British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis

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ABSTRACT

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease which, if untreated, often leads to cirrhosis, liver failure and death. Major advances were made in its management based on controlled trials performed in England and the USA in the 1970s and 1980s. Unfortunately, in recent decades there has been a dearth of controlled clinical trials and, thus, many questions regarding the optimal management of this disease remain unanswered. Many promising newer immunosuppressive therapies await formal comparison with standard therapies and also many important details in relation to the application of standard therapies remain unclear. These guidelines describe the optimal management strategies in adults based on available published evidence, including the American Association for the Study of Liver Diseases practice guidelines for the diagnosis and treatment of AIH published in 2002 and recently updated.

A. INTRODUCTION

A1. Background

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease which, if untreated, often leads to cirrhosis, liver failure and death. The historical development of concepts in relation to AIH has recently been reviewed.¹ Major advances were made in its management based on controlled trials performed in England and the USA in the 1970s and 1980s. Unfortunately, in recent decades there has been a dearth of controlled clinical trials. Indeed, a recent systemic review² identified only 11 randomised controlled trials in AIH and, thus, many questions regarding the optimal management of this disease remain unanswered. Many promising newer immunosuppressive therapies await formal comparison with standard therapies and many important details in relation to the application of standard therapies remain unclear. In these guidelines we will try to describe the optimal management strategies in adults based on available published evidence including the American Association for the Study of Liver Diseases (AASLD) practice guidelines for diagnosis and treatments of AIH published in 2002³ and recently updated.⁴

A2. Grading of evidence and strength of recommendations

These are based on the GRADE system.⁵

Categories of evidence:

I At least one high-quality randomised controlled trial.

II-1 Non-randomised trials.

II-2 Cohort or case-control analytical studies.

II-3 Case series, uncontrolled observations.

III Opinions of respected authorities.

Grading of evidence:

A: High quality. Further research unlikely to change confidence in estimate of effect.

B: Moderate quality. Further research likely to influence confidence in estimate of effect and may change the estimate.

C: Low quality. Further research is very likely to influence confidence in estimate of effect and is likely to change the estimate.

D: Very low quality. Any estimate of the effect is uncertain.

Strength of recommendation:

1. Strong, based on grade of evidence, consensus of opinion and estimated benefit to patients.

2. Weak, based on poor quality evidence and/or divergence of opinion.

A3. Epidemiology and pathogenesis

The reported prevalence of AIH ranges from 10 to 17 per 100 000 in Europe and appears to be similar to that of primary biliary cirrhosis.^{6–10} No published prevalence data are available from the UK. AIH accounted for two of 121 patients presenting to a UK hospital with jaundice.¹¹

AIH has been described in many ethnic groups and seems to be a worldwide disease.^{12–17} Women are affected 3–4 times more frequently than men. Although initially thought to be particularly prevalent in young women, the disease appears to affect all age groups and, in the UK, may actually be more common in older than in younger patients.^{18 19}

Most cases of AIH have no identifiable precipitant. There have been occasional cases presenting shortly after documented infection with hepatitis A,^{20–22} hepatitis E,²³ cytomegalovirus^{24 25} and Epstein-Barr virus.²⁶ Sometimes the disease may be precipitated by a drug. Several cases of AIH have been associated with minocycline,^{27–31} interferon α ,^{32–35} nitrofurantoin^{36–38} and, recently, with infliximab.³⁹ There are anecdotal reports of associations with many other drugs including ezetimibe,⁴⁰ interferon β ,^{41 42} ornidazole,⁴³ diclofenac,⁴⁴ indomethacin,⁴⁵ terbinafine,⁴⁶ methyldopa,⁴⁷ ranitidine,⁴⁸ atorvastatin,⁴⁹ fluvastatin,⁵⁰ fibrates,⁵¹ adalimumab⁵² and after hepatitis A vaccination.⁵³ AIH has also been reported after herbal medicines.^{54 55} However, many of these associations may be coincidental.

In a recent study of 261 patients with AIH,⁵⁶ 24 (9%) were associated with drug ingestion—either nitrofurantoin or minocycline in most cases. Atypically for drug-induced liver injury, many patients with drug-related AIH had been taking the drug from many months or years. Other features included absence of cirrhosis and of

disease recurrence following withdrawal of immunosuppressive treatment.

The immunopathogenesis of AIH has also been reviewed in detail by Vergani *et al.*^{57–59} While not fully understood, it is possible to consider the pathogenesis of AIH as an interaction between a trigger such as a drug or virus and the environment in a genetically susceptible individual.⁶⁰

B. PRESENTATION AND DIAGNOSIS

B1. Modes of presentation

The possibility of AIH is raised by persistently abnormal serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values, usually accompanied by hyperglobulinaemia. About 25% of patients with AIH are asymptomatic at diagnosis,^{10 19 61–64} including some with cirrhosis.⁶⁵ Patients commonly present with fatigue and general ill health, anorexia and weight loss, sometimes dating back years. Nausea is often a prominent symptom and amenorrhoea is common. Joint pains, sometimes flitting, are reported in 30–60% of patients, although joint swelling is uncommon. Rarer features include a maculopapular skin rash and unexplained fever.⁶¹

The traditional view of AIH is that of a chronic disease, diagnosis of which in the past has required serum transaminase elevations over a 3–6-month period. However, in about 40% of cases AIH presents as ‘acute hepatitis’ with jaundice, often preceded by anorexia, nausea and influenza-like symptoms.^{19 61 66} Serum AST levels may be several thousands. Such patients, if treated promptly, have a good outlook.^{67 68}

Up to 50% of patients, even with an insidious onset of disease, may be clinically jaundiced or report previous episodes of icterus.⁶¹ About 30% of patients have cirrhosis at presentation^{10 19 61 62} so some patients (especially the elderly¹⁹) may present with ascites, suggesting liver decompensation and/or a variceal bleed.

AIH sometimes presents with acute liver failure.^{69–73} Some patients classified as having cryptogenic or seronegative fulminant hepatitis are likely to be patients with an acute presentation of AIH. In one series of acute liver failure, 30% had serum autoantibodies.⁷⁴ In some of these the aetiology of the acute liver failure was clearly not autoimmune and the autoantibodies may have been epiphenomena. However, five of the 15 patients with otherwise unexplained acute liver failure⁷⁴ met the International Autoimmune Hepatitis Group (IAIHG) criteria for probable AIH (see section B2c).

When AIH presents as acute hepatitis the liver histology may be atypical: lobular hepatitis and centrilobular necrosis are common and cirrhosis less common.^{66 67 75} Furthermore, serum autoantibodies are sometimes absent initially but develop later. Other causes of acute hepatitis (viral, drug-induced, Wilson’s disease) need to be carefully excluded. In these sometimes very ill patients a definitive diagnosis of AIH (see section C2) and institution of immunosuppressive treatment should not await demonstration of ‘chronicity’ by monitoring liver tests over weeks/months. Patients with liver failure should be referred to a liver transplant centre.

In 30–50% of patients AIH is associated with other ‘auto-immune’ diseases (table 1) which may point to the diagnosis. Its occasional co-presentation with coeliac disease^{10 82–85} is important to recognise because, otherwise, malabsorption of immunosuppressive medication may delay effective treatment.

The presentation of AIH may vary between different races. In some reports African-American patients were younger and had a higher prevalence of cirrhosis and liver failure at presentation than those of Northern European origin.¹⁷ Non-Caucasian patients had more cholestatic biochemical and histological

Table 1 Diseases associated with autoimmune hepatitis (AIH)

Disease	References	Prevalence in AIH (%)
Primary biliary cirrhosis	76	4–14
Primary sclerosing cholangitis	76–78	2–8
Inflammatory bowel disease	10 63 79–81	2–8
Coeliac disease	10 62 82–85	1–2
Rheumatoid arthritis	62 86	2–5
Mixed connective tissue disease	62	2.5
Sjogrens	10 62 87	1–4
Systemic lupus erythematosus	10 62 88	1–2
Fibrosing alveolitis	89	
Glomerulonephritis	90	
Thrombocytopenia	91	
Haemolytic anaemia	92	
Thyroiditis	10 61 62	10–23
Diabetes	10	7–9
Psoriasis	10	3
Vitiligo	93	
Glomerulonephritis	10	1
Uveitis	94	
Polymyositis	95	
Multiple sclerosis	62 96	1
Mononeuritis multiplex	97	
Antiphospholipid syndrome	98	

features and a higher rate of non-response,¹³ which was not explained by differences in access to medical care. South American patients also tend to have more severe disease than their North American counterparts,⁹⁹ whereas Japanese patients tend to have late onset disease that responds to less potent immunosuppression.^{100 101}

B2. Diagnosis

(a) Laboratory features

No pathognomonic features exist for AIH and therefore the diagnosis rests on a combination of compatible biochemical, immunological and histological features together with exclusion of other liver diseases. Despite the formulation of widely accepted criteria for the diagnosis of AIH by the IAIHG in 1992,¹⁰² their revision in 1999¹⁰³ and the recent proposal of simplified criteria,^{104 105} the diagnosis is sometimes not straightforward and requires considerable clinical expertise.

The findings of (a) elevated serum ALT and AST activity; (b) raised serum immunoglobulins; (c) negative serum tests for viral hepatitis; and (d) high titres of circulating autoantibodies (titres of $\geq 1:40$ except in children where lower titres may be diagnostic) are the key laboratory findings of AIH.¹⁰⁶ Serum AST and ALT, bilirubin and γ -glutamyl transpeptidase elevations are variable in AIH.¹⁰⁶ Serum aminotransferases may normalise either on treatment or spontaneously, even with continuing severe hepatic inflammation on biopsy. Previously, a more than threefold increase in either the AST or ALT level was required for the diagnosis of AIH, although this is no longer so.^{102 103} Serum alkaline phosphatase is normal or only mildly raised; a more than twofold elevation suggests an alternative or additional diagnosis (see Overlap syndromes, section G3).

Increased serum γ -globulin and immunoglobulin (Ig) G levels are found in about 85% of patients.^{19 61 107} An increase in serum IgA levels suggests steatohepatitis (alcoholic or non-alcoholic) or drug-induced liver injury rather than AIH, whereas an increase in IgM levels is more characteristic of primary biliary cirrhosis (PBC).¹⁰⁶ Immunoglobulin levels typically return to normal during treatment.

In the serum of most patients with AIH there are detectable non-organ-specific autoantibodies such as antinuclear antibody (ANA) and anti-smooth muscle antibody (ASMA), although the exact function of these antibodies remains unknown. A more complete discussion of the relationship between the full spectrum of autoantibodies, molecular mimicry and autoimmune liver disease is given in reviews by Bogdanos *et al.*^{59 108}

AIH has been categorised into two distinct disease subtypes based on these antibody profiles. Type 1 AIH is associated with the presence of either ANA or ASMA in the serum and accounts for about 75% of patients.^{10 19 61} The ANAs react with histones and DNA and typically show a homogenous staining pattern on immunofluorescence, similar to that seen in systemic lupus erythematosus. Speckled and nuclear work patterns are also seen but are not specific for AIH; they are also found in PBC. Although other staining patterns are seen, these are not known to be of significance.¹⁰⁹ Serum antibodies to double-stranded DNA are found in 15% of patients with AIH. When present, they are highly specific for either AIH or systemic lupus erythematosus. Smooth muscle antibodies react to several cytoskeletal elements including F-actin. Although titres of autoantibodies fluctuate during treatment, disease activity does not correlate closely with titres.¹¹⁰

Type 2 AIH is associated with the presence of either anti-liver kidney microsomal-1 (LKM-1) or anti-liver cytosolic-1 (LC-1) antibodies.^{83 102 103 106} Anti-LKM-1 antibodies target several epitopes of hepatic cytochromes, specifically cytochrome P-450 2D6 (CYP2D6).^{111 112} Moreover, cross-reactivity has been demonstrated between a number of viruses known to infect humans, including hepatitis C virus (HCV).^{111 112} The implications of these findings are that viruses may mimic self and, by cross reactivity with P450 epitopes, trigger hepatic autoimmunity.¹¹² Type 2 AIH accounts for less than 10% of all cases in northern Europe and North America but is commoner in southern Europe.⁶² The clinical phenotypes of disease associated with type 1 and type 2 AIH are summarised in table 2.

In addition, 10–30% of patients with AIH will have detectable antibodies to soluble liver antigen or liver pancreas antigen;

these were shown to be the same antigen which is now designated SLA/LP. These antibodies are specific for AIH, so may also be a useful adjunct in the diagnosis of type 1 AIH when conventional autoantibodies are negative.¹¹³ Controversy has existed in relation to the existence of a third subtype of AIH defined by the presence of these anti-SLA/LP antibodies,¹¹⁴ but these patients display the typical clinical and pathological hallmarks of type 1 AIH and should be treated as such.^{106 113 115–117} Although antibodies to actin and atypical peripheral anti-neutrophilic cytoplasm (p-ANCA) are also frequently seen in type 1 AIH,^{118 119} their applicability is limited by their lack of specificity.^{110 120}

Anti-mitochondrial antibodies are occasionally identified in patients with AIH. Previously it was thought that poor interpretation of staining patterns on immunofluorescence of proximal renal tubules and on liver sections was responsible for the interpretation of LKM-1 positivity as detectable mitochondrial antibodies, although it is clear that such patients do exist. In large series,^{121 122} 8–12% patients with AIH had detectable anti-mitochondrial antibodies throughout their AIH disease course, without any evidence of PBC on serial liver biopsies. This phenomenon has also been reported in smaller numbers of patients in the UK and shows that careful interpretation of available serology is required in all patients.⁶¹

The IAIHG Autoimmune Serology Committee has published guidance on how to test for autoantibodies relevant to liver disease,¹²⁰ including handling of substrates, use of samples, dilution and staining patterns. Indirect immunofluorescence on fresh sections of the liver, kidney and stomach tissues from rodents (especially rat) is the preferred first-line screening test for ANA and ASMA antibodies, although ELISAs have also been developed for anti-LKM and anti-SLA antibodies.

In most centres 10–25% of patients with AIH will have undetectable or very low titres (<1:40) of conventional serum autoantibodies, and these have previously been classified as 'cryptogenic chronic hepatitis'.^{123–125} AIH may still be diagnosed using the IAIHG criteria on the basis of other compatible biochemical, serological and histological findings and, in practice, such patients are indistinguishable clinically from patients who present with conventional autoantibodies^{126–128} and also respond to immunosuppression.

Non-organ-specific autoantibodies are not specific to AIH. They are found in a minority of patients with PBC and with primary sclerosing cholangitis⁷⁶; 20–40% of patients with alcoholic liver disease have low ANA or ASMA titres.^{129 130} In patients with non-alcoholic fatty liver disease, 25% have serum positive for ASMA or ANA and 20% meet the IAIHG criteria for probable or definite AIH prior to biopsy.¹³¹ ANA positivity may also occur in hepatocellular carcinoma.

Up to 25% of patients with AIH have raised serum α -feta protein on presentation.¹³² This is only rarely associated with hepatocellular carcinoma; it is a manifestation of hepatocyte regeneration and normalises with resolution of the inflammation following immunosuppression.

(b) Liver histology

The role of liver biopsy in the diagnosis of AIH has been affirmed by the IAIHG with regard to both the revised and simplified criteria.^{103 104} Biochemical and immunological blood tests are insufficiently specific on their own for a definite diagnosis of AIH. For example, 20% of patients with biopsy-proven non-alcoholic fatty liver disease meet the criteria for a probable diagnosis of AIH prior to liver biopsy.¹³¹ Thus, liver biopsy is recommended in all patients with suspected AIH unless there is

Table 2 Classification of autoimmune hepatitis (AIH) based on autoantibody profiles of patients

Feature	Type 1 AIH	Type 2 AIH
Characteristic autoantibodies	ANA ASMA Anti-actin antibody Anti-SLA/LP antibodies 25% of patients negative ANA	Anti-LKM-1 antibody Anti-LC-1 antibody
Geographical variation	Worldwide	Worldwide
Age at presentation	All ages	Usually childhood and young adulthood
Sex (F:M)	3:1	10:1
Clinical phenotype	Variable	Generally severe
Histopathological features at presentation	Broad range: mild disease to cirrhosis	Generally advanced, $\uparrow$ inflammation/cirrhosis common
Treatment failure	Rare	Common
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	Approximately 100%

Although immunofluorescence is the traditional method for measuring the repertoire of conventional autoantibodies in AIH, many laboratories (especially those in the USA) are increasingly using ELISA-based methods, especially for anti-LKM antibodies. In relation to anti-LKM-1 antibodies, these may be erroneously reported as detectable anti-mitochondrial antibodies. ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; anti-LC, anti-liver cytosol; anti-LKM, liver kidney microsomal antibody; anti-SLA/LP, soluble liver antigen/liver pancreas antigen.

severe comorbidity or a significant contraindication. Review of the histology by an experienced liver histopathologist is recommended.

Interface hepatitis, formerly called piecemeal necrosis (inflammation of hepatocytes at the junction of the portal tract and hepatic parenchyma), is a typical feature of AIH.^{102–104} It occurs in 84–98% of patients^{19 61 133} but may also be seen in patients with drug-induced, viral and other hepatitis.^{133 134} Additionally, the presence of periportal lymphocytic or plasma cell-rich lymphoplasmacytic inflammation, hepatocyte swelling and necrosis is common.^{135–137} However, 34% of patients with AIH have few or no portal or acinar plasma cells.^{133 136} A more diffuse or panacinar hepatitis is less common; it may occur in either AIH of acute onset or in disease that has relapsed following treatment withdrawal.^{133 138 139} Occasionally the abnormalities are mainly in the centrolobular zone.¹⁴⁰

Pyknotic cell necrosis and ballooning degeneration of hepatocytes are present in 39% of all patients with AIH. Other liver biopsy findings in AIH include perivenular/zone 3 necrosis with or without portal-based inflammation^{70 141 142} and giant multinucleated hepatocytes.^{143 144}

Granulomatous inflammation, cholangitis, siderosis, copper deposition and steatosis or steatohepatitis are sometimes seen but, if prominent, make a diagnosis of AIH less likely and receive a negative rating in the IAIHG classification.¹⁰³ However, lymphocytic cholangitis and/or a mixed inflammatory infiltrate encircling and infiltrating bile ducts has recently been described in 10% of patients with AIH.^{145–147}

Liver biopsy also provides information on prognosis. One-quarter to one-third of patients have cirrhosis at presentation,^{10 19 61 62} although cirrhosis is uncommon in patients with drug-related AIH.⁵⁶ Patients with cirrhosis and those with bridging necrosis at diagnosis have a poorer prognosis than those without.^{61 64 148–151} Despite this, patients with cirrhosis and AIH usually have steroid-responsive disease and warrant proactive treatment.

(c) Diagnostic scoring systems

The IAIHG scoring system, originally published in 1993¹⁰² and revised in 1999,¹⁰³ was designed as a research tool to compare study populations better in clinical trials. It uses components that in isolation are not unique to AIH (tables 3 and 4). By weighting of clinical, biochemical and histological parameters in conjunction with responsiveness to corticosteroid therapy,

patients are categorised into a 'definite AIH' group based on a composite score of >15 points before treatment or >17 points after treatment. Lower scores (10–15 points before treatment or 12–17 points after treatment) designate a diagnosis of 'probable AIH'. Two points are awarded for a biochemical response to corticosteroid treatment; however, the required number of points for a diagnosis of AIH then increases by two. A 'positive' response to corticosteroids is therefore neutral with regard to a diagnosis of AIH by the revised IAIHG criteria, but non-response to steroids makes the diagnosis less likely. The revised IAIHG system has been validated in independent groups^{152–154} and is now widely used in clinical practice. Although the points-based IAIHG criteria distinguish between probable and definite AIH, they appear to be the same disease with regard to outlook and response to immunosuppression.^{155 156}

Recently, a simplified scoring system designed for rapid clinical use has been created using the parameters of detectable serum autoantibodies, serum IgG, liver histology and exclusion of viral hepatitis.¹⁰⁴ The score was found to have a sensitivity of >80% and a specificity of >95% at the cut-off levels of ≥7 points, suggesting that it can result in a reliable diagnosis of definite AIH.^{104 105 154 157 158} However, this system is more likely to result in exclusion of atypical cases^{105 154 157} than the revised IAIHG system. The simplified scoring system, which requires further prospective validation, is summarised in table 5.

(d) Differential diagnosis

Given its wide range of clinical manifestations and of characteristic but not pathognomonic laboratory and histological abnormalities, AIH can mimic many other liver diseases and vice versa. It is particularly important to distinguish AIH from other potentially treatable conditions associated with immune activation and/or necroinflammation on liver biopsy such as alcoholic liver disease, non-alcohol fatty liver disease, Wilson's disease, chronic HCV infection and drug-induced injury.

Occasionally, despite full investigative work-up and the IAIHG classification system, a diagnosis of AIH remains in doubt. Under these circumstances it may be reasonable to treat the patient with corticosteroids or to monitor without treatment, depending on disease severity. As discussed above, the failure of serum transaminases to fall with corticosteroids makes AIH less likely. If serum transaminases normalise, it may then be reasonable to phase out corticosteroids, monitor the liver tests and repeat the biopsy in the event of biochemical/clinical

Table 3 Descriptive criteria for diagnosis of autoimmune hepatitis (AIH): adapted from the revised International Autoimmune Hepatitis Group (IAIHG) criteria, 1999¹⁰³

Features	Definite AIH	Probable AIH
Liver histology	Interface hepatitis of moderate or severe activity with or without lobular hepatitis or bridging necrosis. No biliary lesions, granulomas or other prominent changes suggestive of a different aetiology	Same as for definite AIH
Laboratory features	Any serum aminotransferase abnormality, especially if alkaline phosphatase activity normal. Normal levels of alpha-1-anti-trypsin, copper and caeruloplasmin	As for definite AIH but patients with abnormal levels of copper and caeruloplasmin may be included contingent on the exclusion of Wilson's disease by appropriate other investigations
Serum immunoglobulins	Globulin, γ -globulin or IgG concentrations >1.5 $\times$ upper normal limit.	Any elevation in globulin, γ -globulin or IgG concentrations above the upper normal limit
Serum autoantibodies	ANA, SMA or anti-LKM-1 antibodies at titres $\geq$ 1:80. Lower titres acceptable for children, especially anti-LKM-1. Negative AMA.	As for definite AIH but at titres $\geq$ 1:40, or presence of other specified aut antibodies
Viral markers	No markers of current infection with hepatitis A, B and C viruses	Same as for definite AIH
Other exposures	Average alcohol consumption <25 g/day. No recent use of known hepatotoxic drugs	Average alcohol consumption <50 g/day and no recent use of known hepatotoxic drugs. Patients who have consumed larger amounts of alcohol or have had exposure to known hepatotoxic drugs may be considered if ongoing damage after abstinence/withdrawal

AMA, antimitochondrial antibodies; ANA, antinuclear antibody; SMA, smooth muscle antibody; LKM-1, liver kidney microsomal-1 antibody.

relapse. Relapse following corticosteroid withdrawal is positively weighted in the IAIHG criteria and this, together with the absence of a relevant drug history and what are sometimes more typical features on the repeat biopsy, may confirm a diagnosis of AIH.

Recommendations: diagnosis (grade B)

1. AIH has protean clinical manifestations and should be considered in any patient with liver disease (II-3/B1).
2. A full previous medical, alcohol, medication and hepatitis exposure history is essential for diagnosis, as is a full 'non-invasive' liver screen to further exclude viral and metabolic liver diseases (II-3/B1).
3. Liver biopsy is important for the diagnosis of AIH and also provides important prognostic information. It should be performed unless there are active contraindications (II-3/B1).
4. The revised IAIHG criteria constitute a useful guide if the diagnosis of AIH is in doubt. However, the classification of occasional atypical cases remains difficult. In some patients a trial of steroids should be considered (II-3/B1).

C. INITIAL TREATMENT

C1. Who should treat?

Given a prevalence of 1/10 000, it is likely that there will be about 25 patients with AIH in an area served by an average UK district general hospital. Management of all patients in specialist liver units is not necessary. Ideally, patients should be under the supervision of a hepatologist or a gastroenterologist with an interest in liver disease. They should be monitored in a designated liver clinic, ideally with the help of a specialist gastroenterology or liver nurse. At the very least, consideration should be given to having all patients under the care of one or two designated consultants. Arrangements should be in place for regular monitoring of immunosuppressive therapy in either primary or secondary care (see section C5). Monitoring should be lifelong. There should be a forum for regular discussion of problematic patients. Finally, there should be easy access to (a) an immunology laboratory that can assay (and quantify results in titres of) all relevant serum antibodies; (b) a specialist liver histopathologist; (c) a hepatologist with expertise in the management of AIH; and (d) a liver transplant centre. Finally, there should be regular audit of outcomes.

C2. Should everyone be treated?

Patients with AIH and moderate or severe inflammation (defined as one or more of serum AST >5 times normal, serum globulins >2 times normal, liver biopsy showing confluent necrosis) should be offered immunosuppressive treatment because of the clear survival benefits in these patients, demonstrated in the trials discussed below. In patients not meeting these criteria, treatment should also be considered if (a) the patient has symptoms (at least on a trial basis to see if they improve); (b) in patients with AIH and established cirrhosis on liver biopsy, since these are adverse prognostic features^{61 64 149 159}; and (c) in younger patients, in the hope of preventing cirrhosis development over several decades.

The benefits of immunosuppressive treatment in asymptomatic older patients with mild interface hepatitis (Ishak necroinflammatory score 4–6¹³⁷) on biopsy are not established and

Table 4 Modified diagnostic criteria for the diagnosis of autoimmune hepatitis (AIH)¹⁰³

Parameter/feature	Score
Female sex	+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 LKM-1	
>1:80	+3
1:80	+2
1:40	+1
<1:40	0
AMA positive	–4
Hepatitis viral markers	
Positive	–3
Negative	+3
Drug history	
Positive	–4
Negative	+1
Average alcohol intake	
<25 g/day	+2
>60 g/day	–2
Liver histology	
Interface hepatitis	+3
Predominantly lymphoplasmacytic infiltrate	+1
Rosetting of liver cells	+1
None of the above	–5
Biliary changes	–3
Atypical features	–3
Other autoimmune disease(s)	
In either patient or first-degree relative	+2
Optional additional parameters	
Seropositivity for other defined antibodies	+2
HLA DR3 or DR4	+1
Response to therapy	
Remission alone	+2
Remission with relapse	+3
Interpretation of aggregate scores	
Pre-treatment	
Definite AIH	>15
Probable AIH	10–15
Post-treatment	
Definite AIH	>17
Probable AIH	12–17

AMA, antimitochondrial antibodies; ANA, antinuclear antibody; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LKM-1, liver kidney microsomal-1 antibody; SMA, smooth muscle antibody.

a decision not to treat might be justified, especially if there are relative contraindications to the use of steroids. Ten-year survival in such untreated patients with mild disease was 90% in one study¹⁶⁰ and 67% in another study (of only eight patients).¹⁶¹ In another uncontrolled study, untreated asymptomatic patients had similar survival to those receiving immunosuppression. However, 25% of these patients developed symptoms.⁶⁴ Therefore, if untreated, patients with mild AIH should be monitored and, if symptoms develop or if liver tests remain abnormal, repeat liver biopsy should be considered after 2–3 years.

Table 5 Simplified diagnostic criteria for the diagnosis of autoimmune hepatitis (AIH): adapted from Hennes *et al*¹⁰⁴

Feature/parameter	Discriminator	Score
ANA or SMA+	≥1:40	+1*
ANA or SMA+	≥1:80	+2*
Or LKM+	≥1:40	
Or SLA+	Any titre	
IgG or immunoglobulin level	>Upper limit of normal	+1
	>1.1× Upper limit	+2
Liver histology	Compatible with AIH	+1
	Typical of AIH	+2
Absence of viral hepatitis	No	0
	Yes	+2

≥6 points: probable AIH; ≥7 points: definite AIH.

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

ANA, antinuclear antibody; LKM, liver kidney microsomal antibody; SLA, soluble liver antigen; SMA, smooth muscle antibody.

Spontaneous recovery of AIH may occur and it is difficult to justify treating patients with normal serum transaminases and globulin/IgG and with minimal necroinflammatory activity on liver biopsy. A previous history of spontaneously resolving hepatitis is found in 20% of patients re-presenting with AIH.¹⁶² Such apparently resolving patients should be followed up because severe AIH relapse may occur. Drug-related AIH may resolve on drug withdrawal, although this is poorly documented because most reported cases have received immunosuppressive treatment.⁵⁶

Recommendations

1. Patients with moderate or severe AIH, young patients, those with symptoms and those with cirrhosis and even mild histological activity should be offered immunosuppressive treatment (I/A1).
2. The benefits of treating mild (Ishak necroinflammatory score <6) AIH in older asymptomatic patients are not established. Treatment is not indicated if there is no biochemical or histological evidence of disease activity (III/C2).

C3. Standard regimes

Standard induction treatment for patients with moderate or severe AIH (detailed in figure 1) has been firmly established by controlled trials published in the early 1970s and recently reviewed.² Two trials from London^{163–165} demonstrated the efficacy of prednisolone 15–20 mg/day over placebo and over azathioprine alone in improving serum liver tests and globulin and, more importantly, 2–4-year survival. A contemporaneous study from the Mayo Clinic¹⁶⁶ demonstrated the superiority of two regimes: prednisolone alone (starting at 60 mg/day, reducing to 20 mg/day over 4 weeks) and prednisolone (in half this dose) combined with azathioprine 50 mg/day over placebo and over azathioprine alone with regard to improvement in liver tests, liver histology and survival. These two ‘active’ regimes had similar beneficial effects but the combination regime was associated with fewer side effects than prednisolone alone (10% vs 44%). In patients receiving placebo, mortality exceeded 50%.

In the Mayo Clinic study, 80% of patients on either prednisolone alone or prednisolone plus azathioprine combination therapy achieved a serum ALT of less than twice the upper limit of normal within 6 months. Histological remission (loss of

interface hepatitis on 6-monthly liver biopsy) lagged behind clinical and biochemical remission by several months, but was achieved in 75% of patients after 18 months of active treatment (in contrast to only 20% of those given azathioprine alone or placebo).

In a follow-up controlled study¹⁶⁷ the Mayo Clinic group evaluated a fifth treatment strategy in AIH—namely, prednisolone alone, again starting at 60 mg/day but tapered and titrated to maintain serum transaminases at less than twice the upper limit of normal. This regime improved clinical symptoms and serum liver enzymes as well as the other two active regimes and, because the mean maintenance dose of prednisolone was only 10 mg/day, side effects were less severe than the initial prednisolone regime (maintaining dose at 20 mg). However, histological remission was achieved after 24 and 36 months treatment in only 4/16 and 3/9 cases on the titrated prednisolone regime compared with 13/19 and 11/14 of patients receiving prednisolone 20 mg/day and 16/20 and 16/17 receiving the prednisolone/azathioprine combination regime. The significance of continuing activity on follow-up liver biopsy is discussed below. Unfortunately, the combination of titrated dose prednisolone and azathioprine has not been evaluated.

HBV_sAg positivity was found in 4% and 14% of subjects in two of these studies^{165 166} and was not tested in the third.¹⁶³ Inevitably, none of the patients in these studies had HCV excluded. However, the high prevalence of autoantibodies and the raised serum globulins in nearly all the patients in the earlier trials suggest that the vast majority indeed had AIH. Furthermore, only about 5% of patients previously considered to have type 1 AIH were positive for HCV.¹⁶⁸

These studies therefore suggest that, of the regimes evaluated, the best one for most patients (combining maximum efficacy with minimal side effects) is the prednisolone/azathioprine combination regime (figure 1). Until recently no other treatment strategy had been compared with and been shown to be superior or equivalent to this regime. In a recent multicentre randomised controlled trial,¹⁶⁹ patients with AIH and without cirrhosis given budesonide 9 mg/day plus azathioprine 1–2 mg/kg/day for 6 months achieved normalisation of serum transaminases more quickly and had fewer side effects than those given prednisolone plus azathioprine (see also section F). In contrast to the early trials in AIH, viral hepatitis was rigorously excluded. However, no follow-up histology data were presented and the blinded phase of the trial lasted only 6 months. Thus, more long-term results are required for budesonide and, currently, the recommended initial treatment for most patients remains prednisolone plus azathioprine. However, budesonide 9 mg/day plus azathioprine may be considered in non-cirrhotic patients with severe (actual or anticipated) steroid-related side effects such as psychosis, poorly controlled diabetes or osteoporosis (see section C4).

Several variants of the initial prednisolone plus azathioprine regime have been proposed:

1. Prednisolone is sometimes started in a higher dose than 30 mg/day (with azathioprine). This dose is recommended in the AASLD guidelines,⁴ however up to 1 mg/kg/day^{73 170} plus azathioprine has been proposed recently. The prednisolone is then reduced gradually to 10 mg/day over 2–3 months as serum transaminases fall. Such a strategy is likely to cause more steroid-related side effects and this may be problematic in frail elderly patients. However, in non-cirrhotic patients it may result in more rapid normalisation of serum transaminases (77% after 6 months in one preliminary report¹⁷⁰), in contrast to only 39% with standard dose prednisolone in

Figure 1 Suggested induction strategy for autoimmune hepatitis (AIH). ALT, alanine aminotransferase; AST, aspartate aminotransferase; TPMT, thiopurine methyltransferase.

- a recent randomised trial.¹⁶⁹ However, while prolonged failure of transaminases to normalise^{171–173} and absence of an early fall^{68 174} are both associated with worse outcomes (see below and also table 6), the rate of normalisation of transaminases is not adequately established as a prognostic factor to be a ‘hard’ treatment endpoint. This strategy therefore needs a firmer evidence base.
2. Azathioprine is often started a few weeks after the prednisolone. Although not evidence-based, this may be reasonable, especially if there is diagnostic doubt. A rapid improvement of liver tests in response to prednisolone may be reassuring in practice in relation to a diagnosis of AIH, although such a response does not in itself increase the likelihood of AIH by the revised IAHG criteria (see section C2). Also, institution of azathioprine may be delayed pending results of thiopurine methyltransferase (TPMT) assay (see section C4).
 3. High-dose ‘pulse’ prednisolone (90 mg every 5 days) without azathioprine was evaluated in the hope of reducing steroid-associated side effects but was shown to be inferior to the combination regime in inducing remission.¹⁸⁶
 4. Although in the Mayo Clinic trials azathioprine was used in a dose of 50 mg/day, in Europe it is typically started at the (usually) higher dose of 1 mg/kg/day. In some centres prednisolone plus azathioprine in a still higher dose (up to 2 mg/kg/day) is used as initial treatment. The recent AASLD guidelines⁴ recommend prednisolone plus azathioprine 1–2 mg/kg/day. However, use of azathioprine in initial doses exceeding 1 mg/kg/day is not evidence-based.

5. The combination of azathioprine 1 mg/kg and titrated dose prednisolone (to maintain normal ALT) may be as effective as the standard regime (and have fewer side effects) but has not been evaluated.

C4. Side effects

In the above trials^{163 165 166} side effects with the prednisolone-only regimes were problematic. Cushingoid features developed in 20–50% of patients, diabetes in 15–20% and psychosis, hypertension, cataracts and osteoporotic vertebral collapse in 5–10%. These were less common (5%) on the combination regime. However, subsequent studies of patients on this regime^{187 188} suggest about a 30% prevalence of steroid-related side effects including, most notably, weight gain which improves on stopping the prednisolone. In patients without cirrhosis in whom severe side effects such as psychosis, difficult-to-control diabetes or severe osteoporosis preclude the use or continued use of prednisolone, azathioprine alone is ineffective.¹⁶⁶ In these patients, budesonide 9 mg/day plus azathioprine 1 mg/kg/day may be considered based on the results of a recent controlled trial (see section F).¹⁶⁹ However, osteoporosis should largely be preventable by routine prescription of calcium and vitamin D and by selective use of bisphosphonate therapy (see sections C5 and E).

About 25% of patients with AIH develop side effects on azathioprine, requiring withdrawal of the drug in about 10% of cases.^{19 64 188–190} Side effects are more common in patients with cirrhosis.¹⁸⁹ About 5% of patients develop a severe early reaction with fever, arthralgia, a skin rash and influenza-like

symptoms.¹⁹¹ Approximately 10–20% of patients develop nausea and anorexia, which may improve despite continuation but may require dose reduction or withdrawal. Rarer side effects include skin rash, pancreatitis¹⁹² and cholestatic hepatitis.¹⁹³

The most serious side effect of azathioprine is marrow depression, usually manifest as a fall in white cell and neutrophil count which require regular monitoring (see section C5). The risk of marrow toxicity can sometimes be predicted by genotyping for or measuring activity of the enzyme thiopurine methyltransferase (TPMT), which catalyses conversion of 6-mercaptopurine (the active metabolite of azathioprine) into inactive products.¹⁹⁴ About one in 300 people is homozygous for a low-activity allele of the gene and has very low enzyme activity. In these patients active 6-mercaptopurine metabolites accumulate and serious toxicity is common, although it may be avoided by use of low doses with careful monitoring of metabolites in the blood.¹⁹⁵ Heterozygosity for the low-activity allele with intermediate enzyme activity is found in about 10% of people. Studies in patients with AIH suggest that neither heterozygosity for the low-activity allele, modest reductions in TPMT activity nor 6-mercaptopurine metabolite levels are reliably predictive of azathioprine efficacy or toxicity.^{189 190 196} However, TPMT measurement should be considered to exclude homozygous TPMT deficiency, and this is recommended in patients with pre-existing leucopenia (usually due to hypersplenism).

In patients with severe TPMT deficiency and in those intolerant of azathioprine, the prednisolone-only regime or a lower dose of prednisolone combined with mycophenolate (see section F4) may be used. The prednisolone-only regime may also be used in patients with a recent history of cancer because of a potential (though unproven) link between azathioprine and malignancy (see section D1). It may also be preferred in those with severe cytopenia due to hypersplenism or coincidental blood diseases. Moderate leucopenia, common in cirrhosis, probably does not increase the risk of azathioprine-related marrow depression *per se* but is likely to complicate haematological monitoring.

C5. Monitoring and additional management

Patients should be asked about and/or tested for immunity to hepatitis A and hepatitis B infection and susceptible patients should be offered vaccination as soon as possible.

Patients on combination therapy should have baseline and weekly on-treatment monitoring of liver tests, blood sugar and blood count for 4 weeks and then 1–3 monthly thereafter, depending on the responses. All should receive calcium and vitamin D supplementation. DEXA bone density scans should be performed at commencement of prednisolone-containing treatments and repeated at 1–2-yearly intervals while prednisolone treatment is continued (see section E). Screening for glaucoma and cataracts should also be considered after 12 months prednisolone treatment.

C6. Endpoints of initial treatment

In 80–90% of patients with moderate/severe AIH, serum ALT falls after starting treatment. Usually the fall commences within 2 weeks. As transaminases fall, clinical symptoms resolve and liver function (albumin, bilirubin and prothrombin time) shows marked improvement within 3–6 months of starting prednisolone with or without azathioprine. Although ascites and encephalopathy may also resolve, such patients should be discussed with a transplant centre.

In 5–10% of patients liver tests do not improve. Such patients tend to be younger,¹⁹⁷ to have an acute presentation with severe jaundice and a high model for end stage liver disease (MELD)

score¹⁹⁸ which shows little change over 7 days of corticosteroid therapy.¹⁹⁹ In a recent report, only one of 12 patients with AIH presenting as fulminant liver failure improved with corticosteroid treatment and 10 required liver transplantation.⁷² Failure to respond may be associated with confluent necrosis on biopsy.¹⁵¹ Non-response may be more common in non-Caucasian patients.¹³

In non-responding or very slowly responding patients without liver failure, prednisolone may be increased to 60 mg/day and azathioprine to 2 mg/kg/day if tolerated.²⁰⁰ The possibilities of non-compliance and of malabsorption should be considered, as should admission to hospital for intravenous hydrocortisone or methylprednisolone. Of alternative drugs (see section F), tacrolimus may be the most useful¹⁹⁹ but patients are sometimes resistant to all medications. Referral to or discussion with a physician with expertise in treating AIH should be considered.

If there is confluent necrosis on the biopsy, evidence of liver failure or if the serum bilirubin and MELD score do not improve rapidly in patients with jaundice, the chances of mortality are high^{71 72 151 197–199} and early referral to a liver transplant centre is recommended.

As the serum ALT falls, the initial dose of prednisolone should be reduced to 10 mg/day, usually by 5 mg/day every week. Biochemical remission in the initial Mayo Clinic trials and in many subsequent studies was defined as serum AST less than twice the upper limit of normal and was achieved by 80% of patients on prednisolone-based regimes. In most patients serum transaminases eventually fall to within the normal range,^{155 171 177 182} although this may take 12 months or more. Somewhat confusingly, the IAIHG adopted two definitions of remission—a fall to less than twice normal and full normalisation of serum AST.¹⁰³ However, it is now generally agreed (and explicit in the AASLD guidelines)⁴ that complete normalisation of transaminases should be the aim. This is because even mild persisting elevations are predictive of persisting hepatitis,²⁰¹ of relapse following treatment withdrawal,¹⁷⁸ of progression to cirrhosis^{173 174} and of a poor outcome.^{155 171–173}

Even after serum transaminases normalise, treatment should be continued. In the Mayo Clinic trials^{166 167} prednisolone was maintained at 10 mg/day together with azathioprine. Patients on this regime had higher histological remission rates after 2–3 years than those treated with prednisolone alone in a dose titrated to maintain serum transaminases at less than twice normal.¹⁶⁷ Histological remission lagged behind biochemical remission by several months.¹⁶⁶ This might justify a continuing dose of 10 mg/day prednisolone if tolerated. However, the AASLD guidelines suggest continuing at a lower dose of 5–10 mg/day (depending on tolerance) together with azathioprine (50 mg or 1 mg/kg/day) for a total of at least 2 years.⁴

Although there is no consensus on optimal duration,^{3 177} it is recommended that treatment be continued for long enough to make histological resolution ‘likely’, based on the initial Mayo Clinic trials.^{166 167} In practice this means for 2–3 years, with normal transaminases for at least 18 months.

Histological remission (absence of interface hepatitis) has been an important aim of treatment.^{166 167 187 188} It lags behind biochemical resolution and is achieved in only 15–35% of patients after 12 months on prednisolone-based regimes. In the two Mayo Clinic controlled trials this rose to 60% and 78% after 24 months and 60% and 87% after 36 months of treatment.^{166 167} In a further study from the Mayo Clinic, 88 of 115 patients (77%) achieved histological remission.¹⁷⁹

Thus, some patients still have interface hepatitis despite normalisation of transaminases. The proportion was 55% in one study,²⁰¹ but this included many biopsies taken relatively

early in the course of treatment. After treatment was stopped, 20% of patients with normal serum AST and 50% of those with AST 1–2 times normal had interface hepatitis.²⁰¹ Serum globulin did not add to the predictive value of the serum AST. Recently, normalisation of serum IgG has been suggested as being predictive of histological remission together with transaminases,²⁰² but this requires further evaluation.

Reasons for obtaining a liver biopsy about 2 years after liver tests have normalised to confirm histological remission include: (a) regimes to prevent relapse of AIH (see section D1) have been evaluated specifically in patients with documented histological remission; (b) progression of fibrosis on serial liver biopsies occurs in 20–40% of patients with AIH and is positively correlated with the degree of residual histological inflammation^{183 202 203} so fibrosis tends to regress in patients with minimal inflammation on follow-up biopsy and to progress in those with persisting inflammation (indeed, cirrhosis develops *de novo* in 10–50% of patients with AIH while on treatment, see section D2); (c) follow-up biopsy is partially predictive of AIH relapse following treatment withdrawal, so a normal repeat liver biopsy¹⁷⁹ and absence of portal tract plasma cells¹³⁹ are associated with a lower risk of relapse (see table 6); (d) preliminary evidence suggests that histological resolution may be independently predictive of long-term survival, with an optimal outcome associated with follow-up Ishak necroinflammatory grade ≤ 3 .^{203 204}

However, routine follow-up biopsy has not yet been shown to affect ultimate patient outcome and is often not performed. Rather, the aim is sustained normalisation of serum transaminases.^{4 171 177} The decision to perform a repeat biopsy must therefore be individualised. Factors weighing against it include an elderly or reluctant patient or one in whom liver tests had not fully normalised. The positive predictive value of a raised serum AST for active AIH is high (80% if 1–2 times the upper limit of normal and 100% if increased more than twofold).²⁰¹ This justifies delaying the repeat biopsy until the liver tests have normalised over at least 12 months. However, a repeat biopsy should be considered if azathioprine hepatotoxicity is suspected; this is in part dose-dependent and has recently been associated with high blood levels of 6-methylmercaptapurine metabolites.^{205 206}

If there is clinical and histological remission, the prednisolone should be reduced gradually. A suggested regime is reduction of 2.5 mg/day each month with monitoring of liver tests. Whether azathioprine is continued or not depends on the long-term management strategy (see section D3).

If either serum liver enzymes improve but remain abnormal or if, despite normal liver enzymes, the repeat liver biopsy continues to show interface hepatitis, the optimum strategy is unclear. The possibility of non-compliance should be considered, as should discussion with a centre experienced in the management of AIH. Increasing the dose of prednisolone to >10 mg/day is an unattractive option. Increasing the dose of azathioprine to 2 mg/kg/day (the dose to prevent relapse, see section D1) together with 5–10 mg/day prednisolone may be considered. Alternatively, other agents (see section F) may be tried. Of these, mycophenolate appears of limited efficacy in patients not responding to azathioprine.²⁰⁷ Tacrolimus and ciclosporin may be effective. However, more data are needed on these agents. Whatever regime is used, a repeat liver biopsy should be considered after a further 12–18 months. Complete biochemical and histological resolution is the aim; however, this may not be achievable in some patients. The aspiration should be the lowest achievable histological and biochemical activity with a minimum of side effects.

D. LONG-TERM MANAGEMENT

AIH is a chronic relapsing disease which, even after successful induction therapy, may still progress to cirrhosis and liver failure requiring transplantation. Many patients presenting as children or young adults will expect to live with the disease for ≥ 50 years. The long-term outlook in these patients is unknown because very few follow-up studies of AIH to date have extended beyond 20 years. The disease sometimes appears

Recommendations: initial treatment

1. Initial treatment of AIH should be prednisolone plus azathioprine (Grade A). There is currently insufficient evidence to support the routine use of other drugs as primary treatment (figure 1) (I/A1).
2. Based on controlled trials, the recommended regime is prednisolone initially 30 mg/day (reducing to 10 mg/day over 4 weeks) plus azathioprine 1 mg/kg/day. Higher initial doses of prednisolone (up to 1 mg/kg/day) are often used and may result in more rapid normalisation of transaminases than lower doses. Caution is advised in frail elderly patients. The dose of prednisolone should be gradually reduced to 10 mg/day as serum transaminases fall (II-3/C2).
3. TPMT measurement should be considered to exclude homozygote TPMT deficiency and is recommended in patients with pre-existing leucopenia (II-3/B2).
4. In non-responding or slowly responding patients, higher doses of steroids (including methylprednisolone) combined with 2 mg/kg/day azathioprine may be used or, alternatively, tacrolimus, but expert advice should be sought (II-3/C1).
5. In patients with liver failure, bridging necrosis on biopsy or in jaundiced patients whose MELD score does not rapidly improve on treatment, contact should be made with a liver transplant centre (II-2/B1).
6. In non-cirrhotic patients intolerant of prednisolone, an alternative regime is budesonide (I/B1; see section F). In patients intolerant of azathioprine, prednisolone on its own (in higher doses) is effective but often has side effects (I/B2). The recommended initial dose based on controlled trials is 60 mg/day, reducing over 4 weeks to 20 mg/day. Prednisolone 10–20 mg/day plus mycophenolate may also be used (II-3/B2; see section F).
7. If tolerated, treatment with azathioprine 1 mg/kg/day and prednisolone 5–10 mg/day (side effects permitting) should continue for at least 2 years and for at least 12 months after normalisation of transaminases (II-3/C2).
8. Patients should receive calcium and vitamin D supplementation. Bone DEXA scanning should be performed at 1–2-yearly intervals while on steroids and osteopenia and osteoporosis actively treated (I/A1).
9. Liver biopsy to confirm histological remission is of value in planning further management (II-3/C2).
10. In patients who fail after 2 years to achieve remission on prednisolone plus azathioprine, continuing the prednisolone (5–10 mg/day) and azathioprine in the increased dose of 2 mg/kg/day may be tried, with repeat biopsy after a further 12–18 months. Alternatively, other immunosuppressive drugs may be tried (section F and recommendations below) (II-3/C 2).
11. Vaccination against hepatitis A and hepatitis B should be performed early in susceptible patients (III/C1).

Table 6 Factors associated with clinically significant endpoints in autoimmune hepatitis (AIH)

Endpoint Frequency	Relapse (off treatment) 50–90%	Progressive fibrosis or development of cirrhosis 10–50%	Liver-related death or transplantation 10–20%
Factors			
At presentation	Long symptom duration High serum globulin LKM antibody positive ¹⁷⁵ SLA/LP positive ^{113 176} or no immune markers	Low serum albumin and coagulopathy ¹⁸⁰ Confluent necrosis on biopsy ¹⁸⁰	Female ⁶¹ African-American men ¹⁷ Type 2 AIH ¹⁸⁵ and SLA positive AIH ¹¹⁵ Cirrhosis ^{64 155} Confluent necrosis
On treatment	Short treatment duration ¹⁷⁷ Long time to remission ¹⁷²	Persistent AST elevation ^{172 173} Failure to achieve remission over 2 years ^{181 182} Persistent inflammation on liver biopsy ¹⁸³	Poor response, ⁶⁸ failure of AST to halve in 6 months, ¹⁷⁴ long time to achieve remission, ¹⁸² persistent serum AST elevation ^{155 171}
Pretreatment withdrawal	Raised serum ALT or AST ^{172 178} Raised serum globulin IgG ^{172 178} Liver biopsy with any inflammation ¹⁷⁹ or with portal tract plasma cells ¹³⁹		
Subsequently		Multiple relapses ^{155 184}	Multiple relapses ^{155 184} Development of cirrhosis ^{155 172}

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LKM-1, liver kidney microsomal-1 antibody; SLA/LP, soluble liver antigen/liver pancreas antigen.

to 'burn out' after several years; however, how frequently this happens is unknown. Lifelong clinical and biochemical monitoring of the disease, whether actively treated or not, is therefore mandatory.

The main long-term management goals in AIH are to minimise the risk of (a) disease relapse; (b) the combined end point of death from liver disease or liver transplantation; and (c) side effects of treatment such as bone loss, diabetes and obesity with prednisolone and marrow depression and (potentially) excess cancers with azathioprine and perhaps also with other immunosuppressive agents.

D1. Relapse

Within 12 months of stopping treatment following biochemical and histological remission, 50–90% of patients have a disease relapse (defined by IAIHG criteria as serum ALT >3 times the upper limit of normal).^{172 208–211} Occasionally, relapses occur >10 years after treatment withdrawal.²¹² Although other causes of acute liver injury (viral, drugs) should be considered, a liver biopsy is not usually necessary to confirm the presence of AIH relapse because of the high predictive value of AST >2 times the upper limit of normal.²⁰¹ With mild elevations in well patients, liver tests should be repeated after 1–2 weeks before assuming that relapse has occurred.

In retrospective analyses, relapse of AIH has been associated with several parameters (table 6). Relapse is more likely in patients who have been slow in achieving biochemical remission and in those with continuing active inflammation prior to treatment withdrawal, as evidenced by persistent elevation of serum transaminases and/or serum globulins and IgG¹⁷⁸ and by persistence of plasma cells in portal tracts on liver biopsy. In contrast, only 30% of patients with complete resolution of AIH on follow-up liver biopsy relapse.¹⁷⁹ Relapse of AIH following treatment was associated with a shorter length of initial treatment in one retrospective study¹⁷⁷ but not in another.¹⁷⁸ Few of these reported associations have been independently confirmed.²¹³ Relapse also appears to be uncommon when there is an identifiable precipitant for the initial presentation such as a drug.⁵⁶

Following reintroduction of the initial treatment regime, more than 80% of patients again achieve biochemical remission, usually within a few months. There are no data on the rate of histological remission. However, the increased doses of prednisolone required to reinduce remission may have further side effects. Patients with multiple relapses of AIH were more likely

to have treatment-related side effects than patients who were maintained in remission.^{210 211} In some studies they were more likely to develop progressive fibrosis or cirrhosis^{155 184 211} and to either die of liver disease or require transplantation.^{155 184}

Maintenance regimes have therefore been evaluated to try and prevent relapse of AIH. These studies have recently been reviewed.² All have been in patients with documented histological remission. The relapse rate after 1 year was only 8% when standard combination treatment was continued, but was 32% when azathioprine was withdrawn and prednisolone continued.²¹⁴ In a follow-up trial¹⁸⁷ standard combination treatment was continued in one group and, in the other, prednisolone was phased out gradually and azathioprine continued, with the dose increased from 1 to 2 mg/kg/day. The main clinical advantage of this regime was disappearance of steroid-related side effects, although temporary arthralgia after prednisolone withdrawal was problematic in over half of the patients. After 1 year no patient developed clinical or biochemical relapse, although two patients had recurrent inflammation on routine liver biopsy. In a follow-up study of 72 patients maintained on azathioprine 2 mg/kg/day,¹⁸⁸ 83% of patients remained in clinical and biochemical remission over a median follow-up period of 67 months. Note that these patients had already been in histological remission for at least 12 months and an additional 29 patients were excluded from the study because they did not meet this entry criterion.

The main disadvantages of long-term maintenance of azathioprine are the need for continued blood count monitoring (although the risk of serious marrow depression decreases with time) and the theoretical risk of cancer. An increased risk of malignancy has been reported in patients following renal transplantation²¹⁵ and with rheumatoid arthritis treated with azathioprine,²¹⁶ but a cause and effect relationship with azathioprine was not proven. The results of three studies are consistent with a slight increase in the risk of cancer following a diagnosis of AIH (RR 1.34–1.51), although the increase achieved statistical significance in only one.^{217–219} The risk was not related to dose and duration of azathioprine treatment. However, although unproven, an increased risk of malignancy remains possible and might limit enthusiasm for lifelong azathioprine treatment. It may be prudent to advise patients on long term azathioprine to avoid excessive exposure to sunlight.

Although reduction or withdrawal of azathioprine is a reasonable strategy in a patient who has been free of AIH

recurrence over several years on the maintenance regime, this strategy has not been formally evaluated. In 26 patients in one follow-up study,¹⁸⁸ the dose of azathioprine was electively reduced to 1 mg/kg/day; five of these patients subsequently relapsed. In a recent report¹⁹ azathioprine was withdrawn completely after 2–12 years (median 5) in 22 patients. Nine patients remained in remission for 3–12 years (median 7) and 11 relapsed. Following retreatment of the relapse, patients are often maintained on azathioprine and small doses of prednisolone,¹⁹ although the added value of prednisolone in preventing further relapses has not been assessed.

An alternative approach, more commonly used in North America than in Europe, is not to use routine maintenance azathioprine treatment but to stop treatment once remission is attained and to then treat relapses as they occur.^{64 171 210 211} About 25–36% of patients achieve a 'sustained remission', defined as serum AST persistently <3 times the upper limit of normal, a looser definition than that of biochemical remission following initial treatment.^{210 211}

A low-dose prednisolone maintenance regime has also been suggested for patients with multiple AIH relapses.²²⁰ In 22 patients (seven of them also on azathioprine 50 mg/day), the dose of prednisolone was reduced to maintain serum AST at <5 times the normal value. The median maintenance dose of prednisolone was 7.5 mg/day and the main advantage of this strategy was a reduction in the severity of side effects to steroids compared with a group of 31 patients with multiple relapses who received repeated episodes of standard therapy for each relapse. However, although follow-up histology data were not presented, it is doubtful that the AIH was fully suppressed in these patients. Progression to cirrhosis was common (55% overall) and, of the 22 patients on the low-dose regime, two died of liver disease and two required transplantation. The study further illustrates the relatively poor outlook in patients with serially relapsing AIH, and other treatments should be considered in these patients (see section F).

Consideration of the merits of these long-term strategies (expectant management of relapses, maintenance azathioprine and low-dose prednisolone) must be informed by a discussion of disease progression.

D2. Progression of disease

Suggestions that the outlook for patients with treated AIH is not different from that of the general population have been based on mean follow-up periods of about 10 years and maximum follow-up of only about 20 years. They may be over-optimistic in the long term. In some studies 10-year survival is about 90% and not different from the general population.^{180 221} However, others have reported lower survival rates,^{18 64} especially after longer periods of follow-up.^{61 155} The standardised mortality ratio has been reported as above unity: 3.7 in a study from the Danish National Registry²²² and 1.63 in a recent study of 245 UK patients followed up for a median of 9.4 years.¹⁵⁵

Complementary to the main long-term management goal in AIH of preventing liver-related death or need for transplantation is prevention of fibrosis progression. Studies involving serial liver biopsies^{19 223} suggest that fibrosis improves in about half of patients with treatment. However, in about 25% of cases fibrosis progresses despite treatment, and this is associated with failure to suppress inflammation.¹⁸³

Cirrhosis develops during follow-up in 30–50% of patients,^{61 155 180 181 184} although lower rates have also been reported.^{68 172 224} The development of cirrhosis is associated

with several parameters of suboptimal treatment response and also with increased liver-related mortality or transplantation (table 6). Cirrhosis at presentation occurs in about 30% of patients and is associated in some^{61 64 159} but not all^{172 180} studies with a poorer outlook than in patients without cirrhosis.

Associations and predictors of progressive fibrosis, development of cirrhosis and liver-related death or transplantation have been demonstrated in retrospective analyses (table 6). However, it is not known if the long-term treatment strategy (see section D1) influences progression of disease. In the King's College follow-up study¹⁸⁸ of long-term maintenance azathioprine 2 mg/kg/day, only one of 73 patients died of liver failure. However, in recent studies^{19 155} of patients, most of whom received maintenance azathioprine, 14–20% eventually died of liver disease or required liver transplantation. This outlook is not obviously different from that observed in studies in which maintenance azathioprine was not used.^{64 171 172 180} Unfortunately these two long-term strategies have not been formally compared with regard to these 'hard' endpoints. Of concern, it has not been shown that any regime prevents development of cirrhosis.

Hepatocellular carcinoma was previously regarded as a rare complication of AIH.²²⁵ However, recent reports suggest a rate of 4–6% overall and 10–20% in patients with cirrhosis.^{218 226 227} Therefore, although not common practice, screening for hepatocellular carcinoma with 6-monthly serum α -feta protein measurements and liver ultrasound may be considered in otherwise healthy patients with AIH and cirrhosis (both men and women) because of the 10–20% risk over 20 years.

D3. Choice of long-term maintenance strategy in patients who have attained remission

The decision as to which strategy to pursue in patients who have attained remission must be individualised. Features favouring withdrawal of treatment and delaying reinstitution of maintenance azathioprine therapy until after the first relapse would include: (a) absence of cirrhosis or decompensation; (b) absence of the features in table 6 associated with relapse; (c) good tolerance of initial prednisolone treatment; (d) a potential precipitant of the initial episode of AIH such as a drug or documented viral infection; and (e) a history of malignancy. On the other hand, continuing azathioprine long-term as a maintenance strategy is recommended in younger patients and in those with predictors of relapse including LKM- and SLA-positive patients (table 6), in those with observed or anticipated prednisolone-related side effects (including osteopenia, see section E) and in those with cirrhosis or decompensation. After treatment of one relapse, continuation of azathioprine 2 mg/kg/day as long-term maintenance therapy is recommended. Whatever strategy is pursued, monitoring should be lifelong.

E. BONE HEALTH

There are several recent reviews of bone disease in patients with chronic liver disease.^{228–230} Patients with AIH should have an adequate intake of calcium—if necessary, by prescribing calcium supplements. A DEXA bone mineral density scan should be performed before or shortly after commencing treatment and at 1–2-yearly intervals while the patient remains on treatment with corticosteroids. Patients with osteopenia or osteoporosis should receive bisphosphonates. Prophylaxis with bisphosphonates is recommended by the Royal College of Physicians²³¹ in corticosteroid-treated patients aged >65 years and in those with a history of fragility fracture.

F. OTHER DRUGS

F1 Ciclosporin A (CyA)

In patients with AIH not responding to standard therapy, CyA has been shown to be of clinical benefit although relapses occurred if the dose of CyA was reduced.^{232–234} In an open-label trial, 19 patients (9 treatment-naïve) treated with CyA showed reductions in serum aminotransferases and histological activity index scores over 6 months.²³⁵ There was no significant effect on serum creatinine. In a multicentre study of 32 children, CyA was administered as monotherapy for 6 months (target trough levels 200–250 ng/ml), followed by low doses of prednisolone and azathioprine which were given for 1 month, after which CyA was stopped.²³⁶ Two patients were withdrawn from the study and, of the remaining 30 patients, ALT normalised in 25 by 6 months and in all by 1 year. Adverse effects were mild and reversible on withdrawal of treatment. In a study of 84 children recruited from five centres between 1994 and 2001, CyA was administered during the first 6 months in a protocol similar to that described by Alvarez *et al*²³⁶ and, after 6 months for patients with AST/ALT levels lower than twice the upper limit of normal, standard therapy was initiated.²³⁷ Normal aminotransferase levels were observed in 94% of patients, with 72% of normal results achieved within the first 6 months of treatment. Higher bilirubin levels and the presence of portal hypertension at diagnosis predicted a delay in achieving remission.²³⁷ Adverse effects related to CyA appeared mild and transient, with standard therapy not implicated in disease relapse during follow-up.

In other series CyA has been used predominantly as a salvage strategy or in the context of relapsing or non-responsive AIH. Results in these situations have been favourable, although no long-term reports exist to evaluate safety.^{233 238 239} Therefore, in considering initiation of CyA, its toxicity profile including the long-term risks of hypertension, renal insufficiency, hyperlipidaemia, hirsutism, infection and malignancy must be balanced against its potential benefits.

F2. Tacrolimus

Tacrolimus (FK 506) is a macrolide antibiotic with 10–200 times greater immunosuppressive potency than CyA.²¹² Its mechanism of action is similar to that of CyA, although it binds to FK binding protein (an alternative immunophilin). In an open-label preliminary trial in 21 patients with AIH treated with tacrolimus (at trough drug levels of 0.6–1.0 ng/ml), biochemical improvement was demonstrated after 3 months.²⁴⁰ Serum urea and creatinine levels were raised within a year of treatment.²⁴¹ Tacrolimus has been used predominantly as salvage therapy in AIH in relatively small series or in case reports.^{241–245} Recently, tacrolimus was successful in seven of nine patients with acute AIH who did not respond to corticosteroids.¹⁹⁹ For most patients remission can be achieved with tacrolimus, either alone or in conjunction with corticosteroids, although the limitation of all series relates to the short degree of follow-up.

F3. Budesonide and deflazacort

Budesonide is a second-generation corticosteroid with 15 times the affinity of prednisolone for the glucocorticoid receptor. When taken orally it has a 90% first-pass metabolism in the liver, although in patients with cirrhosis with shunts, the metabolism may be variable.^{246 247} In one study²⁴⁸ 13 patients (11 of whom were intolerant of standard therapy) were treated with 6–8 mg/day budesonide, reduced to 2–6 mg/day after 6–10 weeks. Both ALT and serum IgG improved and there were no reported adverse steroid effects. In a second study,²⁴⁹ 10 patients who required continuous treatment to prevent disease exacerbation were

treated with budesonide 9 mg/day with only three patients having a sustained effect. In an uncontrolled study, however, budesonide controlled disease activity in 7/9 patients with refractory or prednisolone-dependent disease without excessive side effects.²⁵⁰ In untreated patients a dose of 9 mg/day was used to induce remission and, in this group, 7/12 patients (58%) reached complete remission and 3/12 (25%) had a partial response, with treatment being well tolerated in 10/12 cases (83.3%).²⁵¹ Information is not available on the long-term outcome in patients treated with budesonide.

In a recent multicentre randomised controlled trial in patients with AIH without cirrhosis,¹⁶⁹ budesonide 9 mg/day plus azathioprine 1–2 mg/kg/day for 6 months was more effective in achieving normalisation of serum transaminases and produced fewer steroid-related side effects than prednisolone plus azathioprine. Given the short trial duration and the fact that no follow-up histology data were presented, routine use of this regime in treatment-naïve patients is not currently recommended. However, its use should be considered in non-cirrhotic patients who are intolerant of prednisolone.

In an open-label trial, 15 patients with AIH maintained in remission on prednisolone were converted to deflazacort 7.5 mg/day.²⁵² ALT and IgG levels were raised minimally in most patients, although there were no apparent ill effects and remission was sustained during 2 years of follow-up.

F4. Mycophenolate mofetil

This is the prodrug of mycophenolic acid (MMF) which blocks *de novo* purine synthesis. MMF has been used predominantly in patients with refractory AIH or with azathioprine intolerance.^{207 244 253–256} Most studies have used 2 g/day in divided doses, initially with corticosteroids but with the aim of reducing these. In one study the dose of prednisolone was decreased from a median of 20 mg/day to 2 mg/day after 9 months, with histological improvement noted in all patients.²⁵³ In a further case series 5–15 patients unresponsive to or intolerant of standard therapy were given MMF with improvement in biochemical and histological indices.^{254 257} In larger series (29–36 patients) up to one-third of patients discontinued the drug due to poor tolerance or side effects.^{207 256 258} Only half of patients attained biochemical remission and follow-up histology data were not reported. Patients in whom azathioprine had been ineffective seemed to have a poorer response to MMF than those who had been azathioprine-intolerant.^{207 258} In a more promising recent report of 59 treatment-naïve patients,²⁵⁹ 88% had a complete biochemical response to MMF and prednisolone. However, further data are needed, especially on efficacy in inducing histological remission, before MMF can be recommended as a first-line treatment for AIH.

There are very few data on the long-term safety of MMF.²⁶⁰ Development of histological changes were noted in a patient with AIH, including cytoplasmic features of adaptation and nuclear alterations within hepatocytes,²⁶¹ and there have been sporadic reports of cerebral lymphoma in patients who have received MMF for other autoimmune diseases.^{262–264} MMF is contraindicated in pregnancy.

F5. Other agents with anecdotal evidence of efficacy

In a Japanese study eight patients received ursodeoxycholic acid (UDCA) 600 mg/day for 2 years in whom a significant biochemical improvement was demonstrated.¹⁰¹ In four patients a biopsy after 12 months showed improvement in inflammation. However, in another study 37 patients refractory to corticosteroid therapy were randomised to UDCA or placebo for

6 months, together with their standard treatment regimen.²⁶⁵ No significant benefit from UDCA was found.

Maintenance therapy with cyclophosphamide for up to 12 years without relapse or serious side effects has been successfully achieved in three patients.²⁶⁶ In case reports, methotrexate,²⁶⁷ infliximab²⁶⁸ and rituximab²⁶⁹ given to patients with resistant AIH resulted in sustained biochemical remission and histological improvement.

Recommendations: long-term management

1. When all treatment is withdrawn after attaining biochemical and histological remission, about 70% of patients relapse within 12 months (II-2A).
2. The rate of relapse after prednisolone withdrawal can be reduced by continuation of azathioprine alone at a higher maintenance dose of 2 mg/kg (IB/2). This regime appears to be safe in the long term. The decision whether to use maintenance azathioprine or to wait for and treat the first relapse depends on the estimated likelihood of relapse, severity of liver disease and anticipated side effects. Routine maintenance therapy is recommended in younger patients and in patients who are LKM antibody or SLA-positive (II-3/B1).
3. Patients who relapse should be retreated as for the first presentation of AIH. Once in remission they should be given maintenance azathioprine, if tolerated (II-3/C1).
4. In patients who relapse on azathioprine maintenance therapy, low-dose prednisolone (in addition to azathioprine) may be continued long-term after remission is re-attained (III/C2).
5. Mycophenolate maintenance therapy may be considered in azathioprine-intolerant patients (II-3/C2).
6. In patients who fail to achieve complete biochemical or histological remission on prednisolone plus azathioprine, mycophenolate appears of limited efficacy. Ciclosporin, budesonide, deflazocort, tacrolimus or cyclophosphamide may also be tried, although efficacy is poorly documented (II-3/C 2).
7. Six-monthly screening for hepatocellular carcinoma with serum α -feta protein measurement and ultrasound should be considered in otherwise healthy patients with AIH and cirrhosis (both men and women) (II-3/C2).

G. SPECIFIC CLINICAL PROBLEMS

G1. Management of AIH in pregnancy^{107 270–272}

Of 162 women with AIH attending King's College Hospital between 1983 and 1998, 18 (7 with cirrhosis) had 35 pregnancies which resulted in 31 live births.²⁷⁰ Birth abnormalities were seen in only two cases. At conception, 15 patients were receiving azathioprine (9 with prednisolone). Azathioprine was continued in 10 patients. Flares in disease activity occurred during four pregnancies and within 3 months of delivery in a further four. In another series of 42 pregnancies in women with AIH there were 11 adverse outcomes and four serious maternal complications.²⁷¹ The unexplained adverse outcomes were associated with the presence of antibodies to anti-SLA/LP and anti-Ro/SSA; 21% of the patients had flares during pregnancy and 52% of patients had post-partum flares. In a survey of 63 pregnancies in patients with AIH a higher rate of cesarian section was observed but there was no increase in stillbirth or fetal malformation rate compared with normal controls.²⁷³

In none of these series was any relationship apparent between azathioprine use during pregnancy and an adverse outcome. Larger studies of patients with inflammatory bowel disease²⁷⁴ also support the relative safety of azathioprine/6-mercaptopurine during pregnancy. Continuation of this drug during pregnancy may therefore be justified. Indeed, in another series of 14 patients with AIH, immunosuppression was reduced during the second trimester.²⁷⁵ Following delivery (or stillbirth in one patient), 12 of the 14 patients had a rapid flare of AIH. AIH presenting de novo following delivery has also been reported.²⁷¹ Taken together, these data provide some support for a strategy of minimal adjustment to prednisolone/azathioprine-based immunosuppressive regimes during the course of pregnancy so that the risk of flare during pregnancy and post-partum can be minimised. Similar considerations may apply to ciclosporin and tacrolimus²⁷⁶ based on experience in patients following liver transplantation. However, the decision to continue or to stop immunosuppression before or after conception should be individualised and should always involve full discussion with the patient. Mycophenolate is potentially teratogenic and is not recommended during pregnancy.

Recommendation

Although available evidence does not allow for a firm recommendation, minimal adjustment to prednisolone/azathioprine-based immunosuppression appears to be justified in AIH during pregnancy (II-3/C2). If stopped, immunosuppression should be reinstituted immediately after delivery because of the high risk of a flare of AIH (II-3/B1).

G2. Liver transplantation

About 10–20% of patients with AIH will require liver transplantation during their lifetime. There are two distinct indications. The first is severe acute AIH resulting in acute or subacute liver failure. The critical importance of early referral to or discussion of these patients with a transplant centre has been previously discussed (sections B1 and C6). The second and more common indication for liver transplantation is decompensated chronic liver disease and/or hepatocellular carcinoma, often in a patient with longstanding AIH. Table 6 (right hand column) lists the features associated with and predictive of this outcome. The same indications for liver transplantation apply as for other aetiologies of cirrhosis in so far as the development of ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis or hepatorenal syndrome impact significantly on survival. These include a MELD score of >15 or a Child-Pugh score of >10.²⁷⁷

However, if possible, patients should be referred for consideration of liver transplantation before they develop end stage liver disease. Pointers to impending liver decompensation include a variceal bleed, ultrasound showing a small 'fibrotic' liver, a falling serum albumin and development of even mild ascites or ankle oedema.

Five-year survival following transplantation for AIH is about 75%.^{278–282} In a recent Europe-wide experience it seemed to be worse than in patients transplanted for PBC.²⁸²

Recurrence of AIH, originally described in 1984,²⁸³ is seen in about 20% of recipients.^{284–286} Diagnosis of recurrent AIH is limited by the absence of a specific marker. Autoantibodies such as ANA or ASMA tend to disappear after transplantation

but may reappear, albeit at lower titres than before transplantation.^{287 288} The features of recurrent AIH in the liver graft are similar to those of AIH before transplantation. The most frequent overlapping diagnosis is acute cellular rejection, and both AIH and acute rejection entities share common biochemical and histological features and both respond to corticosteroids.²⁸⁸ Indeed, patients with AIH hepatitis have an increased risk of acute cellular rejection.^{286 288 289} In addition, recurrent AIH may precipitate chronic rejection.²⁸⁶ A review by the Banff Working Group has recommended diagnostic criteria for recurrent AIH after transplantation.²⁹⁰ Recurrent AIH is usually managed by either maintenance of corticosteroids long term or by continuation of azathioprine in the immunosuppression regimen.²⁸⁴

'De novo' AIH following liver transplantation

This occurs in association with serological and histological features compatible with AIH in patients who have undergone transplantation for aetiologies other than AIH.^{291–293} It has been classified by the Banff Working Group as requiring the same criteria as recurrent AIH after transplantation.²⁹⁰ In some patients retransplantation was required because of severe graft dysfunction.²⁹³ Two patterns of disease were described, one associated with detectable anti-LKM1 antibodies at high titre in conjunction with a serum AST level >500 IU/l and a second associated with the presence of ANA or ASMA at lower titres (>1:80) and lower AST levels.²⁹³ Treatment has usually involved the reintroduction of corticosteroids and azathioprine.^{291 293} Subsequent descriptions of this type of graft dysfunction have been controversial, as has the terminology associated with the condition. The terms 'de novo AIH', 'alloimmune hepatitis' or 'graft dysfunction mimicking AIH' have been proposed.^{293–295}

A phenomenon of immune-mediated hepatitis has also been reported in patients who have undergone treatment for recurrent HCV infections following liver transplantation.^{33 35} In these reports an aggressive plasma cell predominant hepatitis has been described and treatment with steroids and/or azathioprine resulted in prompt and dramatic response of liver enzyme abnormalities, although relapse occurred following discontinuation of the drug.³⁵

Recommendations

1. Referral for transplantation should be considered in patients with decompensation at presentation and also in those with severe disease in whom serum transaminases show no or a very slow response to treatment. Referral is strongly recommended in patients presenting with fulminant hepatic failure (II-2/B1).
2. Referral is also indicated in patients who later develop clinical liver decompensation (ascites, hepatic encephalopathy or hepatorenal syndrome) or who develop hepatocellular carcinoma. Indications also include a MELD score of >15 or a Child-Pugh score of >10²⁷⁷ (II-2/B1).
3. Referral—or at least discussion with a transplant centre—should be considered in patients in whom, despite treatment, there are signs of impending liver decompensation as evidenced by a variceal bleed, ultrasound showing a small 'fibrotic' liver, falling serum albumin and development of even mild ascites or ankle oedema (III/C1).

G3. Overlap syndromes

(a) AIH and primary biliary cirrhosis (PBC)

Isolated features normally associated with PBC are commonly seen in otherwise typical AIH and vice versa.⁷⁶ For example, 8% of patients with otherwise typical AIH have destructive bile duct lesions considered characteristic of PBC,^{146 147} and in 8–12% of patients the serum is positive for antimitochondrial antibody.^{121 122} The prevalence of 'overlap'—that is, both AIH and PBC in the same patient—depends critically on how each disease is defined. Unfortunately definitions have varied between studies and are sometimes imprecise. Indeed, it may be more useful to characterise patients with autoimmune liver disease according to the predominant 'primary' disease and not to regard 'overlap' syndromes as separate entities.⁷⁶

Using the revised IAIHG criteria,¹⁰³ 19% of patients with PBC had probable AIH but none had definite AIH.¹⁵³ These varying frequencies reflect inherent limitations of the IAIHG scoring system, which was not specifically designed for distinguishing AIH from PBC. Defining AIH and PBC as at least two 'typical' criteria for each disease, 9–14% of patients with PBC also had AIH.^{296–298} In about 4% of cases AIH follows the onset of PBC, sometimes by many years, and in 2% PBC followed AIH.²⁹⁷ Patients with AIH/PBC overlap have a high prevalence of HLA B8, not Bs DR3 and DR4, more typical of patients with AIH than with PBC.²⁹⁹

There are no controlled studies of the management of AIH/PBC overlap. In most reports patients received conventional treatment of the dominant disease—UDCA for PBC and prednisolone (with or without azathioprine) for AIH. Joshi *et al* described histological improvement on UDCA treatment alone in three of nine patients but the histology worsened in two other patients.³⁰⁰ In other reports liver tests did not improve on UDCA alone^{296–298} but, following treatment with prednisolone, most patients achieve biochemical remission and serial biopsies show no progression of fibrosis. In one case reversal of cirrhosis was reported with a combination of UDCA and immunosuppression. Despite these responses, the incidence of variceal bleeding, liver failure and liver transplantation may be higher in overlap than in PBC alone³⁰¹ or AIH alone.³⁰² For this reason, diagnosis and proactive treatment of the AIH component is important and liver biopsy should be considered in patients with PBC but in whom serum transaminases persistently exceed 100 U/l.

(b) AIH and primary sclerosing cholangitis (PSC)

Using the revised IAIHG criteria, about 8% of adults with PSC have probable AIH and about 2% have definite AIH.^{152 303} The prevalence was higher using the original IAIHG criteria which assigned less negative weighting to a raised serum alkaline phosphatase.³⁰⁴ The prevalence of AIH appears to be higher in children with PSC.^{305 306} PSC may develop many years after a diagnosis of AIH.³⁰⁷ The prevalence of large duct PSC in adults with AIH has recently been reported as 2% and 10% based on magnetic resonance cholangiopancreatography (MRCP) surveys.^{77 78} Again, a higher frequency has been reported in children.³⁰⁶ Apart from those suggestive of AIH, features of AIH/PSC overlap include raised serum alkaline phosphatase and/or bile duct damage on liver biopsy. MRCP should be considered in a patient with AIH who has a raised serum alkaline phosphatase level which does not settle rapidly with treatment. Coincidental PSC should also be considered in a patient with AIH who has inflammatory bowel disease.

Most patients with AIH/PSC overlap have been treated with prednisolone and azathioprine with or without UDCA. Falls are usually seen in serum transaminases but not in the serum alkaline phosphatase level. The Mayo risk score remains stable.

Liver biopsies may show improvement in inflammation but cholangiographic appearances may progress³⁰⁶ and most patients develop cirrhosis.³⁰⁸ The long-term outlook may be worse than in AIH without overlap,^{302 308} again emphasising the importance of proactive diagnosis and treatment of the AIH component. The long-term benefits of UDCA in preventing the need for liver transplantation remain unproven, as is the case for typical PSC.

Recommendations

1. Overlap syndromes should be considered and looked for in patients with AIH when serum alkaline phosphatase is more than mildly elevated and does not normalise rapidly with immunosuppressive treatment (III/C1).
2. The management of AIH overlap syndromes is that of their component diseases (II-3/C1).

H. CONCLUSIONS

AIH was the first chronic liver disease in which medical treatment was clearly shown to be effective, based on controlled trials. However, treatment remains largely based on these studies, which were performed several decades ago, and is, in many respects, suboptimal. There is therefore a pressing need for further clinical trials in AIH. Newer immunosuppressive drug regimes need formal comparison with standard regimes. Also, the standard regimes need further evaluation, especially with regard to long-term management. The UK liver community is well placed to perform such studies.

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