CURRICULUM BASED CLINICAL REVIEWS

Autoimmune hepatitis and complexities in management

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ABSTRACT

Autoimmune hepatitis (AIH) is a rare heterogeneous immune-mediated liver disease that for the majority has effective therapy, usually resulting in excellent prognosis. Treatment is based on immunosuppression using standard therapy with corticosteroids and azathioprine. Second-line therapeutic options exist for those who are non-responders ('difficult to treat AIH') or intolerant to standard therapy; however, their use is not standardised, and in addition, there is vast variation in practice and efficacy. Given the rarity of AIH, expertise in its management can be limited to large referral programmes. In this case-based review, we aim to discuss common clinical dilemmas encountered by clinicians managing adult patients with AIH and address the related competencies in the 2010 Gastroenterology curriculum.

INTRODUCTION

Autoimmune hepatitis (AIH) is a rare immune-mediated liver disease that in the majority has effective treatment if diagnosed promptly and treated cautiously with standard immunosuppression: corticosteroids and azathioprine. The heterogeneity of AIH and lack of a specific diagnostic marker presents diagnostic and therapeutic complexities. For the minority who are intolerant or unresponsive to standard therapy, second-line therapies exist; however, there is lack of standardisation in clinical practice and variability in treatment outcomes. This review addresses competencies described in the 2010 Gastroenterology curriculum (table 1) and focuses on clinically relevant dilemmas faced when managing adult AIH patients.

BACKGROUND AND CLINICAL PRESENTATION

AIH is a chronic liver disease presenting in all ages, both sexes and all races. Clinical presentation (summarised in table 2) ranges from asymptomatic to acute severe

disease to fulminant liver failure. Approximately 25% of patients present acutely with AIH, and this can be indistinguishable from viral hepatitis. Thirty per cent of patients are cirrhotic at presentation including a significant number who are asymptomatic.

In patients with increased genetic susceptibility, environmental toxins such as drugs and virus can trigger AIH by molecular mimicry. Viral triggers include hepatitis A, cytomegalovirus and herpes simplex virus. Drug triggers include most commonly nitrofurantoin and minocycline.¹ Biological therapy, for example, antitumour necrosis factor (TNF) monoclonal antibodies are also implicated to initiate AIH.

There is no single pathognomonic test for AIH. It remains a diagnosis of exclusion based on several indicative clinical, serological, biochemical and histological findings. Other aetiologies of liver diseases need exclusion. Clinically, AIH is characterised by elevated serum aminotransferase activity, autoantibodies and hypergammaglobulinaemia. Unless contraindicated, a liver biopsy is undertaken in all patients, ideally pretreatment to aid confirmation of diagnosis and staging. Histologically, AIH is characterised by interface hepatitis, dense plasma-rich infiltrates, hepatocyte rosetting and emperipolesis (figure 1).

Autoantibodies, usually detected by indirect immunofluorescence, aid both in diagnosis and subclassification. Type 1 AIH is characterised by antinuclear antibody (ANA) and/or antismooth muscle antibody (anti-SMA). Neither antibody is specific for AIH as they can be present in patients with other liver and autoimmune diseases. Classically, ANA in AIH has a homogenous pattern; however, a coarse or finely speckled pattern can occasionally be seen.² Up to 50% of patients with 'definite' primary biliary cholangitis

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Table 1 2010 Gastroenterology curriculum competencies

(2) Core competencies (e) Hepatology Specific diseases	Autoimmune liver disease, including autoimmune hepatitis, PBC, PSC and overlap syndromes: ► Recognises and appropriately investigates patients with autoimmune liver diseases. ► Aware of management and complications of autoimmune liver disease including extrahepatic manifestations and associations including malignant complications in PSC. ► Appreciates and understands that this range of liver disease is frequently underdiagnosed and may have been inappropriately managed. ► Selects appropriate immunomodulatory therapy, has awareness of side effects and may well require specialist care. ► Responds urgently to the management challenge of these severe and often acute diseases and involves more specialist services where required.
(3) Advanced specialist areas (a) Hepatology	Liver transplantation: ► To appreciate the role of liver transplantation in the management of both chronic and acute liver disease and the management, complications of immunosuppression. ► Knows the indications for liver transplantation, appropriate timing of referral for assessment and outcomes after transplantation.

PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

(PBC) also test positive for disease-specific ANA, the characteristic immunofluorescence patterns being perinuclear/rim-like membranous (anti-gp210) and multinuclear dot (anti-Sp100). SMA antibodies can have three patterns: V (vessels), G (glomeruli) and T (tubules). The VG and VGT patterns, which correlate with F-actin antigenicity, are frequently associated with but not pathognomonic of AIH as compared with the V pattern.² Type 2 AIH occurs mostly in children and is characterised by presence of antiliver/kidney

microsomal type 1 (anti-LKM 1) and/or antiliver cytosol type 1 antibodies. Anti-LKM 1 antibodies are described mainly in the paediatric population in Europe and are seemingly rare in adults in the USA (only 3% of adults in North America³).

A simplified scoring system devised and validated by the international AIH group (2008) (table 3) based on two international multicentre patient cohorts⁴ had 88% sensitivity and 97% specificity (cut-off ≥ 6) and 81% sensitivity and 99% specificity (cut-off ≥ 7) when

Table 2 Epidemiology and clinical features of AIH

Epidemiology	Prevalence ranges from 16 to 18 cases per 100 000 inhabitants in Europe. ¹ Presents in all ages, both sexes and all races. Clinical presentation can vary according to ethnicity and geographical areas. Cirrhosis at presentation is more frequent in black North American patients than white North Americans. Africans, Asians and Arabs have an earlier disease onset than patients from Northern Europe, while patients of Hispanic origin tend to present aggressively both biochemically and histologically and have a very high prevalence of cirrhosis and cholestatic features. ¹
Associations	Concomitant autoimmune diseases in 20% of patients for example, Hashimoto thyroiditis, coeliac disease, Graves disease, Sjögren's syndrome, autoimmune haemolysis, rheumatoid arthritis, ulcerative colitis and idiopathic thrombocytopenic purpura.
Symptoms	Asymptomatic or non-specific symptoms including jaundice, fatigue, lethargy, nausea, anorexia, weight loss, abdominal pain, pruritus, arthralgia, arthritis, acne and amenorrhoea. Acutely it is indistinguishable from a viral illness. Cirrhotics may present with features of decompensation, for example, ascites, variceal bleeds and encephalopathy.
Diagnosis	Diagnosis of exclusion and based on several indicative clinical, serological, biochemical and histological findings.
Biochemistry	Raised serum aminotransferase activity (ALT and AST) $\pm$ bilirubin and IgG. Elevations of ALP can also be seen; however, if greater than three fold, should prompt investigation for biliary disease.
Serology	Non-specific. Autoantibody titres do not correlate with disease activity in adults and may vary throughout the disease course. Seronegative disease (only <5% of patients if autoantibodies are tested correctly ³²) can occur. Repeat testing in such patients and those with low titres is recommended. Autoantibodies in isolation should not be used to diagnose AIH. Similarly if negative, do not preclude a diagnosis of AIH in the presence of other supporting features. Conventional autoantibodies include anti-ANA, SMA (type 1 AIH) and LKM 1, LC 1 (type 2 AIH). Other antibodies relevant to AIH include SLA/LP (has a high diagnostic value and identifies patients with more severe disease course and outcome), AMA (found in 20% of AIH patients with no clinical evidence of biliary disease), F-actin, p-ANCA.
Histology	Interface hepatitis, dense plasma-rich infiltrates, hepatocyte rosetting and emperipolesis. Both hepatocyte rosetting and emperipolesis were shown to be superior histological predictors of AIH. ³³
Differential diagnosis	Viral hepatitis, drug induced, metabolic (alcohol and non-alcoholic) liver disease, Wilson disease, alpha 1 antitrypsin deficiency and hereditary haemochromatosis.

AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; AST, aspartate aminotransferase; ANA, antinuclear antibody; IgG, immunoglobulin G concentration; LC 1, liver cytosol type 1; LKM 1, liver kidney microsomal type 1 antibody; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; SMA, smooth muscle antibody; SLA/LP, soluble liver antigen/liver-pancreas antibody.

Figure 1 Histological features of AIH. (A) H&E stained section showing portal inflammation and interface hepatitis. (B) Haematoxylin Van Gieson stained section (collagen fibres stained red). Interface hepatitis is associated with delicate fibrous entrapment of periportal hepatocytes, which show ballooning and rosetting. Images provided by Professor Stefan Hübscher, Consultant Histopathologist, Department of Cellular Pathology, Queen Elizabeth Hospital, Birmingham.

applied to the validation cohort (n=109). Recently it has been validated in Chile (n=294 patients) and found to be highly accurate for AIH diagnosis in the Chilean-Hispanic cohort.⁵ Although the scoring system is useful in AIH diagnosis, clinical judgement is required as neither autoantibodies nor histological features are absolutely specific to AIH and cannot be used in isolation to make a diagnosis.

Some patients with AIH can have features of primary sclerosing cholangitis (PSC-AIH) or PBC-AIH leading to several terms 'overlap', 'variant' or 'cross-over' syndrome. Such patients can have variable presentations. Some are identified at the time of diagnosis (simultaneous presentation), while others are diagnosed with one disease, which is stable for years before developing features of another disease (sequential presentation). Clinically variant syndrome is considered when a patient's disease course deviates from that expected for the dominant underlying disease. A holistic approach is required to confidently diagnose

Table 3 Simplified diagnostic criteria for AIH (International Autoimmune Hepatitis Group)

Variable	Cut-off	Points
ANA or SMA	Titre $\geq 1:40$	1*
One or more of		
ANA or SMA	$\geq 1:80$	
LKM	$\geq 1:40$	2*
SLA	Positive	
Serum immunoglobulin G	>Upper limit of normal	1
	$\geq 1.1 \times$ upper limit of normal	2
Liver histology	Compatible	1
	Typical	2
Absence of viral hepatitis	No	0
	Yes	2

A total score of ≥ 6 indicates probable AIH, while a score of ≥ 7 indicates definite AIH.

Caution must be taken when applying scoring systems in an acute setting as autoantibodies titres, and IgG concentration may be low/normal and classical histology features be absent or less pronounced. Clinical judgement is required.

*Addition of points achieved for all autoantibodies (maximum of 2 points).

AIH, autoimmune hepatitis; ANA, antinuclear antibody; LKM, liver kidney microsomal type 1 antibody; SLA, soluble liver antigen; SMA, antismooth muscle antibody

overlap taking in to consideration a combination of biochemical, serological, histological and radiological (cholangiography) features. There is no single diagnostic feature. AIH, PSC and PBC are heterogeneous diseases with variations in their clinical features; for example, 8%–12% of patients with all the features of AIH can be persistently AMA positive,¹ while interface hepatitis is common across the three diseases. These variations make the differential diagnosis between the diseases challenging and can lead to overdiagnosis of variant syndrome. Caution should be exercised when considering 'overlap' particularly in patients with a simultaneous presentation; often this is a reflection of disease variation rather than true overlap, and many would delay 'diagnosing' overlap until the dominant disease process is treated and the clinical picture rereviewed. Chazouillères *et al*⁶ has developed the most commonly used criteria to aid in the classification of PBC-AIH. The diagnosis of PSC-AIH requires combination of cholangiographic or histological features typical of PSC, alongside robust histological features of AIH. Further discussion of variant syndrome is beyond the scope of this review.

MANAGEMENT

Management is based on immunosuppression and, in the presence of evident inflammation biochemically or histologically, is usually offered to all patients regardless of symptoms. Current treatment regimens are based on historic studies that showed untreated, moderate to severe AIH has a poor prognosis with a

5-year and 10-year survival of 50% and 10%, respectively.¹ Such patients are offered treatment given clear survival benefit and excellent patient outcome with immunosuppression; 10-year survival rates exceed 80%.⁷ Older patients without histological inflammation or those with minimal changes and no fibrosis may present and be monitored but not immediately treated.⁸ The decision not to treat however remains controversial. Historically, this is because the benefits of treating asymptomatic patients with biopsy proven mild inflammatory activity are less well established, 10-year survival rates being 67%–90%. In contrast, a study showed the 10-year survival rates in untreated patients with mild disease was significantly lower than treated patients with severe disease (67% vs 98%, respectively).⁹ The disease course of mild AIH is unknown, while some do well without immunosuppression; it should be emphasised that untreated AIH has a fluctuating and unpredictable disease trajectory. Mild disease activity can be combined with episodes of severe activity and a substantial proportion of asymptomatic patients may become symptomatic (26%–70%) during follow-up; therefore, risk of disease progression leading most to treat from the outset.^{10 11} Furthermore, papers tend to quote 10-year survival because that is the data to hand, but a patient perspective requires longer survival data. Clinicians need to carefully balance treatment-related side effects versus risk of disease and symptom progression. Patients not on treatment need close monitoring.

The overarching treatment goal is to achieve complete biochemical (normalisation of serum aminotransferase activity and immunoglobulin G (IgG) concentration) and histological remission. Histological remission lags behind biochemical remission by 3–6 months. Remission is achievable in 75%–80% of patients after 24 months of treatment. In some, it may not be possible to achieve complete remission, the goal thereby being to achieve lowest biochemical activity with minimum treatment-related side effects.¹

INDUCTION AND MAINTENANCE REMISSION OF AIH

Prednisolone±azathioprine is used to induce and maintain remission. Two strategies are proposed to induce remission: (1) prednisolone monotherapy and (2) prednisolone/azathioprine combination therapy. Combination therapy is reportedly as efficacious as prednisolone monotherapy with fewer side effects (10% vs 44%, respectively), making it the preferred treatment strategy.

Although guidelines for the management of AIH exist,^{1 7} the optimum prednisolone dosing strategy remains poorly defined, as no trials have directly compared prednisolone dosing. Treatment decisions should not be static but instead be pragmatic and personalised to a patient's age, disease presentation, comorbidities, as well as preference, so as to achieve the

best long-term outcomes. Starting prednisolone doses range from 20 mg/day up to 1 mg/kg/day. Higher prednisolone doses (e.g. 1 mg/kg/day) are however rarely required and are associated with side effects. The addition of azathioprine allows for use of lower prednisolone doses (e.g. 20–30 mg/day) to induce remission. Azathioprine can be commenced at the outset (50 mg/day) or 2–4 weeks after corticosteroid introduction at 1–2 mg/kg/day.¹ The European Association for the Study of the Liver (EASL) guidelines recommend prednisolone as initial induction therapy followed by addition of azathioprine after 2 weeks of prednisolone initiation.¹ Delay in azathioprine introduction can be pragmatically helpful in diagnostic uncertainty (corticosteroid responsiveness aids in diagnosis confirmation). It also avoids the diagnostic dilemma of differentiating azathioprine-induced hepatotoxicity from primary non-response¹ and other general side effects, for example, nausea. In icteric patients, azathioprine initiation is usually delayed until the bilirubin is <100 µmol/L.^{1 12}

In most, a fall in serum aminotransferase activity is seen within 2 weeks of treatment initiation. The prednisolone dose is gradually tapered to the minimum required to maintain normal liver biochemistry and IgG concentration (refer to [figure 2](#) for a proposed treatment algorithm). Dose titrations need to be individualised (considering patient age, comorbidities and severity of presentation) and response guided (falls in alanine aminotransferase (ALT) and IgG). In young patients with aggressive disease, some initiate prednisolone at 30–40 mg/day, while others use higher doses, for example, 1 mg/kg/day. A high and fast response rate was shown to be associated with better outcomes.¹³ As always, treatment-related side effects must be balanced with benefit.

Remission is usually maintained using prednisolone (5–12.5 mg/day) alongside azathioprine (1–2 mg/kg/day) or azathioprine monotherapy (up to 2 mg/kg/day). Both strategies are similar in efficacy and superior to prednisolone monotherapy in maintaining remission.¹⁴ Studies have shown azathioprine monotherapy (2 mg/kg/day) prevented corticosteroid specific side effects and relapse on corticosteroid withdrawal as well as achieved remission rates of up to 83%.^{15 16} Careful monitoring is required with azathioprine given risk of cytopenias and doses adjusted accordingly. Serum thiopurine metabolite levels can be helpful optimising dosing with thioguanine nucleotide concentrations >220 pmol/8×10⁸ erythrocytes predictive of remission.¹⁷ Therapy needs to be tailored to an individual patient, the most appropriate maintenance regimen will depend on both the severity of therapy related side effects and disease activity. In our practice, we rarely start with a goal of 2 mg/kg/day of azathioprine because of the long-term side effect profile, but in individual patients titrate azathioprine dose as needed for that individual, thereby balancing risk and benefit.

Figure 2 Proposed treatment algorithm for AIH based on the authors experience. Although guidelines exist for treating AIH, an individualised and response-guided approach to patient management is required. Adherence to therapy is as important as the clinical management of a patient with AIH. Benefits of therapy should be balanced against the risks of potent immunosuppressants. Specialist opinion is advisable: if a patient does not respond well to first-line therapy, there is uncertainty in the management of an AIH patient and in acute severe AIH. A liver biopsy can guide treatment decisions; however, it is rarely needed if a patient relapses or flares as elevated biochemistry (ALT and IgG) indices are indications to treat/escalate therapy. AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgG, immunoglobulin G concentration; LC 1, liver cytosol type 1; LKM 1, liver kidney microsomal type 1 antibody; MMF, mycophenolate mofetil; SLA/LP, soluble liver antigen/liver-pancreas antibody; ULN, upper limit of normal.

The optimum treatment duration is controversial, but for non-cirrhotic type 1 AIH patients, corticosteroids are usually continued for 12–18 months and azathioprine for 3–5 years. Therapy is continued for minimum 24 months after complete biochemical remission prior to withdrawal. A single attempt at treatment withdrawal is reasonable in non-cirrhotic patients assuming all inflammatory parameters remain repeatedly normal. Approximately 50% of patients in complete biochemical remission have persisting histological activity¹⁸; therefore, a confirmatory liver biopsy prior to withdrawal is considered helpful by some. Treatment withdrawal is undertaken by stepwise reduction with patients monitored throughout.

Relapse occurs in 50%–90% of patients following treatment withdrawal and is more likely in the first year. Late relapses also occur; 81% of patients in a study relapsed after 3 years.¹⁹ If relapses or flares occur,

corticosteroids are reinstituted at induction doses (eg, 20–30 mg/day), and azathioprine can be increased to 2 mg/kg/day.

BUDESONIDE AS AN ALTERNATIVE INDUCTION AGENT TO PREDNISOLONE

EASL recommends that budesonide 9 mg/day (a corticosteroid with a short half-life and low systemic exposure) alongside azathioprine can be used to induce remission in treatment-naïve, non-cirrhotic patients with uncomplicated AIH when there is concern regarding side effects and comorbidities potentially exacerbated by prednisolone, for example, diabetes and osteoporosis.

Budesonide alongside azathioprine effectively induced and maintained remission in non-cirrhotic AIH patients with low corticosteroid-specific side effect rates compared with prednisone²⁰; however,

another study found budesonide was ineffective in corticosteroid refractory/dependent AIH.²¹ Switching from prednisolone to budesonide can be considered to reduce side effects in patients on long-term therapy; care is needed as occasionally this may result in corticosteroid withdrawal symptoms. Given budesonide has a 90% first-pass hepatic clearance, it is contraindicated in patients with cirrhosis or those with portal hypertension/perihepatic shunting. Concurrent extra-hepatic immune-mediated diseases need consideration as exacerbations are reported with budesonide, in keeping with the first-pass hepatic metabolism.

SECOND-LINE THERAPY

Second-line therapy may be considered in incomplete or non-responders (persistence of biochemical and/or histological inflammatory activity) or those intolerant to standard therapy (10%–20% of patients). For incomplete or non-responders, adherence should be confirmed, and alternative diagnosis (particularly hepatitis E infection) as well as variant syndrome should be excluded. Active disease should be excluded in those with concurrent inflammatory bowel disease as such patients have been shown to enter biochemical remission less often as well as fail treatment more commonly and progress to cirrhosis.²² Following this, standard therapy should be optimised prior to second-line therapy. A liver biopsy may guide treatment decisions. In patients requiring high dose long-term corticosteroid therapy, azathioprine can be increased to 2 mg/kg/day alongside prednisolone, while those on budesonide switched to prednisolone. Use of second-line agents is not standardised; there is variability in clinical practice and efficacy. Expert advice is advisable when second-line therapy is being considered or when there is uncertainty in the management of a patient with active AIH.

Mycophenolate mofetil (MMF 1–2 g daily) is the most commonly used second line therapeutic agent in AIH, largely reserved for azathioprine/6-mercaptopurine intolerant patients. Remission rates when MMF is used in azathioprine-intolerant patients range 43%–88%. Previous studies where MMF was used in azathioprine non-responders are disappointing (remission rates between 0% and 25%). However, recent studies have reported higher remission rates. A retrospective multicentre study (n=201 patients with AIH) found that both tacrolimus and MMF as second-line therapies were equally effective in maintaining biochemical remission (91.9% vs 94.1%, respectively) in patients who were previous complete responders but intolerant to standard therapy.²³ However, in non-responders, tacrolimus led to a complete response in a significantly greater proportion of patients as compared with MMF (56.5% vs 34%, respectively). In a second retrospective study of 105 patients with AIH, Roberts *et al* found no differences in the proportion of patients who achieved biochemical remission within the first 2 years

of treatment between patients receiving MMF for non-response and those who were intolerant to standard therapy (57% vs 62%, respectively).²⁴ Reduced biochemical remission rates and higher infection rates were however reported in cirrhotics receiving MMF as compared with non-cirrhotics. Prospective studies are required to better assess the role of MMF as second-line therapy in patients with inadequate response to standard therapy. High rates of intolerance to MMF are reported. It is contraindicated for those contemplating pregnancy making other second-line therapies preferable. A Greek group explored using MMF as first-line therapy to induce AIH remission.^{25 26} In their observational study (n=131), initial biochemical response was achieved in 93.6% (prednisolone +MMF) versus 72.7% (conventional therapy) of patients within 2 months.²⁵ Further studies are required before MMF can be advocated as first-line therapy.

Calcineurin inhibitors: evidence of ciclosporin's use in adults with non-responsive AIH is sparse; remission rates of 80% are reported.¹

Tacrolimus as salvage therapy in difficult-to-treat AIH improved liver biochemistry, histology and enabled corticosteroid dose reduction.²⁷ Target serum tacrolimus concentrations in AIH are unknown but most maintain a concentration of $\leq 6 \mu\text{g/L}$.^{27–29} Attention to the side effects is important, including hypertension and diabetes.

Other second-line agents include: 6-mercaptopurine (6-MP), cyclophosphamide, anti-TNF agents and rituximab. Single-centre experience, for example, in treating refractory AIH patients with rituximab has produced encouraging results with significant biochemical improvements seen following rituximab therapy.³⁰

Surveillance considerations and side effect/monitoring of therapy are discussed in [tables 4 and 5](#) respectively

LIVER TRANSPLANTATION

Liver transplantation should be considered in (1) acute or fulminant liver failure, (2) patients with a Model for End-Stage Liver Disease (MELD) score of ≥ 15 , (3) decompensated liver disease while on treatment and (4) rarely hepatocellular carcinoma development. Untreated patients with AIH have a survival of $<30\%$.⁷ Patients, who present with acute or fulminant liver failure, should be referred urgently to a transplant centre³¹ as emergency transplantation may be required. Overall mortality in such patients ranges between 19% and 45% and rate of liver transplant required range from 9% to 81%.¹ Corticosteroid therapy in an acute setting can be complicated by an increased infection risk; however, a trial for all but the sickest patients may be considered following advice from a transplant centre; the appropriate dose in such settings is not however agreed. Patients need close monitoring for deterioration and sepsis. Failure to improve prognostic

Table 4 Surveillance considerations in patients with AIH

Manifestation	Comment	Intervention
Portal hypertension and varices	Endoscopic surveillance of all cirrhotics* or if splenomegaly or thrombocytopenia is present.	Primary prophylaxis with β -blockers or varices eradication as appropriate.
Malignancy	1. Hepatocellular carcinoma (HCC) ▶ HCC risk 1%–2%/year. 2. Extrahepatic malignancy, for example, non-melanoma skin cancer associated with long-term immunosuppression.	HCC surveillance ▶ 6 monthly liver ultrasound is recommended although not validated in AIH. Routine health screening for other malignancies.
Concurrent autoimmune conditions (1 in 3 patients)	40% will have a family history of autoimmunity; consider in particular thyroid and coeliac disease.	Careful family history may identify rare variants of AIH, for example, APECED.

*Transient elastography (TE) can be useful in the follow-up of patients with AIH and in risk stratifying for complications of cirrhosis. Liver stiffness ascertained by TE positively correlated with histological fibrosis in patients on 6 months of treatment.³⁴ Hepatic inflammation can impact on liver stiffness and therefore accuracy of determining fibrosis stage particularly during the first few months of therapy.

AIH, autoimmune hepatitis; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy syndrome.

scores within 7 days should prompt early consideration of liver transplantation.¹ Outcomes post-transplantation are good with 5-year and 10-year survival rates of approximately 75%.⁷ Post-transplant immunosuppression needs to be broadly more intense than other indications, with use of either long-term prednisolone or azathioprine/MMF alongside a calcineurin inhibitor. Recurrence rates at 5 years range 20%–50% of transplants.

De novo AIH: this is when an AIH or AIH-like syndrome develops after transplantation for other liver diseases. The prevailing view is that de novo AIH represents a variant of rejection. It is managed by addition of corticosteroids to a patient's immunosuppression regime. In the case of inadequate response following corticosteroid introduction and optimisation of calcineurin inhibitor concentration, azathioprine (1–2 mg/kg/day) is instituted.⁷ Usually

Table 5 Side effects of medications used in AIH

Drug	Side effect	Consideration
Corticosteroids	Weight gain/Cushingoid. Diabetes. Cataract. Hypertension/fluid retention. Poor wound healing. Osteoporosis. Adrenal suppression. Susceptibility to infection.	▶ Start calcium and vitamin D supplements. ▶ Consider bone mineral density assessment±bisphosphonate prophylaxis. ▶ Check blood glucose and monitor on therapy periodically. ▶ Screen for cataracts. ▶ Check blood pressure and monitor on therapy periodically.
Azathioprine	Cytopenias/macrocytosis. Pancreatitis/pneumonitis. Nausea/vomiting/flu-like syndrome. Hepatotoxicity. Possible long-term malignancy risk.	▶ Life-long monitoring of haematology and liver biochemistry is required. ▶ Counselling for ultraviolet protective measures.
Mycophenolate mofetil	Cytopenias. Diarrhoea/gastrointestinal upset. Headache. Rare colitis. Possible long-term malignancy risk.	▶ Monitoring of haematology and liver biochemistry is required. ▶ Mycophenolate mofetil is contradicted in pregnancy.
Calcineurin inhibitors	Hypertension. Nephrotoxicity. Hyperlipidaemia. Tremor. Gastrointestinal upset. Headache.	▶ Monitoring of serum concentration levels and renal function.

Other considerations:

Clinicians need to be mindful of the risk of sepsis associated with immunosuppressive therapy particularly in cirrhotics where sepsis can result in decompensation and death.

Prior to initiating rituximab, it is recommended that hepatitis B serology be checked and those who are hepatitis B core antibody positive receive prophylactic hepatitis B treatment to prevent reactivation. In addition, patients are frequently screened for latent tuberculosis and should receive appropriate vaccinations including hepatitis B for those at risk, pneumococcus and influenza.

good response is seen following addition of corticosteroids and azathioprine; however, in some progression to cirrhosis and subsequent graft failure can occur.

CASE EXAMPLES

Case 1

Ms A (aged 21 years) presented with fatigue, serum liver tests: ALT 619 U/L, normal alkaline phosphatase (ALP), bilirubin and synthetic function. Positive liver screen findings: weak positive ANA (1:400; speckled pattern), antisoluble liver antigen (anti-SLA) antibodies and elevated IgG 16.11 g/L. Imaging: unremarkable. Family history of autoimmunity existed. Liver biopsy: mixed pattern of portal/lobular hepatitis and mild periportal fibrosis. Histological changes alongside clinical findings were compatible with a diagnosis of AIH.

Budesonide 9 mg/day was started. Serum liver tests improved: ALT 103 U/L, normal ALP, bilirubin and synthetic function, IgG reduced 15.88 g/L in keeping with corticosteroid responsiveness therefore diagnosis confirmation. After 4 weeks, azathioprine 50 mg/day was started alongside budesonide 9 mg/day. Four months post-therapy, serum liver tests and IgG normalised, budesonide was reduced to 6 mg/day and azathioprine increased to 75 mg (1 mg/kg/day).

This case highlights use of therapy to treat AIH that is tailored to a patient. Given its efficacy and favourable side effect profile, budesonide alongside azathioprine can be used to treat non-cirrhotic patients with uncomplicated AIH, especially when there is concern regarding side effects. Our patient is young and has non-cirrhotic AIH; cosmetic corticosteroid-related side effects were a concern and can impact on adherence. Anti-SLA antibodies are associated with high relapse risk therefore treatment is likely to be lifelong.

Case 2

Ms B (aged 37 years) presented with a 6-week history of malaise, jaundice and worsening serum liver tests: ALT >1000 U/L, ALP 130 U/L, bilirubin 426 µmol/L and normal synthetic function. Positive liver screen findings: weak positive ANA (1:100; homogenous pattern), anti-SMA antibodies and elevated IgG 20.89 g/L. Significant history included a family history of autoimmunity. Imaging: unremarkable. Liver biopsy: moderate portal inflammation with interface activity and periportal hepatocyte rosetting. Confluent hepatocyte loss with focal haemorrhage and congestion was also seen. Diagnosis of probable AIH was made, and prednisolone 20 mg/day was given. After 3 weeks, serum liver tests improved: ALT 249 U/L, bilirubin 99 µmol/L, IgG 13.05 g/L, ALP and liver synthetic function remained normal. Azathioprine 50 mg/day (when bilirubin was <100 µmol/L) was given alongside prednisolone 20 mg/day. Prednisolone dose was gradually reduced to 5 mg/day and azathioprine increased to

100 mg/day (1 mg/kg/day). Serum liver tests and IgG normalised 3 months post-treatment.

This case highlights that AIH is treatment responsive if diagnosed promptly. Diagnosis can be difficult as not all clinical features may be present; thus, application of standard clinical acumen is required. Although our patient was jaundiced, her synthetic function was preserved therefore standard therapy with corticosteroids±azathioprine is appropriate and effective in inducing and maintaining remission in majority of patients. High prednisolone doses and rapid treatment decisions are not always required providing the patient is closely monitored. Combination therapy (prednisolone and azathioprine) allows for the use of lower prednisolone doses, for example, 20–30 mg/day with fewer side effects.

Case 3

Ms C (aged 27 years) has rheumatoid arthritis (RA) and type 1 ANA positive (1:40) AIH (in biochemical remission). In March 2014, she started abatacept injections (CTLA4-Ig protein that blocks T cell activation) for active RA (serum liver tests/IgG were normal at that point). Serum liver tests in September 2015: ALT 859 U/L, ALP 197 U/L, bilirubin 49 µmol/L, albumin 38 g/L, INR 1.2 and IgG 5.76 g/L. Medications then included prednisolone 5 mg/day, azathioprine 1 mg/kg/day and abatacept injections. Imaging: unremarkable. The possibility of drug-induced liver injury was considered; therefore, the abatacept injections were stopped. Liver biopsy revealed an acute hepatitic process. She was treated for an AIH flare; prednisolone increased to 40 mg/day (figure 3). Despite this, serum liver tests deteriorated further: ALT 619 U/L, AST 700 U/L, ALP 243 U/L, bilirubin 163 µmol/L, albumin 36 g/L, INR 1.6, and IgG 6.84 g/L requiring a hospital admission by December 2015. Repeat liver biopsy revealed a severe acute AIH. High dose corticosteroids (intravenous methyl prednisolone 80 mg daily for 3 days then oral prednisolone 80 mg/day for further 3 days then 40 mg/day of prednisolone as maintenance), alongside salvage therapy with rituximab infusion 1000 mg, prophylactic antibiotics and antifungals were administered. Serum liver tests improved by mid-January 2016: ALT 86 U/L, AST 55 U/L, ALP 148 U/L, bilirubin 54 µmol/L, albumin 40 g/L, INR 1.2 and IgG 5.61 g/L. Prednisolone was weaned down to 10 mg/day, and azathioprine increased to 2 mg/kg/day. Six monthly rituximab infusions were continued. Serum liver tests have subsequently normalised for more than a year.

This case highlights (1) biological therapy may precipitate an AIH flare. (2) In acute severe AIH, following guidance from a transplant centre, a single trial of high dose (e.g. ≥1 mg/kg/day sometimes intravenously) corticosteroids to all patients apart from the sickest is reasonable. Lack of improvement in prognostic scores within 7 days should prompt early consideration of transplantation. (3) Similar to other

Figure 3 Course of serum alanine transaminase activity from March 2014 to November 2017. Ms C was maintained on prednisolone (5–7.5 mg/daily) and azathioprine (1 mg/kg/day) throughout her disease course unless otherwise indicated. Maintenance rituximab infusions have been continued until present. ALT, alanine aminotransferase; PO, per mouth.

case series, rituximab was efficacious as salvage maintenance therapy in our patient with treatment refractory AIH. Significant biochemical and histological improvements in treatment refractory AIH patients are reported following rituximab therapy. Given limited studies/experience, rituximab in AIH should preferably be initiated in a specialist centre.

SPECIALITY CERTIFICATE EXAM (SCE) QUESTIONS

1. A 60 year-old woman presents with fatigue and joint pains for 6 weeks. She has a medical history of type 2 diabetes and hypertension. Her body mass index (BMI) is 36 mg/kg². Abdominal examination was unremarkable. Her investigations were as follows:- Hb 12 g/L, WCC 4.0×10^9 /L, platelets 250×10^9 /L INR 1.1, sodium 140 mmol/L, urea 3.1 mmol/L, creatinine 43 μ mol/L, Alb 32 g/L, ALT 294 U/L, AST 230 U/L, ALP 178 U/L, bilirubin 11 μ mol/L, ANA 1:1600 and IgG 20 g/L. Rest of the liver screen including viral screen was negative.

Liver biopsy: lymphoplasmacytic inflammation with moderate interface activity and no fibrosis.

Which one of the following treatment regimens would you initiate for her?

- Azathioprine 50 mg daily.
- Prednisolone 20 mg daily.
- Prednisolone 10 mg daily and azathioprine 50 mg daily.
- Budesonide 9 mg daily and azathioprine 50 mg daily.
- Tacrolimus 1 mg twice daily.

Answer: D

This woman has AIH based on elevated serum aminotransaminase activity, positive serology (ANA), hypergammaglobulinaemia and interface activity on liver biopsy. Budesonide in combination with azathioprine is an efficacious option for inducing and maintaining remission of AIH in a non-cirrhotic treatment-naïve patient and is associated with less corticosteroid-related side effects. Diabetes, hypertension and raised BMI may be exacerbated with prednisolone thus budesonide is a reasonable option

in this case. Azathioprine monotherapy is not recommended as initial therapy. Higher prednisolone doses may be recommended if used as initial monotherapy (e.g. 60 mg daily) or in combination with azathioprine (20–30 mg daily). Tacrolimus is reserved for AIH refractory to standard therapy.

2. A 26-year-old woman with a history of AIH with cirrhosis on combination therapy with azathioprine 50 mg daily and a tapering regimen of prednisolone 20 mg daily orally. After 6 months of treatment, blood tests were as follows:

Hb 126 g/L, WCC 8×10^9 /L, platelets 100×10^9 /L, INR 1.2, sodium 140 mmol/L, urea 4.0 mmol/L, creatinine 63 μ mol/L, Alb 40 g/L, ALT 100 U/L, AST 236 U/L, bilirubin 25 μ mol/L, ALP 190 U/L and IgG 30 g/L.

Her current treatment regimen included: prednisolone 10 mg daily and azathioprine 50 mg daily, and she is tolerating therapy.

Which of the following is the most appropriate next step in her management?

- Discontinue prednisolone and start budesonide 3 mg three times daily by mouth.
- Evaluate for liver transplantation.
- Discontinue azathioprine and start mycophenolate mofetil 1 g twice daily.
- Increase prednisolone to 20 mg daily and azathioprine to 150 mg daily.
- Continue with current treatment regimen.

Answer: D

This patient has on going biochemical activity as evidenced by elevated ALT, AST and IgG at 6 months while on standard therapy. Providing adherence has been confirmed and alternative diagnosis excluded (she has a mildly raised ALP although this can occur in AIH a MRCP may be helpful to exclude biliary disease) then the most appropriate next management step would be to optimise immunosuppression by increasing the prednisolone (20–30 mg) and azathioprine doses (2 mg/kg/day). Budesonide in a patient who is not responding to prednisolone is not recommended; in addition, it is contraindicated in cirrhosis or those with portal hypertension. As she is compensated, liver transplantation is not recommended currently. Although MMF has been investigated in small single-centre studies as first-line or salvage therapy, it is not standard therapy in AIH, and some studies where MMF has been used in azathioprine non-responders have been disappointing.

3. A 45-year-old woman with a 10-year history of AIH with cirrhosis on a long-term prednisolone 7.5 mg daily and azathioprine 150 mg daily (1.5 mg/kg/day). She has steroid side effects and a BMI 35 mg/kg². She was in biochemical remission 6 months ago; however, when you see her in the gastroenterology clinic, she is complaining of malaise and is icteric. Liver blood tests are as follows:-

ALT 980 U/L, AST 700 U/L, ALP 434 U/L, Bil 140 μ mol/L, Alb 42 g/L, INR 1.1 and IgG 21 g/L.

What treatment is the most appropriate option?

- Prednisolone 30 mg daily.
- Prednisolone 15 mg daily.
- Budesonide 9 mg daily.
- Increase azathioprine 2.5 mg/kg daily.
- Switch to 6-MP 1.5 mg/kg daily.

Answer: A

This patient has a flare of AIH. Although she is jaundiced, her liver synthetic function is normal. The appropriate management is to increase the prednisolone to a dose similar to induction (20–30 mg daily). Although the azathioprine dose may also need to be increased, corticosteroids are required acutely to induce remission. Budesonide is contraindicated in cirrhosis, and switching to 6-mercaptopurine (MP) is incorrect as it is not used to induce remission; its use is largely reserved for those patients that are azathioprine intolerant.

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