REVIEW

Current concepts in the diagnosis and management of autoimmune hepatitis

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ABSTRACT

Autoimmune hepatitis (AIH) is a progressive necroinflammatory liver disease associated with significant morbidity and mortality. Mainly affecting females, AIH has a varied clinical presentation from minor symptomatology to acute liver failure. The diagnosis should be considered in anyone with abnormal liver function tests. Diagnostic features include biochemical evidence of transaminitis, elevated IgG and positive autoantibodies. Liver biopsy may show interface hepatitis with portal-based plasma cell infiltrates. A clinical and pathological spectrum of disease exists with other autoimmune liver disease in rare cases. AIH responds promptly to immunosuppression therapy, including corticosteroids (prednis(ol)one or budesonide) with azathioprine. Treatment failure can be addressed with several second-line immunosuppressive agents. Liver transplantation remains a successful salvage therapy for acute autoimmune liver failure or treatment failure in chronic AIH complicated by synthetic dysfunction, portal hypertension or hepatocellular carcinoma.

INTRODUCTION

Autoimmune hepatitis (AIH) is a progressive necroinflammatory condition of the liver. It is rare and its incidence varies geographically. The annual incidence of AIH in Europe is 0.8–1.9 cases per 100 000 with a point prevalence of 11.6–17 per 100 000 population.¹ AIH can be largely divided into two types based on antibody profiles which, however, overlap with other existing autoimmune liver diseases. AIH is a rare but important differential diagnosis of abnormal liver function tests, as untreated patients have high mortality.²

PATHOGENESIS

Fundamentally, AIH is caused by a loss of immunological self-tolerance. The

reasons for this, however, remain incompletely understood. A genetic component to susceptibility is suggested by the preponderance of patients who are female, in addition to the findings of specific allotypes within the major histocompatibility complex alleles. These genetic associations vary between racial and geographical populations; in Northern America and Northern Europe, the human leucocyte antigen allotypes DRB1*0301 and DRB1*0401 are associated with AIH.¹

Molecular mimicry by viral agents has been suggested as a possible mechanism of loss of self-tolerance. Cross-reactive antibodies to hepatic antigens can be found in patients with AIH, cytomegalovirus, herpes simplex virus and hepatitis C.^{3–4} Similarly, multiple drugs have been implicated in the pathogenesis in the genetically susceptible patient including minocycline, nitrofurantoin and atorvastatin.⁵

Recent evidence also suggests that the adaptive and humoral immune response is dysregulated in AIH. A key area of investigation concerns regulatory T cells (CD4⁺ CD25⁺), which promote self-tolerance by suppressing proliferation of auto-reactive T cells. These have been shown to be deficient both in number and function in AIH patients.^{6–9} Figure 1 summarises some of the putative factors in immunopathogenesis.

DIAGNOSIS

Clinical presentation

AIH demonstrates a female preponderance of up to 4:1. Classically perceived as a disease of women in early life, recent evidence suggests that AIH presents in all stages of life and may even be more common in individuals over the age of 60 years.^{10–11} AIH demonstrates a varied

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Figure 1 Immunopathogenesis of autoimmune hepatitis. AIH, autoimmune hepatitis; CMV, cytomegalovirus; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; CYP2D6, member of cytochrome P450 family; HCV, hepatitis C virus; HLA, human leucocyte antigen; HSV, herpes simplex virus; LKM-1, antiliver kidney microsome 1 antibodies; T-Regs, regulatory T cells.

clinical phenotype, and is somewhat chameleonic in its presentation (figure 2). Data from a Swedish population study suggests a small number (12%) of patients are asymptomatic at the time of diagnosis, whereas, fatigue is the most commonly reported symptom (61%).¹² Other associated symptoms may include arthralgia of small joints, nausea, vomiting, abdominal pain, pruritus or skin rash.

An acute icteric illness may be seen in approximately 25% of patients.¹³ A small subset of these patients may go on to develop acute liver failure (ALF); 2%–5% of transplants performed for ALF are attributable to AIH.^{14–16}

Lastly, up to a third of patients are cirrhotic at diagnosis and present with symptoms and signs of chronic liver disease, such as jaundice, ascites or variceal

bleeding.¹⁷ According to some studies, advanced disease is more common in specific populations including black and elderly patients.^{10 18}

Other autoimmune diseases are prevalent in AIH, such as thyroiditis (10%–23%), ulcerative colitis (2%–8%), coeliac disease (1%–2%), type-1 diabetes (7%–9%), rheumatoid arthritis (2%–5%) and systemic lupus erythematosus (1%–2%).¹⁹

Autoantibodies

In conjunction with persistently elevated aminotransferases and hyper-gammaglobulinaemia (in particular IgG) the presence of autoantibodies is the hallmark of AIH. An expanding pool of autoantibodies has been described in AIH including antinuclear antibody (ANA), antismooth muscle (SMA), antiliver kidney

Figure 2 Modes of presentation and clinical outcome in autoimmune hepatitis.

microsome 1 (LKM-1), antineutrophil cytoplasmic, antisoluble liver antigen/liver-pancreas (SLA/LP), antiliver cytosol 1 (LC1), anti-double-stranded DNA, antiactin, antichromatin, antisialoglycoprotein receptor (ASGPR) and anticyclic citrullinated peptide. The roles these autoantibodies play in the pathogenesis of AIH are still poorly understood, although the clearest association exists with LKM-1-associated AIH. Two main types of AIH have been described by their characteristic autoantibodies profiles. Detectable ANA and SMA typify type 1 AIH, while LKM or LC1 typify type 2. Type 2 AIH is far rarer, more common in children, and associated with a more aggressive clinical course.¹⁷

A recent study analysed the diagnostic utility of the conventional autoantibodies in AIH. ANA, SMA and LKM1 had sensitivities of only 32%, 16% and 1%, respectively. The sensitivity of ANA and SMA combined increased to 43% with a positive predictive value of 97%. Importantly, both ANA and SMA were seen in other liver conditions, including alcohol-related liver disease (ALD), hepatitis B and C virus infection, and non-alcoholic fatty liver disease.²⁰

Some autoantibodies have been shown to be important markers of more severe histological changes (SLA, LKM1, LC1, ASGPR, antiactin), associated with need for transplantation or liver failure (SLA, antiactin) and treatment dependence (SLA, ASGPR, antichromatin).²¹

Histology

Liver biopsy remains essential for the diagnosis of AIH. Although no pathognomonic histological findings exist for AIH, the classical findings are those of an interface hepatitis with a lymphoplasmacytic infiltrate at the junction of the portal tract and hepatic parenchyma (figure 3).²² This is found in 84%–98% of patients, but may also occur in liver injury induced by drugs or viruses.²³ Lobular necrosis can be seen in more severe acute forms of AIH.²⁴

Diagnostic criteria

The International Autoimmune Hepatitis Group (IAIHG) has devised several scoring systems (tables 1 and 2) to aid in research and diagnosis in clinical practice.^{22–26} The diagnostic utility of the guidelines has been extensively studied in different ethnic and geographical populations.^{27–33} The 1999 scoring system is noted to be highly sensitive and specific for a definitive diagnosis of AIH, but is cumbersome.³¹ The revised simplified 2008 criteria retain specificity but lack sensitivity (99.5% and 70%, respectively) (table 3).³¹ Those patients presenting with acute or sub-ALF can often be mischaracterised by these scoring systems, as the classical features of AIH are not always present.^{31–34}

AIH is, in essence, a diagnosis of exclusion, and attention must be given to exclude viral-related infection, such as Hepatitis B and C. As with all diagnostic criteria, false positive and false negative results can be attained, and this stresses the importance of critically analysing each of the major components of the scoring system in conjunction with the clinical history.³⁵

The dilemma of 'overlap' syndromes and IgG4 disease

Some patients with AIH may also present with features from the spectrum of other autoimmune liver disease, such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). There is no standardised definition of what constitutes an overlap syndrome. The IAIHG has recently published a report clarifying their expert opinion in this area. They state that overlapping features of AIH and PSC or PBC are present between 2% and 19% of cases, but that clinicians should focus on the predominant disease phenotype and treat accordingly, rather than focusing on the idiosyncrasies of both conditions.³⁶

PBC/AIH overlap

The European Association for the Study of the Liver have adopted criteria for diagnosis of AIH/PBC

Figure 3 Classical histological features of autoimmune hepatitis (AIH). (A) Photomicrograph of a core needle biopsy demonstrating normal liver histology. (B) Photomicrograph of core needle biopsy from a patient with AIH demonstrating an enlarged portal tract, disruption of the limiting plate with interface activity and a significant plasma cell infiltrate. Photomicrographs taken at $\times 200$ magnification and stained with H&E.

Table 1 Revised IAIHG diagnostic criteria (1999)

Parameters/features	Score
Females	+2
ALP:AST (or ALT) ratio	
<1.5	+2
1.5–3.0	0
>3.0	–2
Serum globulins or IgG above normal	
>2.0	+3
1.5–2.0	+2
1.0–1.5	+1
<1.0	0
ANA, SMA or LKM1 titres	
>1/80	+3
1:80	+2
1:40	+1
<1:40	0
AMA positive	–4
Hepatitis markers	
Positive	–3
Negative	+3
Drug history	
Positive	–4
Negative	+1
Average alcohol consumption	
<25 g per day	+2
>60 g per day	–2
Liver histology	
Interface hepatitis	+3
Predominantly lymphocytic infiltrate	+1
Rosetting of liver cells	+1
None of the above	–5
Biliary changes	–3
Other changes	–3
Other autoimmune diseases	+2
Optional additional parameters	
Seropositivity for other defined antibodies	+2
HLA DR3 or DR4	+1
Response to therapy	
Complete	+2
Relapse	+3
Interpretation of aggregate scores	
Pretreatment	
Definite AIH	>15
Probable AIH	10–15
Post-treatment	
Definite AIH	>17
Probable AIH	12–17

Adapted from Alvarez *et al.*²²

AIH, autoimmune hepatitis; ANA, antinuclear antibody; HLA, human leucocyte antigen; IAIHG, International Autoimmune Hepatitis Group; LKM1, anti liver kidney microsome 1; SMA, antismooth muscle.

overlap which require at least two diagnostic criteria to be present from each disease to make the diagnosis. The AIH criteria include (1) alanine aminotransferase

Table 2 Simplified diagnostic criteria for AIH

Variable	Cut-off	Points
ANA or SMA	>1:40	1
ANA or SMA or LKM	>1:80	2
SLA	Positive	2
IgG	>ULN	1
	>1.1 ULN	2
Liver histology	Compatible with AIH	1
	Typical AIH	2

Score >6 probable AIH >7 definite AIH.

From Hennes *et al.*²⁶

AIH, autoimmune hepatitis; ANA, antinuclear antibody; LKM, antiliver kidney microsome; SLA, soluble liver antigen; SMA, antismooth muscle; ULN, Upper limit of normal.

levels at least five times the upper limit of normal (ULN); (2) IgG levels at least two times that of ULN, or positive SMA and (3) a liver biopsy with moderate or severe periportal or interface lymphocytic hepatitis. The PBC criteria include (1) alkaline phosphatase (ALP) levels at least twice that of ULN, or γ -glutamyl transferase at least five times that of ULN; (2) positive anti-mitochondrial antibody (AMA) and (3) a liver biopsy demonstrating a florid bile duct lesion.³⁷ Features of AIH have been described to be present at diagnosis of PBC and also to develop over time. Whether or not PBC-AIH overlap is associated with a different prognosis to the primary disorders, if controversial, and no controlled studies exist for the treatment of PBC-AIH syndromes.³⁶

AIH/PSC overlap

When the IAIHG criteria are applied to PSC patients 7%–14% of cases may have features of AIH.³⁶ Alternatively, patients with AIH may be discovered to have a cholangiopathy at imaging, however, the IAIHG would argue that these cannot be truly classed as an overlap, as cholangiography has often not been performed at initial diagnosis for comparison. PSC-AIH overlap seems to be more common in

Table 3 Sensitivity, specificity, PPV, and NPV of the Simplified and 1999 IAIHG Criteria for diagnosis of AIH

Criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Simplified criteria				
Probable AIH (6–7)	90	98	97	92
Definite AIH (>7)	70	100	100	74
Overall diagnosis AIH (>6)	90	98	97	92
Revised 1999 criteria				
Probable AIH(10–15)	100	97	96	100
Definite AIH (>15)	99	98	97	99
Overall diagnosis AIH (>10)	100	97	97	99

Adapted from Yeoman *et al.*³¹

AIH, autoimmune hepatitis; IAIHG, International Autoimmune Hepatitis Group; NPV, negative predictive value; PPV, positive predictive value.

children where it has been extensively studied and has an apparent better response to immunosuppressive therapy than PSC.³⁸

IgG4-related systemic disease and AIH

Once thought to be an organ-specific autoimmune disease, study of IgG4-related autoimmune pancreatitis (AIP) led to the implication of IgG4 in extra-pancreatic lesions in numerous target organs including the liver.³⁹ Some groups have investigated whether a subgroup of AIH exists that is associated with IgG4. Abnormally high levels of IgG4 may be present in immunostaining of biopsy specimens in 2%–34% of cases depending on the stringency of the histological criteria used. In contrast with AIP, cholangiopathy is absent in IgG4-related AIH, and it seems to demonstrate a prompt response to corticosteroid therapy.^{40–41} However, case series are limited, and the significance of IgG4-related disease in AIH remains uncertain.

MANAGEMENT

Pharmacological therapy

Definitive indications for treatment have been developed on the basis of three randomised control trials that demonstrated features associated with poor outcome. They form the basis for the American Association of the Study of Liver Disease (AASLD) and the British Society of Gastroenterology (BSG) practice guidelines.^{19–42} These include a serum aspartate transaminase (AST) of a least 10 times the ULN or five times the ULN, with a γ -globulin level more than twice the ULN and, lastly, the histological findings at diagnosis of bridging necrosis or multilobular necrosis. Current standard therapy is azathioprine alone, or in combination with prednis(ol)one. However, recent studies have highlighted some potential important alternative treatments.

Induction and maintenance of remission

The mainstay of induction of remission remains corticosteroids with or without the addition of azathioprine. A recent systematic review of randomised control trials since the 1950s confirms that prednis(ol)one monotherapy, or preferably in conjunction with azathioprine, remains an effective induction regimen.⁴³

Variance exists in the induction dose of steroid from 30 mg/d to 60 mg/d. A common starting dose is 40 mg/d. Azathioprine (1 mg/kg per 24 h) can be added at the start of induction or after normalisation in liver biochemistry has been documented, as azathioprine can be associated with an idiosyncratic drug-related hepatitis.^{44–45}

Maintenance therapy with low-dose prednis(ol)one (<10 mg per 24 h) and azathioprine, or azathioprine monotherapy at higher dose (2 mg/kg per 24 h), is more effective than prednis(ol)one monotherapy.^{43–44}

A recent multicentred randomised control trial has demonstrated that budesonide, a glucocorticosteroid with a high affinity for the glucocorticoid receptor, at a dose of 9 mg/kg per 24 h in conjunction with 1–2 mg/kg of azathioprine was more effective than prednis(ol)one and azathioprine at inducing remission.⁴⁶ In addition, it has a high first-pass metabolism which limits its systemic side effects, but also limits its usefulness in cirrhotic patients because of porto-systemic shunting.⁴⁶ Long-term follow-up data is currently lacking, and there have been reports of relapse on budesonide/azathioprine maintenance.⁴⁷

Treatment goals, treatment withdrawal and relapse

Whereas early trials in AIH therapy focused on reducing the aminotransferase activity to within 1–2 times ULN, more recent data suggests that our treatment goal should be the normalisation of transaminases, γ -globulins and, ideally, histological evidence of quiescent disease. Normalisation of biochemical parameters is associated with lower rates of relapse, progression to cirrhosis and more favourable outcomes.^{48–50}

Treatment for AIH may be associated with significant side effects. Withdrawal of treatment should be considered for all patients after demonstrating a period of normal biochemical parameters and liver tissue examination, although no consensus exists in relation to how or when this can be achieved. Relapse is indicated by the increase of the AST/ALT (alanine aminotransferase) to three times ULN, or γ -globulin by two times ULN indicating recurrence of interface hepatitis.⁵¹ Rates of relapse are variable in studies but can be as high as 80% after 1 year of treatment.⁴⁸ However, 2–4 years of maintenance therapy may reduce this risk to around 30%.^{48–52} Relapse may be predicted by shorter treatment duration, slow response to therapy, persistently abnormal biochemistry and the presence of LKM1 or SLA/LP antibodies.^{52–54}

Alternative treatment strategies

Treatment failure inevitably does occur in some patients. A number of second-line agents have been explored in AIH.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an inosine monophosphate inhibitor with both anti-T and -B cell proliferation effects.⁵⁵ Historically, MMF has been used in patients with refractory AIH, or who are intolerant of azathioprine. There have been 11 retrospective small case series published on the use of MMF for this indication with remission rates reported from 25% to 100%.⁵⁶ A recent prospective single-centre case series has been published on the use of MMF for induction and maintenance treatment in naïve AIH patients. Fifty-nine patients were enrolled in the study and were maintained on a dose of between 1.5 and 2 g

MMF per 24 h. A complete biochemical response was reported in 88% of patients.⁵⁷ Long-term safety data is lacking in MMF, and it is contraindicated in pregnancy, limiting its use in young females.

Ciclosporin

The calcineurin inhibitor, ciclosporin, has been studied only in small single-centre case series. In children, small case series have demonstrated high rates of biochemical remission, the largest of which was a multicentre prospective trial in 32 children in which 94% achieved biochemical remission at 12 months.⁵⁸ From organ transplant experience, Ciclosporin carries significant long-term side effects, including hypertension, renal insufficiency, hyperlipidaemia, hirsutism, infection and malignancy.

Tacrolimus

Tacrolimus, also a calcineurin inhibitor, has been assessed for its utility in AIH in a small number of case series. Van Thiel *et al* reported an open label study of 21 patients started at 6 mg/24 h of Tacrolimus at induction which was associated with improvements in aminotransferase activity and also with deterioration in renal function.⁵⁹ A single-centre study of seven patients demonstrated high rates of remission using Tacrolimus as induction therapy.⁶⁰ The utility of Tacrolimus has also been studied for patients with refractory AIH in small case series with varying degrees of response reported.^{61–63} Tacrolimus remains an attractive option at low dose for refractory AIH in women planning pregnancy, as experience in liver transplant recipients has demonstrated a favourable safety profile.^{64–66}

Other immunomodulatory agents

Further small case series have been reported in AIH with methotrexate, rituximab and Abatacept, but as yet have an undefined clinical role.^{67–70}

Long-term management

Long-term survival, cirrhosis and hepatocellular carcinoma

Prognostic information from clinical series is variable. A large retrospective study of AIH patients in Canada demonstrated 10-year survival rates to liver-related endpoints of death or liver transplantation were 94% in non-cirrhotic versus 67% in cirrhotic patients respectively.⁷¹ A recent UK study reported survival data of 245 individuals collected between 1977 and 2007 with a median follow-up period of 9.4 years. They reported increased rates of death from all-cause mortality with a standardised mortality rate 1.63 (95% CI 1.25 to 2.02) as well as from complications of liver disease. Regression analysis suggests that the presence of cirrhosis, >4 relapses per decade and failure to normalise aminotransaminases within 12 months were risks factors for liver-related death or transplantation.⁷²

Approximately 30%–50% of AIH patients will develop cirrhosis.¹⁹ Risk factors for progressive disease include those with cirrhosis, failure to halve the level of AST in the first 6 months of treatment, failure to achieve persistent remission, and those of African-American descent.^{18 53 71 73}

Hepatocellular carcinoma (HCC) has been traditionally thought to be a rare complication of AIH. Case series from America, Japan and the UK suggest HCC is more common than previously thought.^{74–77} In a study from our own institution, HCC occurred at an incidence of 1.1% per year suggesting that HCC screening remains of paramount importance in cirrhotic AIH.⁷⁴

Liver transplantation

Liver transplantation remains a life-saving procedure for individuals with AIH who present with ALF or decompensated cirrhosis. Analysis of the European Liver Transplant Registry data demonstrates a 5-year survival of 76% post-transplant, which is comparable with ALD but inferior to that of PBC.⁷⁸ Similar survival rates have been reported in the USA.⁷⁹

In patients presenting with acute icteric AIH, a subset of patients may develop ALF and require emergency liver transplantation. Predictors of corticosteroid treatment failure in a study from our own institution highlighted higher serum bilirubin levels, higher Model of End Stage Liver Disease scores at presentation, and failure to lower UK End Stage Liver Disease score by two points at day seven of treatment as being predictive of treatment failure.⁸⁰ Some authors have suggested that the increased risk of sepsis associated with intravenous steroid treatment in patients with autoimmune ALF may jeopardise their chances of successful transplant and should be avoided.⁸¹ Indications for transplantation for AIH cirrhosis are identical to those for other chronic liver diseases.⁸² Patients who develop ascites or variceal bleeding should be referred early to a liver transplantation centre.¹⁹

Unwanted effects of therapy

The unwanted effects of corticosteroids are well known and include weight gain, hypertension, diabetes, Cushingoid features, psychosis, osteopaenia and cataracts. Budesonide, on the basis of recent evidence, could offer a potential alternative for those patients at most risk of steroid-related unwanted effects.

Azathioprine may be associated with side effects in up to 25% of patients, and the side effects are more common in cirrhotic patients.¹⁹ While nausea is perhaps the most common, what concerns many patients and prescribers alike is the reported increased risk of malignancy and myelotoxicity. The long-term malignancy risk in azathioprine use is poorly defined in AIH. A recent nested control study in inflammatory bowel disease (IBD) patients treated with azathioprine

for at least 1 year demonstrated an increased risk of ultraviolet light-associated non-melanoma skin cancer with an OR of 4.3 (95% CI 3.1 to 6.0).⁸³ The risk of non-cutaneous cancer with azathioprine treatment outside of the setting of organ transplant is controversial. One meta-analysis study reported a fourfold increase in the risk of lymphoma in patients with IBD treated with azathioprine.⁸⁴ However, in another recent meta-analysis, and along with a large retrospective cohort study of 17 000 IBD patients, no increased risk was demonstrated.^{85–87} As IBD may also confer additional risk of lymphoma, it is difficult to extrapolate fully to AIH, but the risk would appear to be low.

Azathioprine is a pro-drug that is, enzymatically converted to numerous active metabolites. Although the exact mechanism of the action of many of the metabolites is poorly understood, the therapeutic benefits are thought to be derived from thioguanine nucleotide metabolites (TGN) and toxic effects from methylmercaptapurine nucleotides (MeMPNs).⁸⁸ Much research has focused on the prediction of toxic effects of azathioprine by assessing one of the major enzymes responsible for its metabolism, thiopurine methyltransferase (TPMT). Allelic variations of TPMT are common and result in varying degrees of enzymatic activity. Approximately 88% of the population has normal or high activity, 11% intermediate activity and 0.5% low activity.⁸⁹ While TPMT phenotyping and genotyping is recommended to detect the 1:300 of the population homozygous for mutations that result in very low TPMT activity and high risk of myelotoxicity, in all other patients, TPMT activity testing is poorly predictive of toxicity.^{19 90 91} More recent research in azathioprine metabolism has focused on therapeutic monitoring, with recent studies suggesting measurement of TGN, and MeMPN levels may help predict treatment response and toxicity potential irrespective of TPMT activity/genotyping.^{88 92}

AIH and pregnancy

As AIH can often affect women of childbearing age, an important aspect of treatment is one of management of pregnancy where both patients and medical professionals have concerns regarding safety and the use of immunosuppressants. Initial reports from the 1970s suggested high rates of foetal loss and obstetric complications.⁹³ Since then, five international case series have been published.^{94–98} The experience of our own institution is that of 81 pregnancies in 51 women followed-up at King's College Hospital between 1982 and 2009, median age at conception was 26 (range 16–42), and 41% women were cirrhotic at the time of pregnancy.⁹⁸ The live birth rate was 73%, but was significantly lower in those women who were cirrhotic. While flares of inflammatory activity were common (33%), serious maternal events within 12 months of pregnancy, including decompensation, need for liver transplantation or death occurred in only 11% of

pregnancies. Most patients were on therapy for AIH at the time of conception, but this did not seem to impact on rates of miscarriage or foetal malformations.⁹⁸ The low rate of foetal malformations in our study is also reflected in a larger study of pregnancy in IBD patients.⁹⁹ AASLD practice guideline recommend discontinuation of azathioprine during pregnancy.⁴² However, experience of azathioprine use in our study was associated with lower rates of flares of AIH, and those patients with suboptimal disease control, or who were on no therapy, were more likely to have high-risk pregnancies.⁹⁸ BSG practice guidelines stress the importance of individualising treatment decisions around pregnancy after full discussion with the patient.¹⁹ Mycophenolate should be avoided in pregnancy, as it is potentially teratogenic.

CONCLUSIONS AND UNANSWERED QUESTIONS IN AIH

Happily, standard therapy controls the majority of disease in patients with AIH. However some key clinic questions remain. First, the exact role of budesonide in induction and fine-tuning strategies in maintenance therapy require further elucidation. However, budesonide is limited in cirrhotic patients and, therefore, standard therapy with prednis(ol)one is preferred. Second, defining what constitutes remission in AIH is crucial in enabling an evidence-based approach to consideration of withdrawal of pharmacological therapy. Last, the issue of treatment failure remains problematic, as a standardised evidence-based approach which delineates the role of second-line agents does not currently exist. However, current BSG guidelines include a suggested treatment algorithm for the management of treatment failure.¹⁹ For those patients who do progress to cirrhosis, a subset may develop indications for liver transplantation and may expect excellent survival rates following transplantation. Early referral to a transplant centre is recommended for those patients developing treatment failure, portal hypertension or synthetic dysfunction.

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or requirement for liver transplantation of 94% in non-cirrhotic versus 67% for cirrhotic patients, respectively” should read: “A large retrospective study of AIH patients in Canada demonstrated 10-year survival rates to liver-related endpoints of death or liver transplantation were 94% in non-cirrhotic versus 67% in cirrhotic patients.”

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