Chapter 5

A Concise Review of Autoimmune Liver Diseases

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60520

1. Introduction

Autoimmune liver disease (AILD) consists of autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). It is characterised by the immune mediated injury to the hepatocytes and bile ducts. Hepatocyte injury is the predominant features in autoimmune hepatitis and biliary injury is the hallmark of primary biliary cirrhosis (Intrahepatic bile duct injury), primary sclerosing cholangitis or Immunoglobulin (Ig) G4 mediated cholangitis (both intra and extra-hepatic bile duct injury). Overlap or variant syndrome indicates the presence of simultaneous injury to both hepatocytes and cholangiocytes during the course of the disease. Imbalance in effector and regulatory arm of adaptive immune cells had been described as the immunopathogenesis of AILD. Antigenic causative factors are still poorly understood across AILD but genetic, environmental factors and microbiota play a major role in disease pathology.

1.1. Aims

The aim of the chapter is to describe in depth of each disease entity in regard to their immunopathogenesis, diagnosis, investigations and management strategies including standardised care as well as future novel therapies.

1.2. Concerns

Long term global immunosuppressive therapy in AIH with multiple side effects and lack of definitive treatment to tackle the underlying immunopathology in PBC and PSC are major challenging aspects in AILD. Thorough understanding of causative antigens, immunopathogenesis, OMIC profiles (genomic, metabolomics, proteomic and microbiomic) of AILD patients will direct clinicians for stratification and individualized personal care. Novel new

immunological based cell and cytokines therapies are urgently warranted in defined unique group of AILD patients.

The diagnosis and management of AILD can be constantly challenging due to the presence of overlap features at diagnosis or gradual evolution in phenotype of diseases from one spectrum (typical AIH) to others (overlap of AIH/PBC and AIH/PSC) during the disease process. Therefore, the continuous assessment of the disease presentations are essential in follow up of patients with AILD.

2. Background

An autoimmune liver disease (AILD) is an umbrella term for diseases caused by immune mediated reaction to either hepatocytes or bile ducts. Regulatory T cells (Treg) play an important and essential role in the maintenance of homeostasis and prevention of autoimmune responses [1]. Autoimmune hepatitis (AIH) is caused by an immune mediated injury of the hepatocytes and characterised by presence of lobular and interface hepatitis on liver histology, presence of hypergammaglobulinaemia and high titre of antinuclear antibodies (ANA) in the serum with transaminitis on liver biochemistry. The main aim of treatment is to suppress the immune system globally and the first line therapies used are prednisolone and azathioprine. Second line therapies such as tacrolimus and mycophenolate mofetil are also used in AIH patients. Two commonly used biologics in difficult-to-treat AIH patients are anti- tumour necrosis factor (anti-TNF) for example Infliximab and anti-CD20 monoclonal antibody therapy as in Rituximab. New novel antigen-specific autologous regulatory T cells therapy development is also in progress for future treatment of autoimmune hepatitis.

Primary biliary cirrhosis (PBC) is an injury to the intra-hepatic biliary ducts and tends of present in 4th to 6th decade of life. The main therapy is ursodeoxycholic acid (UDCA) but new therapies for PBC such as Obeticholic acid have been emerged recently. Patients with PBC tend to suffer with significant itch and management of itch can be challenging at times. There are therapies available for itch from the spectrum to cholestyramine to immunoglobulins infusion treatment.

Primary sclerosing cholangitis (PSC) is an immune mediated injury, mainly to biliary system either intrahepatic or extrahepatic or both. PSC is common in young, male patient and commonly associated with inflammatory bowel disease (IBD), especially ulcerative colitis. There is a significant risk of developing cancer such as cholangiocarcinoma or gall bladder cancer or bowel cancer in these groups of patients and hence surveillance is important. There are no targeted treatments available for PSC and liver transplantation is necessary in end stage PSC.

Detailed summary of three autoimmune liver disease (autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis) are documented in table 1.

	AUTOIMMUNE HEPATITIS (AIH)	PRIMARY BILIARY CIRRHOSIS (PBC)	PRIMARY SCLEROSIS CHOLANGITIS (PSC)
AGE	Any age	Any age, common over 40 years	Around 40 years of age
GENDER	Female predominance (4:1)	Female predominance (9:1)	Male predominance (7:3)
ASSOCIATED CONDITIONS	Other autoimmune conditions, commonly thyroid disorders, diabetes mellitus, coeliac disease and inflammatory arthritis	Other autoimmune conditions, commonly thyroid disorders, diabetes mellitus, coeliac disease and inflammatory arthritis	Inflammatory bowel disease, mainly ulcerative colitis
TRANSAMINASE LEVELS (ALT OR AST)	Raised (>5x ULN) ⇑⇑⇑	Raised (stable) ⇑	Raised (fluctuating) ⇑
ALP OR GGT	Raised ⇑	Raised (stable) ⇑⇑⇑	Raised (fluctuating)- (> 3 fold increase) ⇑⇑⇑
IMMUNOLOGICAL PROFILE	Raised ANA, ASMA or LKM Raised Ig G	Raised AMA (anti-gp 210, anti-Sp 100) Raised Ig M	None
BILIARY INVOLVEMENT	No	Yes (small duct)	Yes (small to large duct)
LIVER HISTOLOGY [1]			
INTERFACE HEPATITIS	Yes	May be	May be
PORTAL INFLAMMATION	Lymphoplasmacytic infiltrate	Lymphocytic infiltrate	Lymphocytic infiltrate
GRANULOMAS	No	Yes	Rare (<10% of cases)
RESPONSE TO STEROIDS/ OTHER IMMUNOSUPPRESIONS	Yes	No	No
RESPONSE TO UROSDEOXYCHOLIC ACID (UDCA)	No	Yes	Maybe
PROGNOSIS	If untreated, patient have poor prognosis with 5 and 10 year survival rates of 50 and 10% [2].	Prognosis is excellent in patients who achieved biochemical response with UDCA therapy	Median survival without transplantation is 12 to 15 years [3]

ANA: Anti-nuclear antibodies, ASMA: anti smooth muscle antibodies, LKM: Liver- kidney-microsomal antibodies, g G: Immunoglobulin G, Ig M: Immunoglobulin M, Anti-gp 210: Antibodies against the nuclear pore membrane glycoprotein (anti-gp210), Anti-Sp 100: Antibodies against the nuclear protein Sp100, ULN: Upper limit of normal, UDCA: Ursodeoxycholic acid

Adapted from 1) Trivedi, P.J. and G.M. Hirschfield, Review article: overlap syndromes and autoimmune liver *disease.* Aliment Pharmacol Ther, 2012. 36(6): p. 517-33. 2) Strassburg, C.P. and M.P. Manns, *Therapy of autoimmune hepatitis.* Best Pract Res Clin Gastroenterol, 2011. 25(6): p. 673-87.3) Yimam, K.K. and C.L. Bowlus, Diagnosis and classification of primary sclerosing cholangitis. Autoimmun Rev, 2014. 13(4-5): p. 445-50.

Table 1. Summary of Autoimmune liver disease

3. Autoimmune hepatitis

3.1. Epidemiology

Autoimmune hepatitis (AIH) is an immune mediated, chronic inflammatory disease of unknown aetiology, mainly affecting the hepatocytes. It was first defined in 1950 by Waldenström when he described a chronic hepatitis in young woman which eventually lead to liver cirrhosis [2]. It is characterised by the morphological changes of interface hepatitis on liver biopsy, hypergammaglobulinaemia and the presence of high circulating ANA in the serum [3, 4]. It is more common in women (around 75%) and can affect at any age from young to elderly. It is also associated with other autoimmune conditions such as hypothyroidism, ulcerative colitis, type 1 diabetes mellitus, rheumatoid arthritis, coeliac disease or skin disorders such as vitiligo. Therefore, obtaining a detailed history especially family history of autoimmune conditions are important in the assessment of patients with potential AIH diagnosis.

There is limited evidence regarding the incidence and prevalence of AIH. From the data so far, it has been estimated that the prevalence of AIH is around 5 to 20 cases per 100,000 among the Caucasian population in Western Europe [5]. AIH accounts for up to 20% of chronic hepatitis among the Caucasian population of North America and Western Europe [5]. AIH prevalence and clinical expression appear to vary according to ethnicity. Previous studies showed that black patients tend to have more aggressive disease [6] whereas Hispanic populations had a higher prevalence of cirrhosis [7]. Asian patients develop the disease later in life and have a poorer survival [7] and Alaskan native patients presented more frequently with acute AIH [8].

Clinically, there are three forms of AIH. Type 1 AIH is common in adults and characterised by the presence of ANA and/or anti smooth muscle antibodies (ASMA) with raised Immunoglobulin-G (Ig G). Type 2 is seen mostly in children and characterised by the presence of anti-liver-kidney-microsomal (LKM) antibodies directed against cytochrome P450 (CYP-2D6) [9, 10] and with lower frequency against UDP-glucuronosyltransferases (UGT) [2, 11]. Antibodies against soluble liver or liver-pancreas (SLP) antigens are common in type 3 AIH. Around 19% of patients can present with seronegative disease at the time of diagnosis [12].

3.2. Pathogenesis

The exact aetiopathogenesis of AIH is still unknown. It is a complex process interlinking environmental and genetic factors in a susceptible host. The most common environmental trigger thought to cause AIH is viral infection. Drug induced AIH is a recognised entity and the commonly associated drugs are anti-TNF treatment such as Adalimumab, antibiotics such as minocycline or nitrofurantion or statins such as rosuvastatin [13-15]. Both T cells and B cells play an important role in the adaptive immune response to both self and non-self-antigen. T cells, both CD4 and CD8 T cells, play a major role in the immnuopathogenesis with effector responses mediated by Natural Killer (NK) cells and macrophages [16]. Regulatory T cells (Treg) play an essential role in the homeostasis and prevention of autoimmune conditions [1]. They are classified as CD4+ $CD25^{high}$ $CD127^{Low}$ and represent the 2 % of the CD3 subset [17]. Foxp3 (forkhead box P3) is a transcription factor which controls the phenotype, development and function of Treg [18]. Commitment to Treg lineage primary occurs in the thymus as a result of presenting self- antigens by medullary thymic epithelium. In AIH, the number of Tregs is

normal but their function is impaired [19]. Reduction in frequency of Treg has also been reported [17, 20].

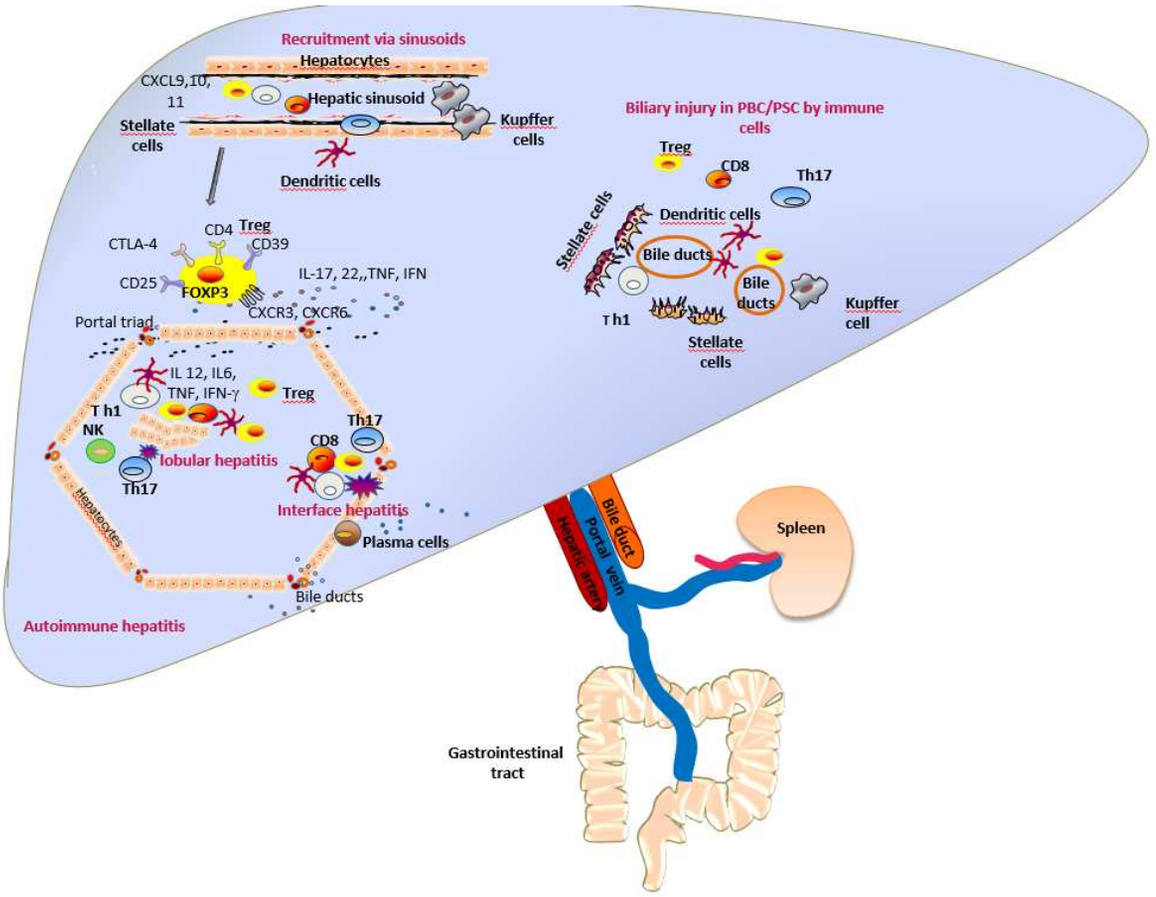
Type 1 AIH is associated with human leukocyte antigen (HLA) DR3 (HLA-DRB1*0301) and DR4 (HLA-DRB1*0401) in white North Europe and North American patients [21, 22]. It has been suggested the presence of DR3 is associated with poorer response to treatment and hence requires liver transplantation (LT) [21, 22]. On the other hand, patients with DR4 are usually older and more responsive to treatment with steroid [21]. A recent geno-wide association study of type 1 AIH in Netherlands showed that type 1 AIH is associated with the rs3184504*A allele in the SH2B3 gene [22]. These single nucleotide polymorphisms (SNP) represent the first genetic AIH locus outside the Major Histocompatibility Complex (MHC) region [22]. It encodes a missense variant in exon 3 of the Scr homology 2 adaptor protein 3 (SH2B3) genes located in the 12q24 region [22]. SH2B3 is a negative regulator of T-cell activation, tumour necrosis factor, and Janus kinase 2 and 3 signalling, and plays an essential role in normal haematopoiesis [22]. Capcase recruitment domain family member 10 (CARD 10) gene with allele rs6000782 has been shown to be associated with type 1 AIH [22]. CARD 10 is a scaffold protein and induces pro-inflammatory nuclear factor kB activation and it is widely expressed in a variety of non-haematopoietic tissue including hepatocytes [22].

Proposed pathway of pathogenesis in AIH has been shown in Figure 1.

3.3. Clinical presentations and diagnosis of AIH

Most patients present with nonspecific symptoms such as fatigue, arthralgia and anorexia at the time of presentation. About 25% of patient present asymptomatically [23] and the majority of patients present late with symptoms of portal hypertension and decompensated cirrhosis. Recent systematic review mentioned that around 25 % of elderly patients (age 60 to 65) were more likely to present asymptomatically, they are more likely to be HLA-DR4 positive and cirrhotic at initial presentation [24]. They are less likely to be HLA-DR3-positive and to relapse after treatment withdrawal after complete remission [24]. AIH can also present during pregnancy or postpartum period. Physical examination can either be normal, or show hepatomegaly, splenomegaly or signs of chronic liver disease. In some patients, AIH present as acute severe hepatitis and rarely, they progress to fulminant form and require liver transplantation [2].

Blood tests can show signs of hepatitis with raised alanine transaminase (ALT, U/L) (usually less than 500 U/L), aspartate transaminase (AST, U/L) and occasionally bilirubin (umol/L). Typical immunology profile in AIH patients are raised Ig G with positive ANA, ASMA (in type 1 AIH) and LKM (in type 2 AIH). Patients with acute presentation of AIH should be monitored for synthetic function such as international normalised ratio (INR) and albumin as well as mental status or sign of hepatic encephalopathy since some patients can progress to acute liver failure rapidly and will need liver transplantation. Viral hepatitis, toxins, drugs should be excluded in patient presenting with acute or chronic form of hepatitis. Men with AIH appear to have a higher relapse rate and younger age of disease onset [25, 26]. Cirrhosis at presentation [27, 28] and presence of SLA antibodies are poor predictive outcomes in type 1 AIH patients [29, 30].



CXCL: chemokine (C-X-C motif) ligand 1, CTLA-4: Cytotoxic T-lymphocyte-associated protein 4, CD: Cluster of Differentiation, CXCR: C-X-C chemokine receptor type, FOXP3: Forkhead box P3, IL: Interleukin, NK: Natural killer, T-reg: T regulatory cells, TNF: Tumour necrosis factor, IFN: Interferon, Th: T helper.

Figure 1. Pathogenesis of Autoimmune hepatitis. Autoimmune hepatitis (AIH) is initiated by the presence of auto antigen peptide onto antigen presenting cells (APC) which activates T helper cells (Th0) due to interleukins (IL) 2 and 4. Upon activation of Th0, it can differentiate into Th1 and Th2 cellular pathway. Th1 produces IL2 and Interferon-gamma (IFN-r) which subsequently activates CD8 lymphocytes.

Liver biopsy is recommended at the time of presentation to establish the diagnosis as well as to guide the treatment, however in patients presenting with acute hepatitis who has suspicious diagnosis of AIH, the treatment should not be delayed [31]. The histological hallmarks of AIH is a lymphoplasmacytic peri-portal infiltrate invading the limiting plate, also called piecemeal necrosis or "interface hepatitis" and eventually lead to lobular hepatitis (Figure 2) [13]. Patients with chronic AIH usually have plasma cell- rich mononuclear infiltrate involving portal and peri-portal regions [16] which subsequently lead to peri-portal fibrosis. Up to 30% of patients with AIH had histological features of cirrhosis at the time of presentation [2]. In 17% of patients with peri-portal hepatitis whereas 82% of patients who had bridging fibrosis, cirrhosis develops within 5 years [2].

The diagnosis of AIH is based on multiple investigations and diagnostic criteria was proposed by the international AIH group in 1993 and subsequently updated in 1999 (Table 2) [13, 32,

33]. In 2008, the groups established the simplified scoring system which is more user friendly in day to day clinical care[13] (Table 3). The scoring is based on combination of the serum immunoglobulins titres (ANA, SMA or LKM), serum liver enzymes and liver histology features with absence of viral hepatitis.

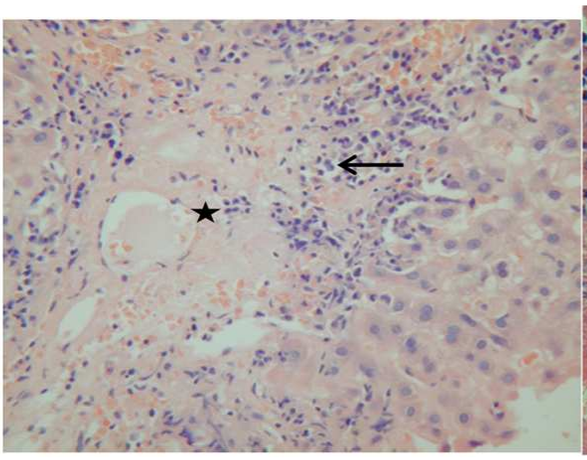


Figure above showed lobular inflammation with mainly plasma rich infiltrates (black arrow) and central peri-venulitis (black star)

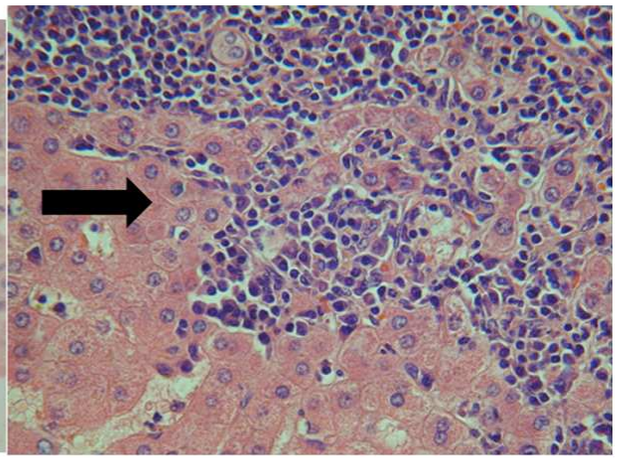


Figure above showed interface hepatitis with rich plasma cell infiltrates (large arrow head).

Figure 2. Histology findings of autoimmune hepatitis

Clinical features	Score
Female	+2
ALP:AST ratio	
• <1.5	+2
• 1.5-3.0	0
• >3.0	-2
Serum globulin or Ig G above normal	
• >2.0	+3
• 1.5-2.0	+2
• 1.0-1.5	+1
• <1.0	0
ANA, SMA or LKM 1	
• >1:80	+3
• 1:80	+2
• 1:40	+1
• <1:40	0
Illicit drug use	
• Positive	-4
• Negative	+1
Average daily alcohol intake	
• <25g/day	+2

Clinical features	Score
• >60g/day	-2
Histological findings	
• Interface hepatitis	+3
• Lymphoplasmacytic infiltrate	+1
• Rosette formation	+1
• None of the above	-5
• Biliary changes	-3
• Other changes	-2
	+2
Other autoimmune disease	
AMA positivity	-4
Viral hepatitis markers	
• Positive	-3
• Negative	+3
Definite AIH	>15
Probable AIH	10-15

ALP: alkaline phosphatase, AST: Aspartate transaminase, Ig: Immunoglobulin, ANA: Antinuclear antibodies, SMA: Smooth muscle antibodies, LKM: Liver kidney microsomal antibodies, AMA: Anti-mitochondrial antibod

Table 2. Revised International Autoimmune Hepatitis Group Scoring System for the Diagnosis of Autoimmune Hepatitis (AIH) (Adapted from Alvarez et al [21] and Chandok et al [22])

Variables	Cut off	Points
ANA or SMA	≥ 1;40	1
	≥ 1:80	2
Or LKM 1	≥ 1:40	2
Or SLA	Positive	1
Ig G	>upper limit of normal	1
	>1.1x upper limit of normal	2
Liver histology	Compatible with AIH	1
	Typical of AIH	2
Absence of viral hepatitis	Yes	2

ANA: anti-nuclear antibodies; SMA: anti-smooth-muscle antibodies; LKM1: liver/ kidney microsomal antibody type 1; SLA: anti-soluble liver antigen.

Definite AIH: A cumulative score ≥7

Probable AIH: A cumulative score =6

Liver histology typical of AIH: interface hepatitis, emperipolesis, hepatic rosette formation

Liver histology compatible with AIH: chronic hepatitis with lymphocytic infiltration, without typical features.

Table 3. Simplified scoring system for autoimmune hepatitis

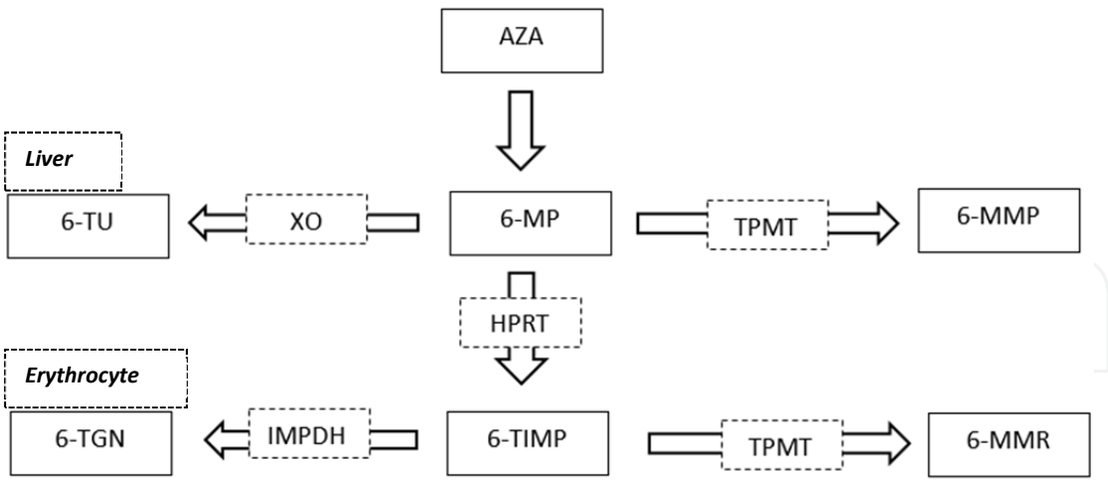
http://dx.doi.org/10.5772/60520

4. Management/treatment

4.1. Standard therapy

The main aim for treatment of AIH is to suppress the ongoing inflammation and the first line therapies used are steroids (either prednisolone or budesonide) with or without azathioprine (AZA). Steroid side effects such as cosmetic changes, osteopenia, hirsutism, steroid induced diabetes are seen in about 44% of patients within 12 months of treatment and 80% within 24 months of treatment [2]. Budesonide is a preferred choice of treatment for patients who do not tolerate prednisolone due to side effects and in patients with diabetes mellitus. It is a synthetic steroid with high first-pass metabolism in the liver, which is in principle capable of limiting systemic side effects compared to conventional steroids [2]. Due to those side effects mentioned above, the adherence to medication can be an issue and hence, compliance needs to be monitored throughout the treatment period. Patients who need long term steroid therapy (> 3 months) should be started on calcium and vitamin D3 supplements to prevent osteoporosis.

The combination regimen of prednisone and azathioprine is associated with a lower occurrence of corticosteroid-related side effects than the higher dose prednisone regimen (10% versus 44%), and it is the preferred treatment in patients with AIH. AZA side effects include abdominal discomforts, pancreatitis, nausea, cholestatic hepatitis, rashes and leukopenia and they can be seen in 15% of patients who received 50mg of AZA [2]. Azathioprine metabolite and Thiopurine S-Methyl Transferase (TPMT) levels will guide the optimal dose for individual patients. Some patients who cannot tolerate AZA benefit from Mercaptourine. The metabolism of AZA has been demonstrated in Figure 3.



Aza: Azathioprine, MP: Mercaptopurine, TIMP: Thiosine 5 mono phosphate, MMP: Methyl mercaptopurine, MMR: Mehty mercaptopurine ribonucleotides, TU: Thiouric acid, TGN: Thioguanine nucleotide. TPMT: Thiopurine S-methyl transferase, XO: Xanthise oxidase, IMPDH: Inosine monophosphate dehydrogenase, HPRT: Hypoxanthine phosphoribosyltransferase

(Adapted from Dubinsky, M.C., et al., Thioguanine: a potential alternate thiopurine for IBD patients allergic to 6-mercaptopurine or azathioprine. Am J Gastroenterol, 2003. 98(5): p. 1058-63)

Figure 3. Azathioprine metabolism

Around 90% of adult patients respond to therapy within first 2 weeks with improvement in serum immunoglobulins and liver enzymes levels [31]. Treatment should be continued until normalisation of serum immunological and, biological parameters as well as improvement in liver histology. Relapsed AIH is characterized by an increase in the serum aminotransferase levels to at least threefold normal and it occurs in 50% to 86% of patients who previously had complete remission of their disease and usually happens during the first 6 months after the termination of therapy [13, 31]. In patients who has sub-optimal response to initial therapy or relapsed AIH should be considered for more potent treatments such as tacrolimus or mycophenolate mofetil.

4.2. Alternative and future therapies

Alternative therapies include tacrolimus, mycophenolate mofetil (MMF), cyclosporine, methotrexate, cyclophosphamide, ursodeoxycholic acid (UDCA), infliximab and rituximab [14]. Although there are some encouraging results with each of the medications, the treatment has not been implemented into standard management due to lack of randomised control data. Most of the evidence is based on from small, retrospective, single centre case series [34]. Therefore, these treatments should be only commenced in the specialised centre with presence of experienced hepatologists.

Cyclosporine A is a lipophilic cyclic peptide of 11 residues produced by Tolypocladium inflatum that acts on calcium dependent signalling and inhibits T cell function via the interleukin 2 gene [2]. Use of cyclosporine is limited due to its side effects of hirsutism, hypertension, renal insufficiency, hyperlipidaemia, increased risk of infection and malignancy [2]. The evidence of cyclosporine in adult AIH is limited due to a small number of case series arising from single centres. In one study of six patients, cyclosporine normalised ALT in all patients and 3 patients had improvement with liver histology in follow up. Another study of 5 patients with cyclosporine treatment showed biochemical improvement in 4 patients who had not responded to standard therapy [35]. In a study of 8 patients, it showed that cyclosporine is safe and all patients achieved remission [36].

Tacrolimus (Tac) is a macrolide compound and its mechanism is similar to that of cyclosporine A but it binds to a different immunophilin [2]. The main side effect is renal toxicity. Both cyclosporine and tacrolimus are calcineurin inhibitors and can be used as a rescue therapy for difficult to treat AIH patients. Compliance can be monitored by drug level in both drugs. An open label preliminary study in which 21 AIH patients were treated with tacrolimus (Tac) showed reduction of liver enzymes (ALT and AST) in 70-80% of patients who received 3 months of therapy [37]. There are only few studies reported use of Tac in the treatment of AIH although wide experience use of this drug exist in cohort of AIH patients who had liver transplantation (LT) [34]

Mycophenolate Mofetil (MMF) is a non-competitive inhibitor of inosine monophosphate dehydrogenase, which blocks the rate-limiting enzymatic step in de novo purine synthesis. MMF has a selective action on lymphocyte activation, with marked reduction of both T and B lymphocyte proliferation [2]. Many patients experience headache, nausea, diarrhoea, dizziness and neutropenia with MMF therapy [14]. It is contraindicated in pregnancy due to its terato-

genic side effects. Recent studies of 59 patients with treatment naïve AIH were treated with MMF and prednisolone as a first line therapies in which the study showed biochemical and immunological parameters improvements in 88% of patients in the first 3 months and 12% had partial response [38]. A study from Canadian group studied 16 patients who failed conventional therapy were given either tacrolimus or MMF [39] and complete response were seen in 50% of patients and 12.5 % had non response to treatment [39]. Another study looking at 36 patients with AIH who were treated with MMF and it showed remission in 39% of patients. The study mentioned in patients who does not respond to AZA, around 75% of those do not respond to MMF either [40].

Infliximab, a recombinant humanized chimeric antibody, has been used in other immunomodulatory conditions such as rheumatoid arthritis and inflammatory bowel disease. However, infliximab has been associated with de novo AIH in some patients with liver transplantation (LT) and therefore, it should be used by the experienced team in specialised centre. A retrospective, single centre review of 11 patients with difficult to treat AIH were treated with infliximab and it showed infliximab led to reduction of inflammation, evidenced by a decrease in transaminases and serum immunoglobulins [41].

Rituximab is an anti-CD20 chimeric monoclonal antibody, a surface marker expressed on B cells, from early pre-B to memory B lymphocytes [42]. Treatment with rituximab leads to B cell depletion through both complement- and antibody-dependent cellular cytotoxicity [42]. AIH is considered to be a T-cell–mediated disease; however, numerous observations would suggest that B cells are also involved in its pathogenesis [43]. Although there were good evidences to suggest that rituximab is effective in autoimmune haemolytic anaemia, cryoglobulinemia and systemic lupus erythematosus, the data on efficacy of rituximab in AIH are limited [44-46]. A study by Burak and colleague showed that Rituximab is well tolerated with no significant side effects and resulted in biochemical response in patients with refractory or intolerant to other treatment [47].

5. Prognosis

Patients with acute, severe AIH who are untreated have poorer short and long term survival compared to treated AIH patients [48-50]. For patients with the severe acute phenotype of AIH, failure to respond to treatment within the first 7–14 days after presentation is associated with a mortality of almost 50% [51]. For patients with established cirrhosis at presentation, treatment can induce remission and improve long-term outcome, with 10-year life expectancies of greater than 90% [52, 53]. Patient with cirrhosis due to AIH usually develop hepatocellular carcinoma at a mean of 9 to 10 years according to previous published case series and hence, routine surveillance with 6 monthly ultrasound scan and alpha feto protein (AFP) is recommended for these cohort of patients [54, 55]. Autoimmune hepatitis is an acceptable reason for liver transplantation, with frequency of survival exceeding 75% at 5 and 10 years after transplant [56, 57]. In summary, the overall prognosis of AIH is good for patient who are treated and responded to immunosuppressive therapy. Therefore, compliance is important which can be

achieved by supporting patient and education to the patient. It is also crucial to recognise and treat the patients who are not responsive to standard immunosuppressive therapies with more novel treatments. It is essential to have smooth handover and transition between paediatric and adult hepatology team which will help young patients with AIH to continue with their treatment and follow up.

6. Primary biliary cirrhosis

6.1. Epidemiology

Primary biliary cirrhosis (PBC) is an autoimmune condition and causes a chronic and progressive destruction of intrahepatic bile ducts resulting in chronic cholestasis, portal inflammation, fibrosis and then gradually lead to cirrhosis and liver failure [58]. The disease is predominantly seen in women than men with a ratio of 10:1 [60] and had a prevalence of 1 in 1000 women over the age of 40 [59].

The highest prevalence and incidence rates have been reported in Great Britain, Scandinavia and the northern Midwest region of the USA [5, 61]. It has been suggested that the incidence of PBC is rising and in the United Kingdom (UK), the incidence rate rose from 2.05 cases per 100,000 populations per year in Sheffield from 1980 to 1999 [5, 62] and from 1.1 to 3.2 cases per 100,000 population per year in Newcastle- Upon- Tyne from 1976 to 1994 [63, 64].

6.2. Pathogenesis

Both genetic and environmental factors such as chemical substances, bacterial and viruses play an important role in the pathogenesis of PBC. In general, data indicate that 1 to 6% of PBC cases have at least one other family member presenting with the disease [60]. The concordance rate observed among monozygotic twins for PBC is 63%, among the highest reported in autoimmune diseases [60]. Prior to the advent of genome-wide association studies, only class II HLA loci (HLA-DRB1*08, *11, and *13) had been reproducibly shown to associate with disease [59]. With the application of genome-wide technology, HLA was confirmed as the strongest association and many other risk loci have been identified, with equivalent effect size to HLA, including IL12A, IL12RB2, STAT4, IRF5-TNPO3, 17q12.21, MMEL1, SPIB, and CTLA-4 [59]. These collectively support an important role for innate and adaptive immunity in development of disease [59].

There is an increased auto reactive CD4 pyruvate dehydrogenase complex (PDC)-E2 specific T cells in liver and regional lymph nodes in patients with PBC and CD8 PDC-E2 T cells infiltrates in the liver suggesting that anti-mitochondrial response is either directed to the aetiology or associated with other environmental or genetic trigger [65].

6.3. Clinical presentations and diagnosis

The majority of patients are asymptomatic at the time of diagnosis. With progression of the disease, patients usually develop fatigue and pruritus. Fatigue is the most common symptom

and is present in up to 78% of patients with PBC [65]. Fatigue is not associated with disease severity or disease duration or histological findings and it is difficult to manage in most patients. Pruritus is a more specific symptom of PBC than fatigue and formerly occurred in 20%-70% of patients with PBC [65]. It can be local or diffuse, usually worse at night and tend to be in the palms and soles of the feet. Pruritus is often exacerbated by contact with wool, other fabrics, heat, or during pregnancy [65]. Sicca syndrome, hypothyroidism, vitamin D deficiency, osteopenia and hypercholesterolemia are commonly seen in patients with PBC and should be investigated and managed appropriately.

Individuals with abnormal cholestatic liver function tests such as raised alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and elevated conjugated bilirubin should be investigated for underlying PBC [66]. Immunologically, the majority of patients (around 95%) have positive anti-mitochondrial antibodies (AMA) in their serum and raised levels of immunoglobulins-M (Ig M) [67].

AMA reactivity is classically studied by immunofluorescence and considered positive at a titre of ≥1:40 [66]. The targets of the disease-specific ant mitochondrial response are all members of a family of enzymes, the 2-oxo-acid dehydrogenase complexes and include PDC-E2, branched chain 2-oxo-acid dehydrogenase complex, and 2-oxo-glutaric acid dehydrogenase complex [65]. These enzymes catalyse the oxidative decarboxylation of keto acid substrates and are located in the inner mitochondrial membrane [65].

Patient who had raised ALP and high titre of AMA (tire of ≥ 1:40) or AMA type 2 (M2) can be diagnosed with PBC without liver biopsy as per EASL (European Association for the Study of the Liver) guideline [66]. Positive ANA titres are also found in 30–50% of individuals with PBC (more commonly in the few who are AMA negative), but in this setting ANA reactivity is, in contrast to AIH, often antigen specific (anti gp-210 and anti sp-100) [12, 68].

Stage	Findings
1 (Portal tract Inflammation)	Portal tract inflammation from mainly lymphoplasmacytic infiltrates with or without florid bile duct lesions resulting in septal and interlobular bile ducts.
2 (Peri-portal fibrosis)	Gradual increase of peri-portal lesions extending into the hepatic parenchyma-referred as interface hepatitis.
3 (Bridging fibrosis)	Distortion of the hepatic architecture with numerous fibrous septa. Ductopenia (defined as loss of >50% of interlobular bile ducts) becomes more frequent at this stage.
4 (Cirrhosis)	Cirrhosis with the existence of regenerative nodules.

The stages of PBC are shown in Figure 4.

(Adapted from Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. Primary biliary cirrhosis. Hepatology 2009;50:291-308)

Table 4. Liver histology stages seen in primary biliary cirrhosis

Liver biopsy is rarely needed in the diagnosis of PBC. However, in patients with overlap of AIH/PBC might need liver biopsy to access the degree of the liver injury. In PBC, liver histology

is divided into 4 stages (Table 4, Figure 4). Nowadays, the degree of fibrosis can be determined by performing non-invasive procedure such as transient elastography or Fibroscan. Magnetic resonance cholangio-pancreatography (MRCP) and Endoscopic retrograde cholangio-pancreatography (ERCP) are sometimes required to exclude other biliary pathology or PSC.

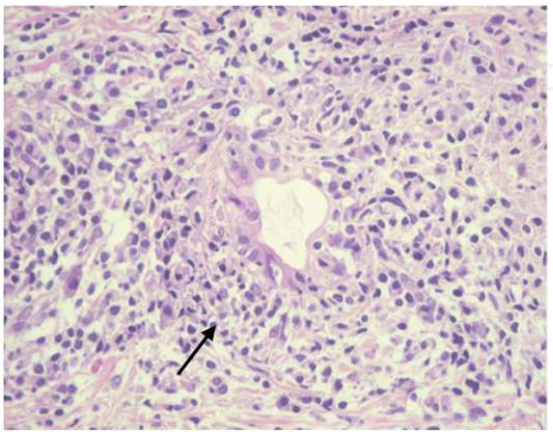


Figure above showed lymphocytic cholangitis seen in PBC (black arrow).

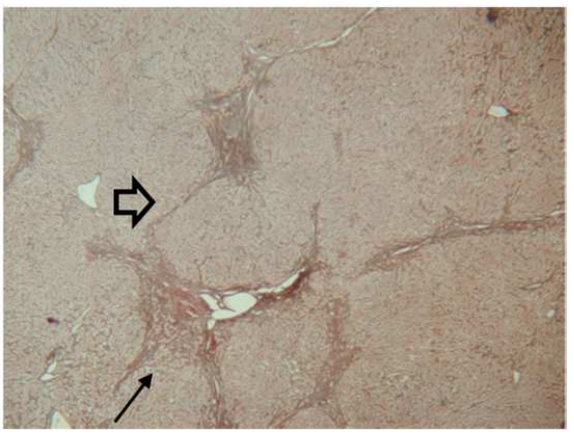


Figure above showed peri-portal (thin arrow) and bridging fibrosis (thick arrow) with reticulin stain

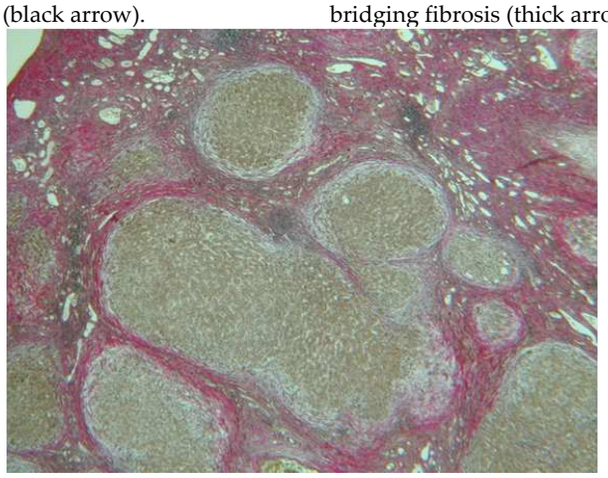


Figure above showed established cirrhosis (Haematoxylin Van Gieson stain)

Figure 4. Histology finding of Primary biliary cirrhosis (PBC)

7. Management/treatment

7.1. Standard therapy

7.1.1. Ursodeoxycholic acid (UDCA)

Ursodeoxycholic acid (UDCA) is the only approved treatment for patients with PBC and shown to be associated with improvement in liver biochemistries, delayed histologic progression of disease, and delayed development of oesophageal varices and prolong transplant free

survival [67, 69]. UDCA at a dose of 13-15 mg/kg is proven benefit. Various risk scores have been validated to access the response of UDCA in patients with PBC and these are Barcelona, Paris I and II, Rotterdam and Toronto criteria (table 5) [127-131].

Criteria	Biochemical response
Barcelona	Decrease of serum ALP > 40% or ALP normalisation (after 1 year)
Paris I	ALP ≤ 3 x ULN, AST ≤ 2 x ULN and serum albumin ≤ 1mg/dl (after 1 year)
Paris II	ALP and AST < 1.5 x ULN, serum bilirubin <1mg/dl (after 1 year)
Rotterdam	Normalisation of abnormal serum bilirubin and/or serum albumin (after 1 year)
Toronto	ALP < 1.67 x ULN (after 2 years)

ALP: alkaline phosphatase, AST: Aspartate transaminase, ULN: upper limit of normal

Table 5. Assessment of response to UDCA in patients with PBC

Ursodeoxycholic acid is a hydrophilic bile acid and normally present in about 3% of bile in humans [70]. In patient with cholestasis, there is a decrease in endogenous production of bile acids as well as reduction in the absorption of UDCA [70]. After oral administration of UDCA, it is absorbed in small intestine and colon and transported to liver via portal tract. The absorption of UDCA is increased after meal consumption due to alkaline pH status. Administration of 13-15 mg/kg of UDCA in PBC patients causes enrichment of 40 to 50 % in primary bile acids [70].

Other drugs have been tested, but none have been found as single agents to be of benefit. These include chlorambucil, penicillamine, cyclosporine, corticosteroids, azathioprine, mycophenolate mofetil, thalidomide, methotrexate, malotilate, and colchicine [65].

7.1.2. Treatment for fatigue

Fatigue can be difficult to manage and other underlying conditions such as anaemia, thyroid disorder should be investigated and ruled out. There is no proposed treatment for fatigue and it can sometime persist even after Liver transplantation. A study by Jones et al showed that Modafinil at a dose of 100 to 200 mg/day was associated with a significant improvement in fatigue and improved day time somnolence [71].

7.1.3. Treatment for pruritus

There are few effective treatments available for pruritus in PBC patients. Cholestyramine is a non-absorbable resin and it is the first line therapy in the management of pruritus. The recommended dose of cholestyramine is 4 g per dose to a maximum of 16 g/day given 2-4 hours before or after UDCA [65]. In general, cholestyramine is well tolerated, although some patients report bloating, constipation, and diarrhoea [65].

Rifampicin is a P450 enzyme inducer and used in treatment of pruritus for PBC patients. The recommended dose is 150 mg once daily or twice daily based on the level of bilirubin. Side

effects of rifampicin remain a serious concern because cases of hepatitis and hepatic failure, haemolysis and renal impairment and therefore, patient should be closely monitored during the treatment [65]. It should not be used together with serotonin reuptake inhibitor (SSRI) in patient with severe depression since it decrease the effect of SSRI[65].

Opioid antagonist, Naltrexone 50 mg daily, has been shown to be effective in treatment of pruritus in PBC patients. Other agents are SSRI (sertraline), Etarnacept (TNF-alpha inhibitor), Amitriptyline, Anti histamine. Some patient with difficult to treat pruritus can be managed with plasmapheresis.

7.2. Future therapies

Several pilot studies and randomized controlled trials have evaluated various agents in PBC. Trials with mesenchymal stem cells, Rituximab, Ustekinumab, Moexipril which is an angiotensin-converting enzyme (ACE) inhibitor and Abatacept treatments in PBC is currently ongoing (www.clinicaltrials.gov).

There is a suggestion that beta retrovirus might be involved in the pathogenesis of PBC and hence, a randomised controlled trial with lamivudine and zidovudine was studied in PBC patients [72]. There is a good biochemical response seen in patient taking lamivudine and zidovudine but complete biochemical normalisation was not observed [72]. The study did not showed any correlation with virus and biochemical response and as a result, treatment is not recommended in PBC [72].

Recently, fibrates have been thought to be beneficial in PBC since it has anti-inflammatory effect via peroxisome proliferator activated receptor alpha (PPAR-a) [67]. Fenofibrate is a fibric acid and thought to modulate immune response and the cell proliferation and pilot study which treated 20 patients with fenofibrate and UDCA showed significant improvement in liver biochemistry (ALP and ALT) and Ig M although albumin and bilirubin remained unchanged [73]. Larger studies are needed in future. Similar findings were seen in study with bezafibrate.

Obeticholic acid (OCA) is a farnesoid X receptor (FXR) agonist [74]. FXR is expressed in liver, intestine, adrenal glands and kidneys and has an important role in the enterohepatic circulation of bile acids [74, 75]. FXR reduces bile acid synthesis by acting on the enzyme cholesterol 7a hydroxylase and also by down-regulating the expression of the sodium/taurocholate co-transporting peptide, a bile acid uptake protein[75]. Preliminary studies of OCA in patients with PBC have demonstrated marked biochemical improvement when administered in combination with UDCA and alone [74]. Pruritus is the most common side effects and seen at high dose. Currently, there is a phase 3 trial ongoing for OCA treatment in PBC patients.

8. Prognosis

There are many criteria used to assess biochemical response to UDCA (Table 5). The 1-year biochemical response to UDCA provides significant prognostic information even in the early stage of PBC [70]. Early-stage patients who show ALP and AST ⊚1.5× upper limit of normal

(ULN), and normal bilirubin level after 1 year of treatment appear to be at very low or no risk of liver failure or progression to cirrhosis. In those patients, they had a 10-year transplant-free survival rate of 90% compared to 51% for those who did not (p <0.001) [76]. About 40% of patients have a suboptimal response to UDCA and subsequently need additional therapy. Liver transplantation is the treatment for patients with decompensated liver cirrhosis and recurrence of PBC is seen in 20% after LT [77].

9. Primary sclerosing cholangitis

9.1. Epidemiology

Primary sclerosing cholangitis (PSC) is a rare autoimmune liver disease and primary affects larger bile ducts. It is caused by chronic inflammation which then leads to fibrotic strictures and dilatation of hepatic biliary system and leading to chronic cholestasis. Chronic cholestasis can subsequently lead to liver cirrhosis with portal hypertension and liver failure [78]. PSC can affect any part of the biliary system including the gallbladder [78].

It is more common in male with median age of around 40 and affects mostly Northern European descendants [79]. The most important underlying risk factor associated with PSC is inflammatory bowel disease and PSC is seen in 75 % of cases of patients with IBD [79]. Around 60 to 80% of patients with PSC have underlying ulcerative colitis, mainly on the right side of the colon and 4% of patients with UC have co-existing PSC [80].

A recent study in UK showed the incidence of PSC to be 0.41 cases per 100,000 populations [81], although the true incidence may be underestimated since it is a relatively rare diseases and needs expertise and invasive procedures to make the diagnosis [79].

9.2. Pathogenesis

The exact mechanism of pathogenesis in PSC is unknown but thought to be multifactorial. It has thought that PSC occurs in individuals with genetic predisposition triggers various environmental stimuli [80]. Patient who has first degree relative with PSC have 9 to 39 fold increased risk of developing PSC and the most associated HLA are HLA DRB1 and DRQ1 [80]. Gut and liver axis theory had been proposed in the pathogenesis of PSC [82]. Manipulation of the intestinal micro flora changes the immune and metabolic pathway [83]. There has been hypothesized that translocation of microbial flora across the inflamed, permeable gut via the portal system to liver and biliary system activate the immune system and cause inflammation of the biliary tree [84-86]. Homing of mucosal lymphocytes which possess (C-C motif chemokine receptor-9) CCR9 and alpha4beta7 in the liver leads to biliary damage in PSC [87, 88]. Recently mucosa associated innate T cells and innate lymphoid cells has been proposed in the pathogenesis of PSC [89]. Although the putative gut-derived trigger(s) of hepatobiliary pathobiology in PSC has not been determined, microbial metabolites or products (i.e., pathogen-associated molecular patterns, PAMPs) such as lipopolysaccharide (i.e., endotoxin,

LPS) and peptidoglycan (i.e., a bacterial cell wall polymer, PG) have been proposed as likely candidates [90].

9.3. Clinical presentations and diagnosis

About 15-40% of patients are asymptomatic during the early stage of the clinical course and at later stage, the most common symptoms are jaundice, pruritus, fatigue and abdominal pain [79]. Any patient who has underlying IBD and abnormal liver blood tests especially raised ALP should be investigated for PSC. In 95 % of cases, ALP rose 3-10 times the upper limit of normal and other liver enzymes ALT and AST were 2-3 times above the normal limit [79]. Bilirubin tends to be within normal range in about 60% of patients. In 69-95% of patients with PSC, 50 to 80% of patients with UC and 10-20% of patients with Crohn's colitis have positive perinuclear antineutrophil autoantibodies (pANCA) [79].

Mayo risk score is used in PSC and the score is calculated using age, bilirubin, albumin, liver transaminase, AST and varcieal bleed and it is used to estimate survival of patient with PSC for up to 4 years [132]. The Mayo Risk Score= (0.0295 * (age in years)) + (0.5373 * (total bilirubin in mg/dL)) - (0.8389 * (serum albumin in g/dL)) + (0.5380 * (AST in IU/L) + (1.2426 * (points for variceal bleeding; 0= No, 1=Yes)). The score of less than or equal to zero is regarded as low risk, between 0 and 2 as intermediate and above 2 as high risk groups.

The diagnosis is best confirmed by MRCP, which is a non-invasive and first line investigation for the diagnosis of PSC. ERCP is used mainly for therapeutic purposes such as stenting, balloon dilatation and biliary brushing in patient with PSC. Contrast cholangiography, which reveals characteristic features of diffuse, multifocal strictures and focal dilation of the bile ducts, leading to a beaded appearance [79]. Liver biopsy is rarely necessary due to good diagnostic yield with MRCP or ERCP investigations except in suspicion of small duct PSC or overlap with AIH. Periductal concentric ("onion-skin") fibrosis is a classic histopathologic finding of PSC, but this observation is infrequent in PSC [91] (Figure 5).

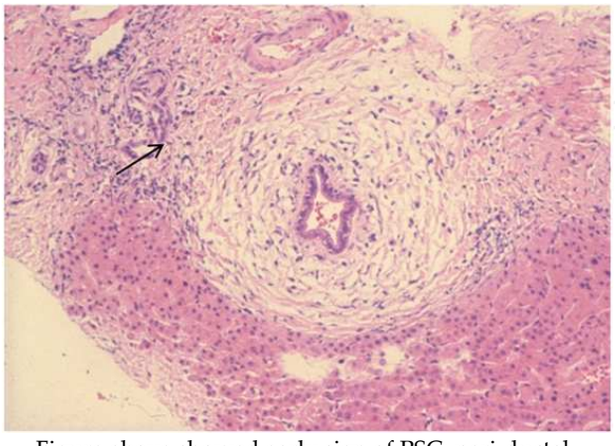


Figure above showed early sign of PSC: peri-ductal fibrosis (black arrow).

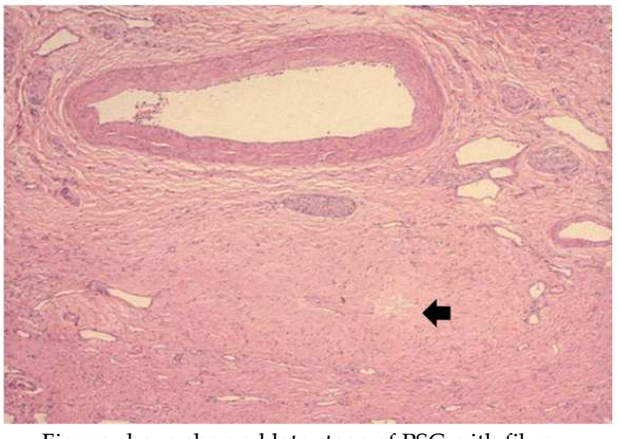


Figure above showed late stage of PSC with fibro-obliterative duct lesion, in which the bile duct is completely filled with fibrosis (large arrow)

Figure 5. Histology findings in Primary Sclerosing Cholangitis (PSC)

In addition to biliary cirrhosis, complications of PSC include dominant strictures of the bile ducts, cholangitis, cholangiocarcinoma, colon dysplasia and cancer in patients with IBD, gallbladder polyps, gallbladder cancer, and hepatic osteodystrophy [79]. Cholangitis occurs in 10 to 15 % of patients with PSC [80]. The cumulative lifetime risk for cholangiocarcinoma in PSC is estimated at 7 to 15% [67]. About half of those cholangiocarcinomas are diagnosed within one year of PSC diagnosis and the rate of cancer development is 0.5 to 1.5% per year subsequently after the first year[67]. Suspected dominant stricture should be investigated by Endoscopic ultrasound scan (EUS) and biopsy along with Positron Emission Tomography (PET) scan.

Immunoglobulin G4 (Ig-G4) associated cholangitis is similar to PSC and is characterized by the presence of biliary strictures, lymphoplasmacytic infiltration and elevated Ig G4 serum levels [92]. Ig G4 elevation is seen in 12% of PSC patients [92]. The biliary features are similar on the cholangiogram in these two conditions and hence, it is important to check Ig G4 level and review the anatomy of pancreas on imaging. Tissue from liver biopsy can be stained using monoclonal anti-human IgG4 antibody. It is important to differentiate between the two because Ig G4 associated cholangitis or pancreatitis responsive to steroids unlike PSC.

10. Management/treatment

10.1. Standard therapy

To date, there are no effective therapies for patients with PSC and the only treatment for end stage PSC is liver transplantation. Timing for liver transplantation is challenging in PSC as these patients sometimes do not fulfil MELD criteria MELD criteria but they can deteriorate rapidly thus early referral to experience centres is essential. UDCA has been used in cholestatic patients with PSC although the data suggested that the medication has not improved overall survival. Studies utilizing doses between 10–15 mg/kg/day were associated with biochemical and histologic improvement [93, 94]. Two previous studies looking at high dose UDCA at a dose of 17-23 mg/kg/day [95] and 28-30 mg/kg/day [96, 97] showed that there were no difference in mortality or LT but increased in adverse events. A recent meta-analysis found no difference in fatigue, mortality, histologic progression or development of cholangiocarcinoma for standard or high dose UDCA [92, 98] and therefore, high dose UDCA is not used in routine clinical practice.

Antibiotics are used in patients with biliary sepsis in the background of PSC and some clinicians used rotating antibiotics in patients with resistant bacteremia. Published data looking into vancomycin or metronidazole treatment suggests that both are efficient in treatment of infection but vancomycin achieved improvement in ALT more than metronidazole with less side effects [99]. A recent randomised pilot study of vancomycin or metronidazole treatment in PSC patients showed that both antibiotics are effective although only vancomycin group reached the primary end point of reduction in ALP at 12 weeks [99].

10.2. Future therapies

There are many ongoing clinical trials in PSC such as obeticholic acid, mitomycin, thalidomide, LUM001: an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTi), GS-6624: a Monoclonal Antibody against Lysyl Oxidase like 2 (LOXL2), Xifaxan, Cladribine and the combination of UDCA and all trans-retinoid acid (ATRA) (www.clnicaltrial.gov). There are ongoing phase 1 and 2 trials on anti-fibrotic therapies in PSC.

11. Overlap syndrome

The term 'overlap syndrome' described co-existence of AIH with features of PBC or PSC [12]. The diagnosis can be challenging and there is no single test available to diagnose. Therefore, it is important to revisit clinical history or repeat investigation if there is in doubt with the diagnosis. The diagnosis can be made with combination of tests such as blood biochemistry, immunology with addition of radiology and tissue biopsy. It is assumed that overlap syndrome can be found in 5-20% of cases [12].

11.1. AIH/PBC overlap

AIH/PBC should be considered in patients with mixed pattern of cholestastic and hepatitis features or anyone with suboptimal response to immunosuppressions. It has been reported that AIH/PC occurs in 8% of patients with either AIH or PBC. Some PBC patients express negative AMA with positive ANA serology or SMA serology and hence, diagnosis based on immunology alone can be tricky. In general, IgG elevation is common in AIH and IgM is manly observed in PBC. Treatment should be targeted both AIH and PBC in these patients.

11.2. AIH/PSC overlap

In adults with both AIH and IBD, cholangiographic changes suggestive of PSC are present in up to 44% patients and may affect therapy and prognosis [13]. Those who develop AIH during childhood or Autoimmune sclerosing cholangitis are most common to develop into AIH/PSC overlap. MRCP and repeat liver biopsy is recommended. Treatment should be directed towards PSC and immunosuppression should be slowly weaned off unless they are indicated for inflammatory bowel disease.

12. Liver Transplantation (LT)

Liver transplantation (LT) is the treatment for patients with end stage AIH, PBC or PSC disease. The common indications are decompensated liver cirrhosis as indicated by the presence of refractory or resistant ascites, hepatic encephalopathy or uncontrolled variceal bleeding. Hepatocellular carcinoma, hepatopulmonary syndrome and portopulmonary hypertension are the other indications for LT. Model for End Stage Liver Disease (MELD) score is calculated

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by using renal function (Creatinine), International Normalised ratio (INR) and Bilirubin. MELD score= [0.957x Log_e (creatinine in mg/dL) + 0.378x Log_e (bilirubin in mg/dL) + 1.120x Log_e (INR) + 0.643) [133]. Patients with MELD score of above 16 with other indication is considered for liver transplant assessment. MELD score was initially developed to predict survival in patients undergoing Trans jugular Porto systemic shunt [100, 101]. In 2002, UNOS (the United Network of Organ Sharing) adapted a new approach to allocate organ giving priority to the sickest patient and the assessment is based on MELD score [102]. Implementation of MELD in 2002 led to an immediate reduction in LT waiting list registrations for the first time in history of LT (12% decrease in 2002) [103] as well as reduction in mortality on the waiting list [104].

Since 1996, listing for transplantation in the United Kingdom was based on the following principles: selecting patients if the expected survival without transplantation was 1 year or less or liver disease that was associated with an unacceptable quality of life and expecting that patients would have an at least 50% survival at 5 years with acceptable quality of life [105]. Serum sodium was associated with a higher risk of mortality independent of the MELD score in patients listed for orthotropic liver transplantation [106]. In United Kingdom, UKLED score (United Kingdom End Stage Liver Disease has been used since 2008 and it is calculated from patient's INR, serum creatinine, serum bilirubin and serum sodium) has been used in assessment of liver transplantation. UKELD score of 49 is the baseline entry criteria for LT assessment. Patients with UKELD score of 49 have 9% one year mortality and score above 60 has mortality of 50% [105].

LT is required in about 10% of patients with AIH and in Europe; 4-6 % of LT are for the indication of AIH [2, 7]. Long-term survival is excellent in AIH patients with 5 year survival being up to 92 % [2]. Recurrence of AIH can occur post LT and the rate of recurrence is between 8-12 % at year 1 and higher after 5 years follow up with the rate of around 36-65% [107]. The treatment should be either increase with the ongoing immunosuppressive therapies or change to alternative therapies such as addition of MMF, replacement of tacrolimus with cyclosporine or the replacement of calcineurin inhibitor (CNI) with sirolimus [108].

In patients with PBC, LT is indicated for decompensated liver cirrhosis, hepatocellular carcinoma and intractable pruritus with unacceptable quality of life. Patient should be referred for LT assessment when the bilirubin reaches around 100 umol/L with MELD >12 and Mayo risk score of 7-8 [134]. PBC can recur in post LT and the median time is 3 to 5.5 years although it can happen within the first year of transplantation [108]. PBC recurs in 15 to 30% of patients after LT and most of the patients do not lose their graft [67]. The treatment of recurrence PBC is UDCA, which causes improvement with ALP and ALT but not the patient or graft survival [109].

In addition to above mentioned indication for LT, some patients with PSC will need LT due to intractable pruritus, recurrent cholangitis in the presence of dominant bile duct strictures that cannot be managed endoscopically and the presence of limited stage cholangiocarcinoma [108]. 5 year survival post LT is around 80%[92]. Recurrence of PSC have been documented among LT recipients and its prevalence ranges from 15 to 30% and the median time for

recurrence is between 3 and 5 years post LT [108] and can be associated with poor survival and graft loss [67].

13. De novo autoimmune hepatitis post LT

De novo autoimmune hepatitis (d-AIH) in LT patients whom were transplanted for other reasons than AIH was documented in late 1990 [110]. De novo autoimmune hepatitis occurs in 1-7 % of patients 0.1-9 years after transplantation, especially in children [135]. Risk factors for de novo-AIH had been associated with older age donor, female donor, acute cellular rejection and the use of tacrolimus [111, 112]. The disease is usually characterized by features of acute hepatitis in otherwise stable transplant recipients. The characteristic feature is a marked hypergammaglobulinaemia with positive ANA. Antibodies against glutathione S-transferase T1 (GSTT1) has been reported in patients with de novo immune hepatitis following liver transplantation, thus suggesting that immune system recognizes the Glutathione S-transferase theta-1 (GSTT1) protein as a non-self-antigen, and mount an allo-reactive immune response and molecular mimicries that override self-tolerance[113]. Antibodies against cytokeratin 8/18 in patient with de novo autoimmune hepatitis after living-donor liver transplantation had also been reported thus the changes in cytokeratin 8/18 in hepatocytes might be one of the sources of pathogenesis of de novo autoimmune hepatitis after liver transplantation[114]. A histologic pattern of centri-lobular injury including increased necroinflammatory activity and increased plasma cell infiltration correlates with measurements of autoimmunity in de novo AIH recipients [115]. Treatment with increased dose of steroids or Azathioprine results in an improved outcome. However, maintenance therapy is usually required [116]. Standard liver tests do not reflect the extent of these changes, so protocol liver biopsies may be required to detect these changes [117].

14. Pregnancy and AILD

Pregnancy constitutes a major challenge to the maternal immune system. AIH tends to improve after the second trimester of pregnancy, allowing a decrease in immunosuppressive therapy. It is due to a variety of immunological alterations that are induced by pregnancy in order to protect the semi-allogeneic fetus from rejection. Immuno-regulation induced by pregnancy polarizes the immune system to T-Helper (TH)-2 predominant phenotype. The increase of circulating inhibitors of pro-inflammatory cytokines occurring in pregnancy could act as a potent anti-inflammatory agent in AIH. T regulatory (Treg) cells are a recently discovered subset of T-lymphocytes with potent suppressive activity and pivotal roles in curtailing destructive immune responses and preventing autoimmune disease[118]. Systemic expansion of the maternal T suppressor or CD4+CD25+ regulatory T cell pool during pregnancy suppress an aggressive allogeneic response directed against the fetus[119].

Premature birth is the greatest risk and fetal mortality is reported to be around 21%, perinatal mortality is 4% and maternal mortality is 3% [14]. Poor disease control in the year prior to

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pregnancy and the absence of drug therapy are associated with poor outcomes [120]. Adverse pregnancy outcomes were highly associated with the presence of antibodies against soluble liver antigen/liver-pancreas (SLA/LP) and Ro/SSA [121] Preconception advice and discussion is important and should be emphasised. More than half of the women reduced or stopped the immune suppression during pregnancy or breastfeeding. AZA is a Food and Drug Administration (FDA) category D drug and safety in pregnancy has not been well established in human studies [14] however, current pharmacological treatment including azathioprine appears to be safe during pregnancy and lactation. There are no reported increased in congenital malformations with AZA and it is safe to use in mother who plan to breast-feed the baby. AIH commonly exacerbates following delivery [122, 123] and therefore, vigilance is required during the postpartum period. Patients with AIH need to be monitored carefully during pregnancy and for several months post partum [124]. Women with advance cirrhosis and portal hypertension have an increased risk of variceal bleed during the pregnancy and therefore, eradication of varices either with banding or pharmaco-therapy are recommended prior to conception. Pregnant women with cirrhosis and portal hypertension should undergo upper GI endoscopy during the second trimester and careful discussion with obstetric team and fetal medicine team is required for the safety of mother and the baby.

There are limited data for pregnancy and PBC. It has been noted that early diagnosis of PBC and early used of UDCA have a favourable outcomes on the pregnancy [125]. PSC rarely occur in female but the condition does not seem to reduce fertility in both men and women according to case series [126].

15. Conclusion

AILD is a spectrum of autoimmune condition mainly affecting liver (in the case of AIH) and biliary system (in PBC and PSC). The diagnosis is guided by clinical, biochemical and immunological parameters, although liver biopsy is still useful especially in patients with AIH to diagnose as well as for the assessment and monitoring of the disease status. In AIH, the aim of the treatment is to suppress the immune system with long term immunosuppressive medications such as azathioprine. There are new therapies emerging on the horizon. In PBC, women are more affected and the current treatment used is UDCA although there are many trials running ongoing in the treatment of PBC and it is an exciting era. For PSC, the definitive treatment is liver transplantation and more research is needed to understand that pathogenesis and treatment in this field of subject.

Acknowledgements

The histology slides were kindly provided by Professor Stefan Hubscher, Liver Histology Department, University Hospital Birmingham NHS Trust, Birmingham, UK. N.N.T is funded

by National Institute for Health Research (NIHR) and Y.H. O is funded by Medical research council (MRC).

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