In PBC, liver stiffness tests show high performance in diagnosing significant fibrosis, severe fibrosis and cirrhosis. Progression of liver stiffness has also been used as an accurate measure of overall prognosis in PBC[92-94]. The addition of serological markers to the liver stiffness score does not appear to improve test outcome[93]. In a study also involving both PBC and PSC patients, liver stiffness was also shown to correlate with progression of fibrosis and histological scores[95]. Using a cohort of 404 patients with varied liver diseases, including PBC, PSC and AIH, Malik *et al*[96] (2010) found that liver stiffness scores accurately identified patients with compensated cirrhosis. Although highly promising, these results, particularly in the context of AIH, need to be confirmed in larger cohorts of patients.

CIRRHOSIS IN AILDS

Cirrhosis in PBC

PBC progresses through a number of stages: Preclinical, asymptomatic, symptomatic, and liver failure. The preclinical phase is symptom-free and is associated with AMA positivity in the absence of biochemical indications of liver disease[6,97]. Biochemical abnormalities eventually appear after a median time of 5.6 years (range, 1-20 years)[6], but this phase is not yet associated with the presence of symptoms. When symptoms eventually develop, they are most commonly fatigue and pruritus, and later varices, oedema or ascites.

Liver failure is characterised by the accelerated development of jaundice, and is associated with poor prognosis[98]. Mean survival for patients with a bilirubin of 2.0 mg/dL is 4 years, while for those with bilirubin of 6.0 mg/dL is only 2 years[98]. PBC prognosis has dramatically improved in the last 20 years thanks to earlier diagnosis and the introduction of UDCA as the mainstay of treatment[99,100].

UDCA slows fibrosis progression and delays cirrhosis development[101]. In clinical trials, UDCA treatment of PBC patients decreased the development of oesophageal varices and prolonged survival[102-106]. Cirrhosis does, however, still develop in UDCA-treated PBC patients[107]. Indeed, the development of cirrhosis under UDCA treatment is an independent predictor of negative outcome[101,107].

Histologically, PBC can be divided according to the presence of fibrosis/cirrhosis into four stages[108,109]. Stage one is characterised by portal inflammatory cell infiltrate, which, in stage two, invades the liver parenchyma. In stage three, bridging fibrosis, in which fibrotic septa extend from and link the portal tracts, can be seen. Stage four is characterised by progression to cirrhosis[109]. The development of cirrhosis does not occur uniformly throughout the liver, thus features of all four stages can ocur simultaneously in a single biopsy specimen. Histological staging should depend upon the most advanced histological features[25].

Histological stages can predict survival of PBC patients[110]. In untreated PBC patients, the median time to the development of extensive fibrosis is 2 years. The probability of remaining in early stages after 4 years is 29%, whereas development of cirrhosis occurs in 50% of patients originally demonstrating histological evidence of interface hepatitis without fibrosis[111]. In two studies the proportion of patients developing liver failure during a follow-up time of 5 years was found to be 15%[112] and 25%[113]. The development of oesophageal varices, and the associated impact on survival, has been examined in a prospective study over the course of 5.6 years, which included 256 patients[114]. Twenty-eight percent of patients were cirrhotic. Nearly one-third of patients developed oesophageal varices, after which the 3-year survival was 59%. Survival after the first bleeding episode was 46%[114].

The introduction of UDCA as first line treatment for PBC patients has changed the natural history of the disease[25,100,115,116]. Indeed, the number of PBC patients requiring liver transplantation (LT) decreased by 20% in between 1996 and 2006[115]. Additionally, PBC has fallen in the ranking of the most common indications for LT

from the first to the sixth place LT over a period of 20 years[25].

Several papers have also assessed the impact of UDCA therapy on the progression rate of cirrhosis in PBC patients. Corpechot *et al*[107] examined progression to cirrhosis in 183 UDCA-treated PBC patients. In this study, 21% of patients developed cirrhosis during follow-up. The incidence of cirrhosis in patients followed up from stages 1, 2 and 3 was 4%, 12% and 59% respectively and the median length of times to cirrhosis development was 25, 20 and 4 years respectively. Albumin and bilirubin levels, and the histological severity of interface hepatitis were independently associated with progression to cirrhosis; cirrhosis was most likely to develop in patients with serum bilirubin over 17 μmol/L, serum albumin below 38 g/L and in patients with moderate to severe interface hepatitis[107]. The impact of UDCA treatment oesophageal varices development has been examined in a 4-year prospective study including patients who received UDCA *vs* patients who received placebo. In the UDCA arm, the risk of varices development was 16%, while for those in the placebo group was 58%[103].

Cirrhosis in PSC
Typical symptoms of PSC, occurring in a variable number of patients include pruritus, abdominal pain, malaise, weight loss, and episodes of fever and chills[117]. About 50% of PSC patients will present symptomatically[118,119]. Similarly to PBC, PSC progresses through four histological stages[120]. In stage 1, which is known as the portal stage, changes are restricted to the portal tracts with features of mild hepatitis and cholangitis. Stage 2, known as the periportal stage, is characterised by extension of the lesion to include periportal fibrosis and occasionally interphase hepatitis. In this phase, the portal tracts are often notably enlarged. By stage 3, the septal stage, bridging fibrous septa have developed and the bile ducts have begun to degenerate and disappear. Stage 4 is characterised by cirrhosis[120]. The rate of progression through these stages has been investigated. Of PSC patients in the periportal stage, 42%, 66% and 93% progressed over 1, 2 and 5 years respectively. Of patients in the septal stage, 14%, 25% and 52% progressed over 1, 2 and 5 years respectively. In 15% of total observations, regression of histologic stage could be observed, highlighting the problem of sample variability when serial liver biopsies are used during the period of follow-up[121].

PSC can present at later stages of disease development, with complications of cirrhosis and portal hypertension[122]. Similarly to other causes of cirrhosis, portal hypertension gradually develops in cirrhotic PSC patients[119]. In one study, 36% of 283 newly diagnosed PSC patients had varices[123].

Cirrhosis in AIH
In a cohort of over 450 AIH patients, 30% had evidence of cirrhosis at diagnosis, with a further 10% developing cirrhosis during a median follow-up time of 7.2 years.

The presence of cirrhosis at diagnosis correlated with negative outcome (LT or death)[124]. In another study, including 126 AIH patients, Feld *et al*[125] (2005) reported that 33% of patients had histological evidence of cirrhosis at diagnosis. With the exception of platelet count, which was lower in patients with cirrhosis, laboratory parameters, patient demographics and AIH scores did not differ between cirrhotic and non-cirrhotic patients. A similar frequency of patients from each group were symptomatic at diagnosis and an equivalent proportion had good response to treatment[125]. Importantly, similar response to treatment has also been reported elsewhere[126]. Feld *et al*[125] (2005) also found, however, that the presence of cirrhosis significantly increased risk of progression to LT or death. Consistent with the above studies, Verma *et al*[127] (2004) reported that 28% of AIH patients were cirrhotic at diagnosis. In this study, a further 20% of patients developed cirrhosis during 52 mo of follow-up. Again, cirrhosis was an independent predictor of poor outcome in this cohort[127]. On the other hand, studies in the adult[126,128] and paediatric[129] settings, of comparable size and methodology to those described above, have not found associations between the presence of cirrhosis at diagnosis and the likelihood of poor outcome.

In one study, patients diagnosed between the ages of 21 and 60 years of age were more likely to present with cirrhosis than those outside of this range. Male patients were also more likely to have cirrhosis compared to their female counterparts. Low serum albumin concentrations, prolonged INR and low platelet count were all more frequently associated with the cirrhotic group of AIH patients[130].

There are indications that cirrhosis is more common among AIH type-1 patients compared to patients with type-2 AIH. In a paediatric study, 69% of ANA/SMA positive patients had evidence of "definite cirrhosis" on initial biopsy, whereas only 38% of patients positive for anti-LKM-1 were cirrhotic. On follow-up these values increased to 74% and 44% respectively[131].

LT IN AILDS

LT is indicated for AILD patients who have progressed to end-stage chronic liver disease or developed intractable symptoms or hepatocellular carcinoma (HCC)[132,133]; in addition, LT may also be indicated for patients presenting with acute liver disease due to AIH who do not respond to steroids[134]. In total, AILDs accounts for almost one fourth of LTs performed in the United States and in Europe[135].

LT for PBC
The indications for LT in PBC are, for the most part, identical to those in patients with end-stage chronic liver disease of other aetiology[100,132]. The majority of transplants occur due to end-stage chronic liver disease when the MELD score is higher than 16[136]. Other indications for LT include HCC, portopulmonary hypertension or hepato-pulmonary syndrome[137]. Other than this, few

PBC patients with non-cirrhotic portal hypertension associated with obliterative portal venopathy or nodular regenerative hyperplasia will benefit from transplant[138]. Finally, even when liver function is sufficient[139], LT may be indicated if intractable symptoms, most notable refractory pruritus, are present[137,140].

The immunosuppressive regimen most commonly used following LT is a combination of corticosteroids, which are withdrawn over a period of three months, a calcineurin inhibitor (CNI) and mycophenolate mofetil or azathioprine. This regimen has a very successful outcome[136]; with 1, 3 and 5 year patient survivals of 94%, 91% and 82% respectively, and graft survivals of 85%, 83% and 75% respectively[141]. Analysis of the UNOS database showed that PBC living donor transplant recipients had estimated 1, 3 and 5 year patient survivals of 93%, 90% and 86% and deceased donor transplant recipients had estimated survivals of 90%, 87% and 85% respectively. Estimated graft survivals at 1, 3 and 5 years for living donor LT was 86%, 81% and 77% respectively, and for deceased donor LT was 85%, 83% and 81% respectively[142].

LT for PSC
Similarly to PBC, and other liver diseases associated with cirrhosis, LT is indicated in PSC patients with end-stage liver disease (*i.e.*, with a MELD score above 16)[143,144]. HCC can occur in PSC patients with cirrhosis, and in this context, LT prioritisation follows the same rule as that for other cirrhotic patients with HCC[137,145]. In PSC, LT may also be indicated in patients with intractable pruritus or those with recurrent bacterial cholangitis, and limited stage cholangiocarcinoma[118,122,143].

LT for PSC usually has good outcome[139]. In one report, the 1, 2 and 5 year actuarial patient survivals for LT for PSC were 90%, 86% and 85%, and graft survivals were 82%, 77% and 72% respectively[146]. In a study from the Mayo Clinic comprising 150 transplanted PSC cases, similar patient survival at 1, 2, 5 and 10 years of 94%, 92%, 86% and 70%, and graft survival of 83%, 83%, 79% and 61% was reported[147].

LT for AIH
Overall, AIH accounts for some 3% of paediatric and up to 6% of adult LTs[40]. The natural course of AIH is understood mostly thanks to the last placebo-controlled trials published 4 decades ago[148-150]. These reports demonstrated that, without treatment, AIH patients have poor survival with 40% of deaths within 6 mo from diagnosis. With treatment, 10-year survival rate of AIH patients is over 80%[125,151].

LT is indicated for AIH patients presenting with acute liver failure who do not respond to steroids, for those patients with advanced cirrhosis and for those with HCC[136,152].

The immunosuppressive strategy most commonly adopted consists in the combination of prednisolone and a CNI[153], leading to excellent outcome with 5 and 10 year patient survivals of 90% and 75%[51], and 1 and 5 year graft survivals of 84% and 75%[51,154].

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