Autoimmune hepatitis

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Abstract | Autoimmune hepatitis (AIH) is a severe liver disease that affects children and adults worldwide. The diagnosis of AIH relies on increased serum transaminase and immunoglobulin G levels, presence of autoantibodies and interface hepatitis on liver histology. AIH arises in genetically predisposed individuals when a trigger, such as exposure to a virus, leads to a T cell-mediated autoimmune response directed against liver autoantigens; this immune response is permitted by inadequate regulatory immune control leading to a loss of tolerance. AIH responds favourably to immunosuppressive treatment, which should be started as soon as the diagnosis is made. Standard regimens include fairly high initial doses of corticosteroids (prednisone or prednisolone), which are tapered gradually as azathioprine is introduced. For those patients who do not respond to standard treatment, second-line drugs should be considered, including mycophenolate mofetil, calcineurin inhibitors, mechanistic target of rapamycin (mTOR) inhibitors and biologic agents, which should be administered only in specialized hepatology centres. Liver transplantation is a life-saving option for those who progress to end-stage liver disease, although AIH can recur or develop de novo after transplantation. In-depth investigation of immune pathways and analysis of changes to the intestinal microbiota should advance our knowledge of the pathogenesis of AIH and lead to novel, tailored and better tolerated therapies.

Chronic hepatitis is a heterogeneous syndrome; the definition and classification are primarily based on aetiology and then grading and staging[1]. Autoimmune hepatitis (AIH) is an entity of chronic hepatitis that must be distinguished from chronic viral hepatitis, drug-induced and alcohol-induced hepatitis and idiopathic chronic hepatitis. AIH occurs globally in all ethnicities and affects children and adults of all ages, with a female predominance. A loss of tolerance against the patient's own liver antigens is regarded as the main underlying pathogenetic mechanism, which is probably triggered by environmental agents such as pathogens and xenobiotics, in genetically susceptible individuals[2,3].

Although AIH by definition is a chronic disease that may lead to cirrhosis, hepatocellular carcinoma (HCC), liver transplantation and/or death, it can often start with an episode of acute hepatitis (that is, with malaise, nausea, abdominal pain, jaundice and elevation of transaminase levels). AIH may even present as fulminant hepatic failure and, therefore, must be considered in the differential diagnosis of acute liver failure. AIH was first described in 1951 by Waldenström[4]. Shortly thereafter, the syndrome was further characterized in the United States, including a description of the female predominance, high γ-globulins in the absence of cirrhosis and response to corticosteroids[5]. Additional diagnostic hallmarks are circulating autoantibodies[6]. Antinuclear antibodies (ANA; antibodies against nuclear antigens (for example, nucleic acids, histones and ribonucleoproteins)) were the first to be described in AIH, and the term 'lupoid hepatitis' was coined[5]. However, AIH is distinct from systemic lupus erythematosus.

Debate is ongoing on whether AIH is a single disease entity or a heterogeneous syndrome with different underlying aetiologies. One possibility to further subtype AIH is based on marker autoantibodies circulating in patient sera. ANA together with the later described anti-smooth muscle antibodies (SMA)[7], which mainly target actin, troponin or tropomyosin present in smooth muscle cells, are regarded as markers of AIH type 1 (AIH-1), which affects children and adults. AIH type 2 (AIH-2) is characterized by the presence in the serum of anti-liver kidney microsomal type 1 (anti-LKM1) antibodies[8], anti-liver cytosol type 1 (anti-LC1) antibodies[9] and/or anti-LKM3 antibodies[10]; AIH-2 predominantly begins in childhood and adolescence. Note that even if AIH starts in childhood, the disease usually runs a chronic course over years, leading into adulthood. There may be additional subtypes characterized by other marker autoantibodies, such as those against soluble liver antigen/liver pancreas antibodies (previously referred to as anti-SLA/LP antibodies, now known as anti-SLA antibodies)[11–13]

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or autoantibody-negative AIH. However, the existence of these additional subtypes is still controversial and hard to prove because the triggers of AIH have not been identified. In addition, the antibody profile can change during the disease course. As a consequence, some researchers and clinicians opt for considering AIH as a whole, without using the subtypes[14]. In this Primer, we separate AIH on the basis of the age profile into juvenile AIH (including AIH-1 and AIH-2) and AIH in adults (mainly AIH-1) (TABLE 1).

AIH is the first liver disease for which medical therapy was shown to improve survival[15]. Corticosteroids alone or in combination with azathioprine are the standard of care and are effective in most patients. The main trials establishing this treatment strategy were performed before the discovery of the hepatitis C virus (HCV); thus, an HCV infection mimicking AIH could not be excluded[2]. Normalization of serum transaminase and immunoglobulin levels is generally accepted as an end point for the treatment of AIH and used to define complete remission[6,16]. Patients not achieving complete remission usually experience histological progression[17,18]. Patients not achieving remission or not tolerating standard management are particularly challenging, and their therapeutic needs remain unmet. No medications have thus far been approved for these patients, and alternative drugs are used off label.

To understand the pathogenetic mechanisms of AIH, animal models are of considerable importance. Our growing knowledge of the molecular basis of AIH should enable us to control the disease long term without considerable adverse effects and to avoid liver transplantation in the future. Hopefully, future therapies will replace the nonspecific immunosuppressive agents, which, despite their effectiveness in terms of treatment outcomes, cause considerable adverse effects, particularly with long-term use. We need to identify the right therapeutic targets and to design appropriate clinical trials to develop therapies for difficult-to-treat patients who do not respond to or do not tolerate the standard of care. In this Primer, we explore the epidemiological, pathogenetic, diagnostic and management aspects of both the adult form and the juvenile form of AIH, including information on quality of life and the outlook for future research and management.

Epidemiology

Prevalence and incidence

AIH occurs globally in children and adults of all ages and in all ethnicities, including in white individuals, black individuals, those of Asian descent or native and indigenous Americans[19,20]. Accurate figures for the prevalence of AIH are almost impossible to obtain given the paucity of population-based data. Incidence data are strongly influenced by methods of ascertainment as well as difficulties in definitions used over the years, including the absence of histological confirmation and scoring systems. Older figures may reflect nonalcoholic fatty liver disease and/or chronic viral hepatitis, which can also be associated with autoantibodies.

Estimates of the incidence of AIH-1 in adults and children in the second part of the 20th century from Japan, France, Austria, the United Kingdom, Norway and Spain ranged from <0.1 to 1.9 cases per 100,000 individuals per year[21,22]. More-recent values from the early years of the 21st century are generally higher and likely more accurate; incidence is estimated at 1.5 cases in Japan, 1.68 cases in Denmark, 3.0 cases in the United Kingdom and 2.0 cases in New Zealand per 100,000 individuals per year[23].

As noted in the proceedings of a 2016 Asia-Pacific symposium on autoimmune liver diseases[24], few data are available on the prevalence and incidence in countries of south and east Asia owing in part to the high prevalence of chronic hepatitis B. In addition, the demographics vary between countries in south Asia and east Asia in terms of the distribution of AIH-1 versus AIH-2, female predominance and age of onset[24]. Recent reports from these regions indicate an increase in the diagnosis of AIH compared with the past[24–30], but whether this increase is true or ascertainment bias is unclear[24,31].

The mean incidence of AIH-1 in Norway calculated over a 10-year period from 1986 to 1995 was 1.9 cases per 100,000 individuals per year[32]. In a large Swedish cohort, AIH-1 point prevalence was reported as 17.3 cases per 100,000 inhabitants in 2009, with a yearly incidence of 1.2 cases per 100,000 inhabitants between 1990 and 2009 (REF. 33). An even larger study conducted in the Netherlands shows an AIH-1 prevalence of 18.3 cases per 100,000 population, with an annual incidence of 1.1 per 100,000 population per year in adults, the peak incidence being in women aged 40–60 years[34]. An increase in incidence of AIH-1, which seems to represent a true increase of the disease, has been reported in Denmark, where population-based values were calculated using the health-care registration system. An increase in incidence over the 1994–2012 period from 1.37 to 2.12 cases per 100,000 individuals per year was recorded[35]. This increase was also reflected by an increase in prevalence[35]. Preliminary unpublished figures on the incidence and prevalence from Finland, calculated from a national reimbursement system, indicate an incidence

of 0.8 cases per 100,000 individuals per year from 1995 to 2015 and a prevalence of 10.5 cases per 100,000 individuals (L. Puustinen, personal communication).

The prevalence of AIH-2, which mainly affects children and adolescents, is unknown. In a study in Canada that included 159 children and adolescents with AIH, the annual incidence was 0.23 cases per 100,000 children; AIH-1 was diagnosed 5.5-times more frequently than AIH-2 (REF. 36).

The risk of developing primary HCC in AIH is associated with the presence of cirrhosis, akin to other chronic liver diseases[37–42], although HCC has also been anecdotally described in the absence of cirrhosis[43]. Both the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver AIH guidelines recommend active surveillance for HCC[6,16].

Risk factors

Genetic predisposition. Genetic studies have shown that predisposition to developing AIH can be attributed in part to polymorphisms of the human leukocyte antigen (*HLA*) region, encoding the major histocompatibility complex (MHC). The prominent predisposing role of genes encoded in the *HLA* region has been confirmed in the largest genome-wide association study performed to date in AIH[44]. The *HLA* genotypes vary between different ethnic groups and geographical regions[45]. In Europe and North America, susceptibility to AIH-1 in adults is conferred by HLA-DR3 (*HLADRB1*0301*) and HLA-DR4 (*HLADRB1*0401*) genotypes, both of which are heterodimers containing a lysine residue at position 71 of the DRB1 polypeptide and the hexameric amino acid sequence LLEQKR at positions 67–72 (REFS 46,47). In Japan, Argentina and Mexico, susceptibility is linked to *HLADRB1*0405* and *HLADRB1*0404* alleles encoding arginine rather than lysine at position 71 but sharing the motif LLEQ-R with *HLADRB1*0401* and *HLADRB1*0301* (REF. 48). Thus, the two basic amino acids lysine and arginine at position 71 in the context of LLEQ-R may be critical for susceptibility to AIH, favouring the binding of autoantigenic peptides, complementary to this hexameric sequence. In northern Europe, paediatric AIH-1 is also associated with *HLADRB1*03*, whereas *HLADRB1*04* confers protection[46,49]. In Brazil and Egypt, the primary susceptibility allele for paediatric AIH-1 is *HLADRB1*1301*, but a secondary association with *HLADRB1*0301* has also been identified[50,51]. Interestingly, in South America, possession of the *HLADRB1*1301* allele not only predisposes to paediatric AIH-1 but is also associated with persistent infection with the endemic hepatitis A virus[52,53]. Presumably, epigenetic factors[54] might have a role in AIH as well.

AIH-2 is associated with *HLADRB1*07* and, in HLA-DR7-negative patients, with *HLADRB1*03* (REFS 55,56). In Egypt, AIH-2 is also associated with *HLADRB1*15* (REF. 50). AIH-2 can be part of the autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome, an autosomal recessive monogenic disorder[57,58]; 20% of patients with this syndrome have AIH[59,60].

Sex and age. One feature of population studies of AIH that has been almost universal has been a female preponderance. Regardless of subtype, 75–80% of patients with AIH are women[23], a characteristic common to most autoimmune diseases.

AIH-1 affects people of all ages with two peaks, one in childhood or adolescence between 10 years and 18 years of age and the other in adulthood around the age of 40 years. Only 20% of patients are diagnosed after the age of 60 years[6,16,61]. AIH-2 mainly affects children, including infants (<1 year of age) and adolescents and young adults (<25 years of age), and is rare, although not absent, in older individuals (>25 years)[6,16,62].

Table 1 | **Subtypes of AIH**

Feature	AIH-1 (adult-predominant)	AIH-2 (paediatric-predominant)
Age at diagnosis	Two characteristic peaks: one in childhood or adolescence and one at ~40 years of age	Mainly in children, including infants but also young adults
Characteristic autoantibodies	ANA and SMA	Anti-LKM1 antibodies, anti-LC1 antibodies and/or anti-LKM3 antibodies
Incidence in white populations	1.5–3.0 cases per 100,000 individuals per year	<0.5 cases per 100,000 individuals per year
Genetic predisposition	*HLADRB1*0301*, *HLADRB1*0401*, *HLADRB1*0405*, *HLADRB1*0404*, *HLADRB1*1301* and *HLADRB1*0301*	*HLADRB1*07*, *HLADRB1*03* and *HLADRB1*15*
Features or characteristics	Occurs in all ages and ethnicities, associated with extrahepatic autoimmune disorders in 20% of cases (such as autoimmune thyroid disease, arthritis and inflammatory bowel disease)	More frequent concomitant extrahepatic autoimmune disorders (such as autoimmune thyroid disease, insulin-dependent diabetes, Addison disease and arthritis)
Disease severity	Usually mild to moderate	Usually moderate to severe, including acute-onset liver failure
Treatment response	Usually good response to steroids plus azathioprine standard of care	Good response to steroids plus azathioprine standard of care but more frequently requiring liver transplantation when presenting with acute liver failure

AIH, autoimmune hepatitis; AIH-1, AIH type 1; AIH-2, AIH type 2; ANA, antinuclear antibodies; anti-LC1, anti-liver cytosol type 1; anti-LKM1, anti-liver kidney microsomal type 1; SMA, anti-smooth muscle antibodies.

Viruses and the microbiota. More recently, environmental factors (such as viral infections) have also been implicated in the development of AIH (see below). Intestinal microbiota may also be involved in the pathogenesis of AIH. For example, alterations in the composition of the intestinal microbiota (dysbiosis) in terms of reduced diversity and reduced total load of gut bacteria have been described in experimental models of AIH[63]. Compared with healthy volunteers, AIH seems to be associated with dysbiosis due to a decreased presence of anaerobic bacteria in the gut, increased gut permeability and increased translocation of intestinal microbial products into the systemic circulation[64].

The increase in AIH prevalence observed in Scandinavia might parallel that in other autoimmune and autoinflammatory diseases, including inflammatory bowel disease, which may occur in association with AIH[65]. These increases in developed countries are thought to be attributable, at least in part, to changes in microbial exposure during childhood that are accompanied by alterations in immune function and might promote allergic and autoimmune disease — the so-called hygiene hypothesis. The immunological mechanisms at play are not well understood but presumably include dysregulation postulated in the pathogenesis of AIH (see below).

Mechanisms/pathophysiology

The precise aetiology of AIH is unknown, but research conducted over the past four decades has revealed that in both adult and juvenile AIH, the interaction between genetic and environmental factors is central to the pathogenesis.

Molecular mimicry

In patients with increased genetic susceptibility to AIH, immune responses to liver autoantigens could be triggered by molecular mimicry, whereby immune responses to external pathogens become directed towards structurally similar self-proteins. T cells targeting the self-epitope become primed and expand, which leads to initiation and perpetuation of autoimmune-mediated liver injury. Molecular mimicry is well illustrated in AIH-2, in which the key target of humoral and cellular autoimmune responses has been defined as the liver enzyme cytochrome P450 2D6 (CYP2D6), which is the target of the anti-LKM1 antibody. An amino acid sequence of CYP2D6 shows a high level of homology with proteins encoded by HCV and members of the herpesvirus family (for example, cytomegalovirus, Epstein–Barr virus and herpes simplex virus)[66].

The hypothesis that exposure to self-mimicking exogenous sequences can trigger AIH is supported by a case report in a child who acquired HCV infection after liver transplantation for end-stage liver disease due to α1-antitrypsin deficiency; anti-LKM1 immunoglobulin M (IgM) was detected 2 weeks after transplantation, switching over time to anti-LKM1 IgG[67] and the development of AIH-2 10 years later even though the HCV infection was cleared[68]. These data suggest that HCV infection initiated an anti-LKM1 immune response and support the involvement of molecular mimicry in the pathogenesis of AIH. An epidemiological link between HCV infection and AIH-2 has been reported[69,70]; conversely, antibodies to HCV have been found in 50% of patients with AIH-2 (REFS 71,72).

Molecular mimicry has also been implicated in a murine model of AIH-2 in which mice that were exposed to CYP2D6 within an adenoviral vector developed anti-LKM1 antibodies[73]. Autoimmunity, once induced against a self-antigen, may spread via molecular mimicry to other homologous self-antigens (epitope spreading). A mouse model of AIH-2 was used to show that the autoreactive response can extend from the dominant epitope to less-dominant sequence homologies within the same antigen (CYP2D6) through molecular mimicry[74]. In AIH-2 in humans, molecular mimicry has also been implicated in the spread of autoimmunity to anatomically distant tissues, such as the endocrine pancreas (resulting in type 1 diabetes mellitus) and the adrenal glands (resulting in Addison disease), through immunological cross reactivity[75].

Immune activation upon self-antigen presentation

Putative mechanisms of autoimmune-mediated liver damage are depicted in FIG. 1. The immune response in AIH is likely initiated by the presentation of self-antigens to uncommitted naive $CD4^+$ T helper (T_H0) cells. Antigen-presenting cells (APCs), such as dendritic cells (DCs), macrophages and B cells, are involved in the processing and presentation of self-antigens to the T cell receptor (TCR) on T_H0 cells. The liver is home to several types of specialized APCs, including liver sinusoidal endothelial cells, Kupffer cells and DCs; consequently, antigen presentation to both $CD4^+$ and $CD8^+$ effector T cells can occur locally, potentially avoiding the need for trafficking to the regional lymph nodes and, in doing so, skewing immune responses towards tolerance[76,77].

$CD4^+$ T_H0 cells become activated during antigen presentation in the presence of appropriate co-stimulatory signals and undergo maturation into distinct T helper cell populations, depending on the cytokine milieu to which they are exposed. T_H0 lymphocytes differentiate into T helper 1 (T_H1) cells in the presence of IL-12, whereas they differentiate into T helper 2 (T_H2) cells in the presence of IL-4. The predominance of transforming growth factor-β (TGFβ), IL-1β and IL-6 favours differentiation into T helper 17 (T_H17) cells.

Differentiation into T_H1 cells leads to the production of IL-2 and interferon-γ (IFNγ) and the concomitant activation of cytotoxic $CD8^+$ T lymphocytes (CTLs) that produce IFNγ and tumour necrosis factor (TNF) and exert cytotoxicity upon recognition of an antigen–MHC class I complex[78]. Exposure of hepatocytes to IFNγ results in the upregulation of MHC class I molecules and in the aberrant expression of MHC class II molecules, which leads to further T cell activation and to the perpetuation of liver damage[79,80]. IFNγ also induces monocyte differentiation, promotes macrophage and immature DC activation[81] and contributes to increased natural killer (NK) cell activity[82].

Differentiation of T_H0 cells into T_H2 cells leads to the secretion of IL-4, IL-10 and IL-13, cytokines that are essential for B cell maturation to plasma cells that secrete autoantibodies, which can induce damage through antibody-mediated cellular cytotoxicity and complement activation[23]. Thus, titres of several autoantibodies correlate with indices of disease activity[83,84]. Moreover, CYP2D6, the target of anti-LKM1 antibodies, is present in the endoplasmic reticulum and the cell membrane of hepatocytes, making the hepatocyte membrane accessible to direct humoral immune attack[85].

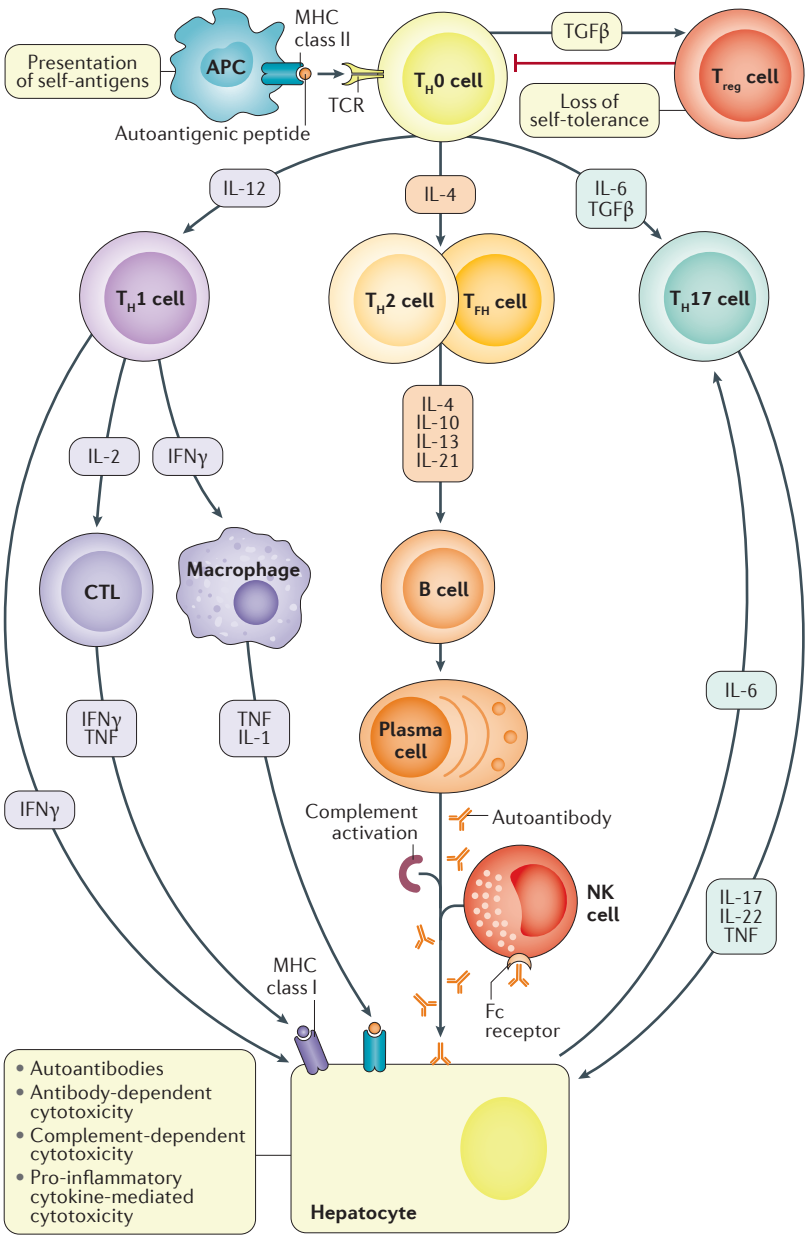

Figure 1 | **Possible pathways of autoimmune attack of hepatocytes in AIH.** Autoimmune-mediated liver injury associated with autoimmune hepatitis (AIH) is probably caused by an immune response to liver autoantigens triggered in genetically susceptible individuals. The immune response involves a variety of immune cells, cytokines, autoantibodies and complement-mediated cytotoxicity. APC, antigen-presenting cell; CTL, cytotoxic $CD8^+$ T lymphocyte; Fc, crystallizable fragment; IFNγ, interferon-γ; MHC, major histocompatibility complex; NK, natural killer; TCR, T cell receptor; T_{FH}, T follicular helper; TGFβ, transforming growth factor-β; T_H0, naive $CD4^+$ T helper; T_H1, T helper 1; T_H2, T helper 2; T_H17, T helper 17; TNF, tumour necrosis factor; T_{reg}, regulatory T.

T_H17 cells contribute to autoimmunity by producing the pro-inflammatory cytokines IL-17, IL-22 and TNF and inducing hepatocytes to secrete IL-6 (REF. 86), which further enhances T_H17 cell activation. Although a high number of T_H17 cells has been reported in AIH, their role in the pathogenesis of AIH is under investigation[86,87]. Additionally, a possible role of T follicular helper (T_{FH}) cells in the pathogenesis of autoimmune diseases is increasingly been reported[88]. T_{FH} cells are specialized $CD4^+$ T cells that induce the activation and differentiation of B cells into immunoglobulin-secreting cells. This helper function is provided in the form of expression of molecules such as CD40 ligand, inducible T cell co-stimulator and cytokines such as IL-21. Excess activation of T_{FH} cells may result in autoimmunity. T_{FH} cells are located in secondary lymphoid tissues, but their counterparts can be found also in the circulation. The serum level of IL-21, secreted by T_{FH} cells, is increased in AIH, and its level correlates with disease activity[87–90].

A specific type of T cells, γδ T cells, might be involved in liver damage, but further research is needed. This subset is more abundant in the liver compared with the circulation[91] and is responsible for granzyme B and IFNγ secretion in AIH. The expression of these molecules correlates with biochemical indices of liver injury[92]. A harming role for macrophages in AIH is sustained by the observation that soluble CD163, produced during macrophage activation, is markedly elevated during active disease and normalizes with successful treatment[93].

Loss of self-tolerance

The development of autoimmune disease is favoured by the breakdown of self-tolerance mechanisms. Circulating autoreactive T cells are present in healthy individuals, but intrinsic and extrinsic peripheral tolerance mechanisms limit their ability to cause tissue damage. Key to this homeostatic process is the control exerted by regulatory T (T_{reg}) cells. Among T cell subsets with potential immunoregulatory function, T_{reg} cells — $CD4^+$ T lymphocytes constitutively expressing the IL-2 receptor subunit-α (IL2-RA; also known as CD25) — represent the dominant subset. These cells derive from T_H0 cells in the presence of TGFβ and constitute 5–10% of all peripheral $CD4^+$ T cells in healthy individuals; they control innate and adaptive immune responses by limiting the proliferation and effector function of autoreactive T cells[94]. T_{reg} cells act by direct contact with the target cells and, to a lesser extent, by releasing immunoregulatory cytokines, such as IL-10 and TGFβ. Aside from CD25, which is also present on T cells undergoing activation, T_{reg} cells express additional markers associated with the acquisition of regulatory properties, including the glucocorticoid-induced TNF receptor, CD62 ligand, cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and the forkhead/winged helix transcription factor FOXP3. Importantly, they express little or no IL-7 receptor (CD127).

Most but not all[95] published data indicate a numerical and functional defect in T_{reg} cells in AIH[96]. In patients with AIH, the number of circulating T_{reg} cells is lower than in healthy individuals, with this reduction being more evident at diagnosis and during relapses than during drug-induced remission[92,97,98]. The number of T_{reg} cells correlates inversely with markers of disease activity, such as anti-SLA and anti-LKM1 autoantibody titres, suggesting that a reduction in the number of T_{reg} cells favours manifestations of AIH[99]. Moreover, T_{reg} cells derived at diagnosis from patients with AIH have a lower ability to control the proliferation of $CD4^+$ and $CD8^+$ effector cells than T_{reg} cells isolated from patients with AIH at remission or from healthy individuals[92,97]. The immunoregulatory defect is magnified by a reduced susceptibility of effector $CD4^+$ T cells to control by T_{reg} cells[100]. Moreover, in AIH, T_{reg} cells expressing ectonucleoside triphosphate diphosphohydrolase 1 (NTPDase 1; also known as CD39) are decreased in number, do not hydrolyse pro-inflammatory nucleotides adequately and are inefficient at suppressing IL-17 production by effector $CD4^+$ T cells[101]. $CD39^+$ T_{reg} cells are also unstable upon pro-inflammatory challenge, suggesting that defective immunoregulation in AIH results not only from reduced number and function of T_{reg} cells but also from increased conversion of T_{reg} cells into effector cells[101]. In AIH, it has also been reported that the low responsiveness of T_{reg} cells to IL-2 results in defective IL-10 production, contributing to functional impairment of the T_{reg} cells[98].

An increase in $FOXP3^+$ cells in the livers of patients with AIH, particularly during active phases of the disease, has been reported and interpreted as an enrichment of T_{reg} cells in the liver[102–104]. However, these studies rely only on the expression of FOXP3 in tissue lymphocytes, a molecule that is also associated with activation of $CD4^+$ T cells (including effector cells[105]), without functional demonstration of regulatory properties.

An interesting animal model characterized by deletion of medullary thymic epithelial cells, which regulate T cell tolerance by ectopically expressing self-antigens and eliminating autoreactive T cells in the thymus, shows that the mice do not have multi-organ autoimmune disease, as might be expected. Instead, the animals develop a condition closely resembling human AIH-1 (with interface hepatitis (defined as extension of lymphoplasmacytic inflammatory infiltrates from the portal tracts into the periportal hepatocytes on liver biopsy), production of ANA, anti-SLA antibodies and antibodies directed to liver-specific antigens), supporting a key role of regulatory mechanisms in the pathogenesis of AIH[106].

If loss of immunoregulation is central to the pathogenesis of AIH, treatment should concentrate on restoring the ability of T_{reg} cells to expand, with a consequent increase in their number and function. However, further confirmatory data are needed, and it is important to devise strategies to prevent T_{reg} cells from becoming effectors of damage within an inflammatory milieu[107,108].

Diagnosis, screening and prevention

AIH in adults

Clinical presentation. AIH in adults is characterized by a female predilection, autoantibodies that react with antigens in both hepatic and non-hepatic tissues, high frequency of concomitant extrahepatic autoimmune diseases, increased levels of γ-globulins (mainly IgG) and interface hepatitis[23,109]. Adults with AIH are currently subdivided on the basis of their autoantibody profiles (TABLE 1) into AIH-1 (frequency of ~95%) and AIH-2 (frequency of ~5%). The clinical presentation of adults with AIH varies widely. The majority of patients have no signs or symptoms of hepatobiliary disease and present with elevations of serum aspartate transaminase and alanine transaminase. However, nonspecific, mild fatigue is common in these otherwise asymptomatic patients.

In patients with concomitant extrahepatic autoimmune diseases, signs or symptoms are often attributable to these autoimmune diseases, which include Hashimoto thyroiditis with later progression to hypothyroidism, Coombs-positive autoimmune haemolytic anaemia, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, coeliac disease, type 1 diabetes mellitus, psoriasis, inflammatory bowel disease and multiple sclerosis. All patients with autoimmune diseases should have biochemical liver tests, and those with abnormal liver biochemical tests should be evaluated for AIH. A minority of patients have unsuspected cirrhosis and present with signs and symptoms of advanced portal hypertension, such as ascites, gastro-oesophageal variceal bleeding, hepatic encephalopathy or jaundice. Patients uncommonly present with acute icteric hepatitis with symptoms mimicking those of acute viral hepatitis, including fatigue, malaise, jaundice and mild right upper quadrant pain. Very rarely, patients present with acute liver failure, defined as the onset of jaundice, coagulopathy and hepatic encephalopathy within 8 weeks of the clinical recognition of liver disease in a patient without prior evidence of chronic liver disease. Thus, AIH must be considered in the differential diagnosis of all adult patients presenting with acute liver failure, acute hepatitis, chronic liver diseases or cirrhosis[23,109].

Biochemical features. The typical biochemical profile is characterized by elevations of aspartate transaminase, alanine transaminase and γ-glutamyltransferase levels with either normal or slightly elevated alkaline phosphatase levels[6,16]. Spontaneous fluctuations of aspartate transaminase and alanine transaminase levels, even dropping into the normal range, should not dissuade diagnostic testing[16]. Levels of total and direct bilirubin vary from normal to significantly abnormal; Gilbert syndrome and haemolytic anaemia are key considerations in the differential diagnosis of indirect hyperbilirubinaemia. Direct-reacting bilirubin generally is ≥50% of the total bilirubin when hyperbilirubinaemia is due to necroinflammation. At diagnosis, γ-globulin or IgG levels are elevated in ~85% of patients[6,16].

Table 2 | **Autoantibodies and the differential diagnosis of AIH**

Autoantibody	Autoantigen	Associated diseases	Use
ANA	Chromatin, ribonucleoproteins and ribonucleoprotein complexes	AIH, PBC, PSC, DILI, chronic hepatitis B, chronic hepatitis C, Wilson disease and NAFLD	Diagnostic for AIH-1 after exclusion of other liver disease; if the ANA specificity is against glycoprotein 210 or nuclear autoantigen Sp-100, the diagnosis is likely PBC, not AIH
SMA (including anti-F-actin antibody)	Microfilaments, such as F-actin and intermediate filaments, such as vimentin and desmin	AIH, PBC, PSC, DILI, hepatitis B, hepatitis C, Wilson disease and NAFLD	Diagnostic for AIH-1 after exclusion of other liver disease
Anti-LKM1 antibody	Epitopes of CYP2D6	AIH, chronic hepatitis C and halothane-induced hepatitis	Diagnostic for AIH-2 after exclusion of other liver disease
pANCA	β-Tubulin isotype 5, mimicry with bacterial cell division protein FtsZ	AIH, PSC, IBD and potentially overlap syndrome	Diagnostic for AIH-1 and, potentially, overlap syndrome with PSC after exclusion of other liver disease
Anti-SLA antibody	*O*-Phosphoseryl-tRNA(Sec) selenium transferase	AIH-1 or AIH-2	Diagnostic of AIH; prognostic for severe disease, relapse after withdrawal of immunosuppression and fetal loss
Anti-LC1 antibody	Formimidoyltransferase cyclodeaminase	AIH-2	Diagnostic of AIH-2; the autoantibody is specific for liver tissue
Anti-LKM3 antibody	Family 1 UDP-glucuronosyltransferases	AIH-2 and chronic hepatitis D	Diagnostic for AIH-2, after exclusion of hepatitis D virus infection
AMA	Pyruvate dehydrogenase complex (E2 subunit lipoyl domains)	PBC, rarely AIH and potentially overlap syndrome	Rarely observed in AIH-1 and might be indicative of overlap syndrome
Anti-LM antibody	Epitopes of CYP2A6	APECED and hepatitis C	Diagnostic for APECED, after exclusion of hepatitis C
Anti-ASGPR antibody	ASGPR	AIH, PBC, DILI, chronic hepatitis B, chronic hepatitis C and chronic hepatitis D	The autoantibody is specific for liver tissue; detected in AIH-1 and AIH-2; prognostic for severe disease, higher histopathological activity scores and relapse after withdrawal of immunosuppression

AIH, autoimmune hepatitis; AIH-1, AIH type 1; AIH-2, AIH type 2; AMA, anti-mitochondrial antibody; ANA, antinuclear antibodies; anti0LC1, anti-liver cytosol type 1; anti-LKM1, anti-liver kidney microsomal type 1; anti-LM, anti-liver microsomal; anti-SLA, anti-soluble liver antigen; APECED, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy; ASGPR, asialoglycoprotein receptor; CYP2A6, cytochrome P240 2A6; CYP2D6, cytochrome P240 2D6; DILI, drug-induced liver injury; F-actin, filamentous actin; IBD, inflammatory bowel disease; NAFLD, nonalcoholic fatty liver disease; pANCA, perinuclear neutrophil cytoplasmic antibody; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SMA, anti-smooth muscle antibodies; UDP, uridine 5′-diphospho-glucuronosyltransferase.

Autoantibodies. Autoantibodies serve as biomarkers of AIH-1 and AIH-2 (TABLE 2), but AIH can rarely occur without detectable autoantibodies[6,16,23,109]. ANA, SMA and anti-LKM1 antibodies have been regarded as sufficient to screen for AIH-1 and AIH-2; however, a recent guideline recommended the addition of anti-SLA antibody testing[16]. Only a subset of patients with SMA has anti-filamentous actin (F-actin) specificity; thus, SMA should be used for screening[110]. When ANA, SMA and anti-LKM1 antibodies are undetected, additional testing for perinuclear neutrophil cytoplasmic antibody (pANCA) and anti-SLA, anti-LC1 and anti-LKM3 antibodies should be performed (TABLE 2). Paradoxically, patients without autoantibodies, more commonly those presenting acutely, may develop detectable autoantibodies after responding to an empiric trial of immunosuppression[6,111,112].

ANA, SMA and anti-LKM1 antibodies occur in liver diseases other than AIH. Thus, they are not diagnostic in isolation of AIH (TABLE 2). Indeed, a study of the diagnostic utility of these antibodies in patients with AIH or another chronic liver disease showed that the diagnostic sensitivities for AIH were only 32% for ANA, 16% for SMA and 1% for anti-LKM1 antibodies. As a result, their diagnostic accuracy was only 56–61%[113,114]. Positivity for multiple autoantibodies, especially a combination of ANA and SMA, strongly favours a diagnosis of AIH with a diagnostic specificity of 99%, a positive predictive value of 97% and a diagnostic accuracy of 74%. Only anti-SLA antibodies have high specificity (98.9%) for AIH[6,16,115].

Liver histology. Histological features have prominent roles in the diagnosis of acute or chronic AIH[6,16] (FIG. 2). Thus, a liver biopsy is necessary for an accurate diagnosis of AIH and is helpful to exclude alternative diseases in the differential diagnosis, to identify comorbid diseases and to stage fibrosis. Interface hepatitis is the primary histological feature of chronic AIH; however, it also occurs in other liver diseases, including acute and chronic viral hepatitis, Wilson disease, drug-induced liver injury, primary biliary cholangitis and primary sclerosing cholangitis[109]. Central zonal necrosis and/or perivenulitis of the central veins is now regarded as an important histological lesion in AIH; it has been reported in up to 66% of patients presenting with acute liver failure or acute hepatitis[116,117]. In acute liver failure, a transjugular liver biopsy is indicated owing to coagulopathy[116,117]. Central zonal perivenulitis also occurs in patients with chronic AIH with or without interface hepatitis[118,119]. In the absence of interface hepatitis, lesions of central zonal perivenulitis are considered consistent with a diagnosis of AIH. Mild bile duct injury and ductular reaction are common in AIH biopsies before starting immunosuppressive treatment, despite the absence of considerable cholestatic biochemical abnormalities[120]. These histological findings should not be considered as evidence of a cholestatic variant or overlap syndrome.

Cholestatic variant syndrome and overlap syndromes. AIH can be associated with biochemical cholestasis (cholestatic variant syndrome) or with various features

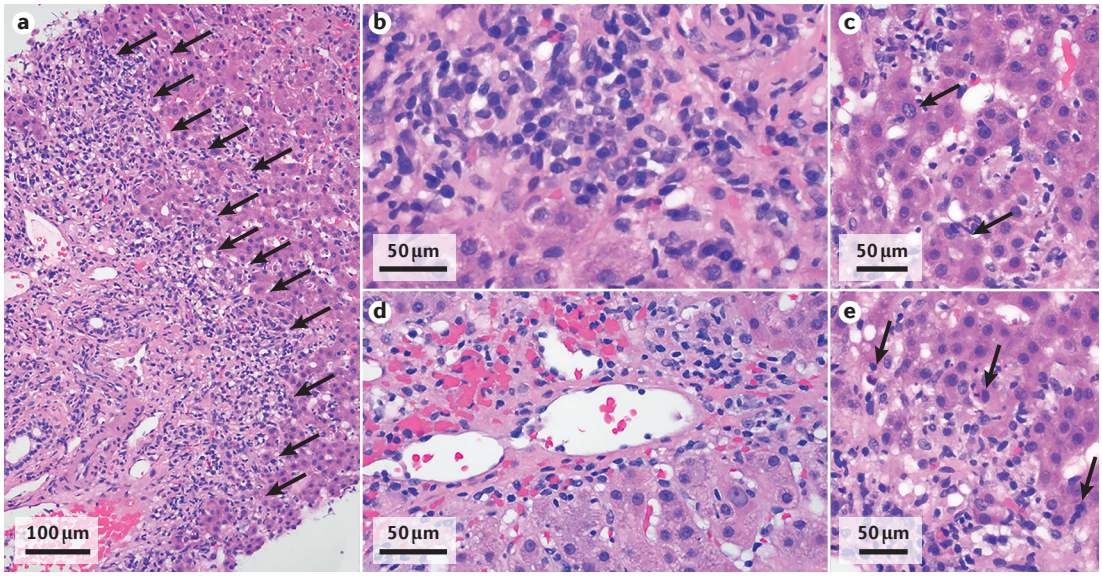

Figure 2 | **Histopathology of AIH.** Chronic autoimmune hepatitis (AIH) with lymphoplasmacytic portal inflammation extending into the lobule (arrows) and interface hepatitis (part **a**). Chronic AIH with an inflammatory infiltrate consisting of plasma cells, which exhibit a prominent pale staining of Golgi adjacent to nuclei (part **b**). Chronic hepatitis with rosettes (arrows) of regenerating hepatocytes (part **c**). Acute AIH with perivenulitis of central vein and central zonal necrosis (part **d**). Hepatocyte emperipolesis (presence of an intact cell in the cytoplasm of another cell; arrows) showing a lymphocyte within cytoplasm of a hepatocyte with displacement of nucleus and early phase of apoptosis in AIH (part **e**). Clinicians should interpret features of a biopsy specimen in the context of all clinical, biochemical and serological features using either the revised diagnostic criteria (RDC)[45] or simplified diagnostic criteria (SDC)[125] of the International Autoimmune Hepatitis Group. If pathology reports lack the necessary details for RDC or SDC scoring, an expert pathologist should be consulted. Experienced pathologists can categorize a biopsy sample as typical, compatible or incompatible with AIH[117]. All slides are haemotoxylin and eosin-stained. Images courtesy of Sadhna Dhingra, Baylor College of Medicine, USA.

of either primary biliary cholangitis or primary sclerosing cholangitis (commonly termed an overlap syndrome). The advantage of the term 'cholestatic variant syndrome' is that it prompts testing for aetiologies of cholestasis other than primary biliary cholangitis or primary sclerosing cholangitis, which include biliary obstruction, granulomatous or other infiltrative diseases, cholestatic viral hepatitis and cholestatic drug-induced liver injury. The term 'overlap syndrome' implies coexistence of AIH with either primary biliary cholangitis or primary sclerosing cholangitis[121]. However, diagnostic criteria for overlap syndromes of AIH with primary biliary cholangitis or primary sclerosing cholangitis have not been validated[117,122]. The International Autoimmune Hepatitis Group critical review concluded that overlap syndrome should be defined as a distinct type of autoimmune liver disease but should be classified according to the predominant autoimmune liver disease as AIH, primary biliary cholangitis or primary sclerosing cholangitis with features of another autoimmune liver disease[117,122].

Although overlap between AIH and primary biliary cholangitis does not exist in the paediatric setting, an overlap between AIH and sclerosing cholangitis is much more common than in adults (as frequent as AIH-1 (REF. 123)). Indeed, it is considered a distinct nosological entity called autoimmune sclerosing cholangitis (ASC; see below)[124].

Diagnostic criteria. The International Autoimmune Hepatitis Group published revised diagnostic criteria (RDC) for AIH in 1999 (REF. 45) and simplified diagnostic criteria (SDC) in 2008 (REF. 125) (BOX 1). Both the RDC and SDC include histological features and assign extra points for high titres of autoantibodies tested by indirect immunofluorescence. Unfortunately, in the United States, ANA, SMA, anti-F-actin antibodies, anti-LKM1 antibodies and anti-SLA antibodies are detected using molecular-based assays such as enzyme-linked immunosorbent assay (ELISA)[111]. As ELISA units cannot be translated into specific autoantibody titres, extra points cannot be assigned using ELISA units. Thus, autoantibody testing with ELISA may result in underestimates of RDC or SDC scores[23,109]. Unfortunately, comprehensive autoantibody testing is also inconsistently available throughout the world; however, the probability of the diagnosis can be established in most patients using only ANA, SMA and anti-LKM1 antibody testing and RDC.

The NIH Acute Liver Failure Study Group proposed that additional diagnostic criteria for patients presenting with acute liver failure should include histological evidence of multilobular necrosis, lymphoplasmacytic inflammatory infiltrates, lymphoid follicles and central zonal necrosis with perivenulitis of the central vein[116]. As the transjugular liver biopsy technique required for such patients is often unavailable locally and liver

transplantation may be necessary, these patients should be urgently transferred to a liver transplant centre.

The RDC are more accurate than the SDC for diagnosis of AIH in patients with complex medical histories of comorbid diseases, multiple medications or alcohol use[23,109]. However, the diagnostic accuracies of the more complex RDC and simpler SDC are equivalent for AIH with classic features itemized in these criteria. Thus, the SDC are preferred for patients with typical biochemical, serological and histological features of AIH. A retrospective comparative study confirmed high specificities of the RDC (97.9%) and SDC (97%)[126]. As expected, the frequency of a 'probable' diagnosis in adults with AIH was lower using RDC (9%) than SDC (15%), and the concordance between RDC and SDC scores was only 79%[127]. RDC scoring can revise the probability of AIH to 'definite' in patients with 'probable' or 'non-diagnostic' SDC scores. Validation studies of RDC and SDC in China[27] concluded that the RDC were superior primarily because these studies included scores for associated immunological diseases[128]. Thus, any patient with SDC scores of 'probable' or 'non-diagnostic' should be reassessed using the RDC.

Differential diagnosis. In the absence of diagnostic biomarkers specific for AIH (other than the infrequently detected anti-SLA antibody), a systematic approach is required to distinguish AIH from other liver diseases with similar clinical, biochemical, serological and histological features. These include hepatitis associated with viral infections (including the hepatitis viruses A–E, Epstein–Barr virus, cytomegalovirus and herpes simplex virus), primary biliary cholangitis, primary sclerosing cholangitis, drug-induced liver injury and Wilson disease. Exclusion of Wilson disease is critical but difficult because serum ceruloplasmin (a ferroxidase) levels, which are usually below the normal range in Wilson disease, may rise into the normal range owing to increased ceruloplasmin synthesis caused by pro-inflammatory cytokines[129]. Conversely, acute liver failure, regardless of aetiology, is associated with low ceruloplasmin levels owing to massive hepatic necrosis[130]. The diagnosis of Wilson disease in these patients is based on slit-lamp evaluation of the eye for Kayser–Fleischer corneal rings and substantial elevations of hepatic and 24-hour urinary copper concentrations[129,131].

Juvenile AIH

There are two forms of juvenile AIH (TABLE 1). AIH-1 accounts for two-thirds of the juvenile cases and presents often around puberty, whereas AIH-2 affects younger children, including infants.

Clinical presentation. As in the adult disease, the majority of patients with juvenile AIH are female[124]. There are three clinical patterns of AIH presentation in children and adolescents: acute in ~40% of patients, although fulminant hepatitis is rare, being more common in AIH-1 than in AIH-2; insidious in ~25–50% of individuals, characterized by progressive fatigue, relapsing jaundice, headache, anorexia and amenorrhoea; and

Box 1 | **Diagnostic criteria for AIH in adults**

Revised diagnostic criteria (RDC)[45]

A 'definite' diagnosis of autoimmune hepatitis (AIH) before treatment requires an aggregate score of >15 points using the system below, whereas a 'probable' diagnosis requires an aggregate score of 10–15 points. After observing the response to treatment, a definite diagnosis is based on an aggregate score of >17, whereas a probable diagnosis requires a score of 12–17[a].

- Female sex (+2 points)
- Ratio of alkaline phosphatase levels to aspartate aminotransferase or alanine aminotransferase levels: <1.5 (+2 points), 1.5–3 (0 points) and >3 (−2 points)
- γ-Globulin or immunoglobulin G (IgG) level >2-fold the upper level of normal (ULN) (+3 points), 1–1.5-fold the ULN (+1 point) and <1-fold the ULN (0 points)
- Antinuclear antibodies (ANA), anti-smooth muscle antibodies (SMA) and anti-liver kidney microsomal type 1 (anti-LKM1) antibody titres[b]: >1:80 (+3 points), 1:80 (+2 points), 1:40 (+1 point) and <1:40 (0 points)
- Antimitochondrial antibody positivity: positive (−4 points) or negative (0 points)
- Viral serological markers: positive (−3 points) or negative (+3 points)
- Use of drugs with hepatotoxic potential: yes (−4 points) or no (+1 point)
- Alcohol use: <25 g daily (+2 points) or >60 g daily (−2 points)
- *HLADR3* or *HLADR4* genotypes: positive (+1 point) or negative (0 point)
- Concurrent immunological diseases (for example, thyroiditis and colitis): present (+2 points) or absent (0 points)
- Histological features
  - Interface hepatitis (+3 points)
  - Plasma cells (+1 point)
  - Rosettes (+1 point)
  - Absence of interface hepatitis, plasma cells and rosettes (−5 points)
  - Biliary changes (−3 points)
  - Other features (−3 points)
- Immunosuppressive treatment response: complete (+2 points) or relapse (+3 points)

Simplified diagnostic criteria (SDC)[125]

A pretreatment aggregate score of ≥7 defines definite AIH, whereas ≥6 defines a probable diagnosis

- Presence of autoantibodies:
  - ANA or SMA titres of ≥1:40 (+1 point) or ≥1:80 (+2 points)
  - Anti-LKM1 antibody titres of ≥1:40 (+2 points)
  - Anti-soluble liver antigen (anti-SLA) antibody positivity (+2 points)
- Immunoglobulin level:
  - IgG level greater than the ULN (+1 point)
  - γ-Globulin level of >1.1-fold the ULN (+2 points)
- Histological features
  - Compatible with AIH (+1 point)
  - Typical of AIH[c] (+2 points)
- Viral hepatitis: absent (+2 points) or present (0 points)

[a]A pretreatment RDC score of 15 is considered definite for the diagnosis of AIH on the basis of a sensitivity of 95%, a specificity of 97% and an accuracy of 94%[45]. A pretreatment RDC score of 10 denotes a probable diagnosis of AIH with a sensitivity of 100% and a specificity of 73% but a lower accuracy of 67%. [b]Positive test using indirect immunofluorescence following dilution of the serum sample as indicated. [c]Typical histological features are those contained in the RDC, principally interface hepatitis.

with complications of portal hypertension in ~10% of patients[132]. Hence, AIH should be suspected in all children and adolescents with symptoms or signs of liver disease not due to other known pathologies that can have similar clinical and laboratory features (for example, Wilson disease, viral hepatitis and drug-induced liver injury). AIH-2 can be part of the autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome, in which liver disease is present in 20–30% of cases[133]. As 20–40% of individuals with juvenile AIH have associated autoimmune disorders, these should be actively sought as some of these disorders, such as thyroiditis, coeliac disease and inflammatory bowel disease, which may still be asymptomatic, require prompt treatment.

Biochemical features. AIH-1 is associated with ANA and/or SMA, whereas AIH-2 is associated with anti-LKM1 antibodies and/or anti-LC1 antibodies. Another autoantibody of diagnostic importance is anti-SLA antibody, which is highly specific for AIH and is found in 30–50% of children with AIH-1 or AIH-2. The presence of anti-SLA antibodies defines a more-severe disease course[134]; anti-SLA antibodies are the only autoantibody present in a minority of children with AIH. Anti-SLA antibodies are not detectable by indirect immunofluorescence but only by molecular-based assays and should be always requested when AIH is suspected for both diagnostic and prognostic reasons. IgG levels are usually increased, but 15% of children with AIH-1 and 25% of children with AIH-2 have levels within the normal range. IgA deficiency is common in AIH-2 (REF. 132). In children and adolescents, elevations of alkaline phosphatase associated with bone growth must not be misinterpreted as cholestasis, indicative of disease of the bile ducts.

Liver histology. Liver biopsy is essential for diagnosis of juvenile AIH and, as in adult AIH, liver biopsy samples are characterized by interface hepatitis, portal lymphoplasmacytic infiltrate, rosette formation and emperipolesis[124]. As children and adolescents with AIH often have an acute presentation, histological damage in the centrilobular area with necrosis and multilobular collapse is observed more frequently than in adults with AIH[124].

Autoimmune sclerosing cholangitis

As mentioned above, an overlap between AIH and sclerosing cholangitis is much more common in children and adolescents than in adults and has been called ASC[124]. ASC has strong autoimmune features, characterized by ANA and SMA positivity and high levels of IgG and interface hepatitis, and is as prevalent as AIH-1 in children and adolescents[123]. In the absence of bile duct imaging, these children and adolescents are usually diagnosed as having AIH-1, but they experience a more-severe course of disease. ASC is more often associated with inflammatory bowel disease (~45%) than is AIH (~20%) and affects boys and girls equally. Approximately 75% of patients with ASC and 40% of those with AIH-1 have circulating atypical pANCA, particularly in association with inflammatory bowel disease[134]. Additionally, ~30% of patients with ASC are also positive for anti-SLA antibodies[123].

Diagnostic criteria. The International Autoimmune Hepatitis Group scoring systems for AIH in adults (BOX 1) are not suitable for juvenile AIH because diagnostically relevant autoantibodies often have titres lower than those considered positive in adults[124] and because the criteria do not distinguish between AIH and ASC, which can be distinguished only by cholangiography. A recent European Society of Paediatric Gastroenterology, Hepatology and Nutrition position paper proposes a diagnostic scoring system for juvenile AIH and ASC[124] (BOX 2).

Prevention

As the cause of AIH is unknown, prevention of the disease is impossible. However, a low threshold for the diagnosis of AIH with unexplained liver disease, leading to early treatment, prevents the progression of liver damage in the majority of patients with excellent long-term survival without the need for liver transplantation.

Management

The aim of treatment is induction of stable remission. Biochemical remission is defined as lowering of transaminase and IgG levels to normal[6,16]. However, the normal range is quite wide for transaminases and even wider for

Box 2 | **Proposed scoring criteria for the diagnosis of juvenile AIH**

In the scoring system proposed by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition[124], a score of ≥7 is consistent with probable juvenile autoimmune hepatitis (AIH) or probable autoimmune sclerosing cholangitis (ASC), whereas ≥8 points is consistent with definite AIH or definite ASC.

- Presence of autoantibodies
  - Antinuclear antibodies (ANA)[a] or anti-smooth muscle antibodies (SMA)[a] with titres of ≥1:20[b] (+1 point for AIH and ASC) or ≥1:80 (+2 points for AIH and ASC)
  - Anti-liver kidney microsomal type 1 (anti-LKM1) antibody[a] titres of ≥1:10[b] (+1 point for AIH and ASC) or ≥1:80 (+2 points for AIH and +1 point for ASC)
  - Anti-liver cytosol type 1 (anti-LC1) antibody-positive[b] (+2 points for AIH and +1 point for ASC)
  - Anti-soluble liver antigen (anti-SLA) antibody-positive[b] (+2 points for AIH and ASC)
  - Anti-perinuclear neutrophil cytoplasmic antibody (pANCA)-positive (+1 point for AIH and +2 points for ASC)
- Immunoglobulin level
  - Immunoglobulin G (IgG) level more than the upper limit of normal (ULN) (+1 point for AIH and ASC)
  - IgG level >1.2-fold the ULN (+2 points for AIH and ASC)
- Histological features
  - Compatible with AIH (+1 point for AIH and ASC)
  - Typical of AIH[c] (+2 points for AIH and ASC)
- Other clinical features
  - Absence of viral hepatitis, Wilson disease, nonalcoholic steatohepatitis and drug exposure (+2 points for AIH and ASC)
  - Presence of extrahepatic autoimmunity (+1 point for AIH and ASC)
  - Family history of autoimmune disease (+1 point for AIH and ASC)
- Cholangiography normal (+2 points for AIH and −2 points for ASC) or abnormal (−2 points for AIH and +2 points for ASC)

[a]Antibodies measured by indirect immunofluorescence on a composite rodent substrate (that is, kidney, liver or stomach). [b]Addition of points achieved for ANA, SMA, anti-LKM1 antibodies, anti-LC1 antibodies and anti-SLA autoantibodies cannot exceed a maximum of 2 points. [c]Typical histological features are those contained in the revised diagnostic criteria of the International Autoimmune Hepatitis Group[45], principally interface hepatitis.

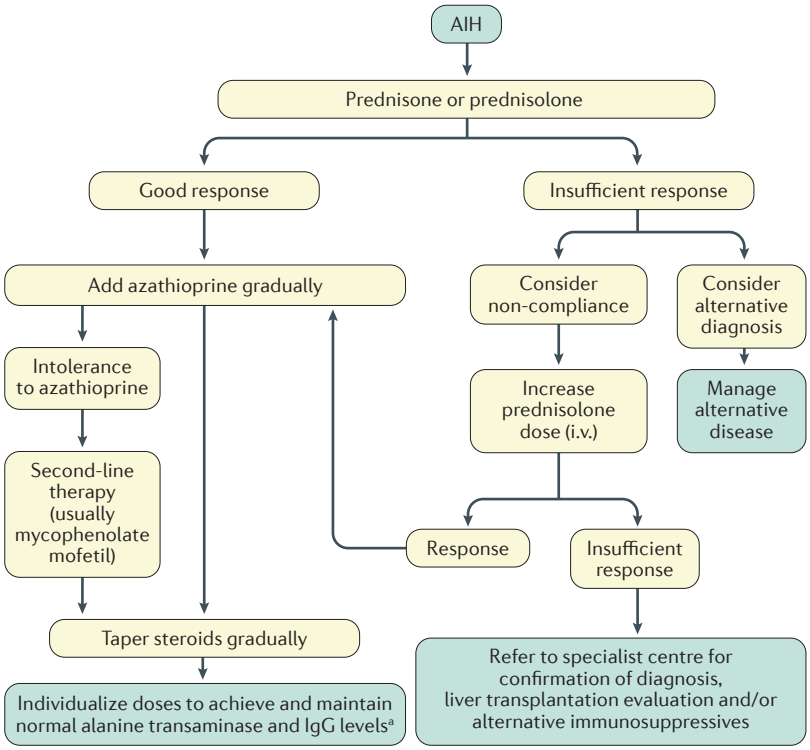

Figure 3 | **Management of AIH in adults.** Management of autoimmune hepatitis (AIH) involves induction of remission and long-termmaintenance therapy. Biochemical end points are normalization of transaminase and immunoglobulin G (IgG) levels. i.v., intravenous. [a]Consider checking 6-thioguanine levels. Adapted with permission from REF. 16, Elsevier.

IgG. Thus, patients in the upper range of normal may still have considerable histological disease activity as well as risk of reactivation (relapse and/or flare). The better the biochemical response is, the less a histological confirmation of remission is required. A follow-up biopsy is advisable if laboratory tests remain abnormal despite optimal drug therapy and may sometimes detect drug toxicity or another concurrent liver disease such as nonalcoholic steatohepatitis[135]. When considering a follow-up biopsy, it is important to be aware that histological remission takes longer to achieve than biochemical remission.

AIH in adults

Standard of care. AIH should always be treated with immunosuppressive drugs with very few exceptions[6,16,136]. For example, in patients with decompensated liver disease, the risks of therapy may sometimes outweigh the risks of the disease. Expectant management might also be recommended for patients with very mild disease. However, as fibrosis may progress subclinically and disease flares, which are often diagnosed too late, are common, immunosuppression using a drug dose tailored to the individual patient is strongly recommended[16]. In patients with AIH who have decompensated liver cirrhosis and in those with no evidence of inflammatory activity, immunosuppressive therapy may not be indicated, but these patients should be closely watched for signs of reactivation or flares of the inflammatory disease[6,16].

The drugs of choice for the induction of remission in AIH are corticosteroids, and the drug of choice for maintenance of remission is azathioprine (a purine analogue) with or without corticosteroids depending on an individual benefit–risk evaluation (FIG. 3). If azathioprine is not tolerated, maintenance of remission using only corticosteroids might be preferred. In patients presenting with acute hepatitis and suspected AIH, a starting dose of 0.5–1.0 mg per kg body weight of prednisolone or prednisone is recommended to achieve a rapid response, which both benefits the patient and confirms the diagnosis, as AIH almost invariably responds to steroid therapy within 2–3 weeks[16]. If patients do not respond, the diagnosis should be questioned. Lower doses of prednisolone or prednisone can be given in patients with mild disease, whereas in very active or fulminant disease it may be advisable to start treatment with high-dose (for example, 100 mg) intravenous prednisolone. Starting with steroid monotherapy is best until a response is observed.

Budesonide has been shown to be an effective alternative steroid to prednisolone or prednisone in treating AIH[2,137,138]. However, the experience is still limited. The advantage of lower systemic adverse effects associated with budesonide compared with prednisolone or prednisone is counterbalanced by several disadvantages. The response to the standard dose of 3 mg three times a day is slower than the response to prednisolone or prednisone starting at the equivalent dose (usually 1 mg per kg body weight); as a consequence, the prednisolone dose can be reduced more rapidly than the budesonide dose[137]. No data on reduction schedules for budesonide are available, and its short half-life probably makes it necessary to give the drug at least twice a day[139]. Conceivably, the systemic effects of AIH, such as IgG elevation but also arthralgia, may respond less well to budesonide with its high hepatic first-pass effect than to prednisolone. For this reason, most specialized centres as well as the European Association for the Study of the Liver clinical practice guidelines continue to favour prednisolone as the steroid of choice for treating AIH[16]. In approximately half of patients, steroids can be tapered completely within the first year of therapy, and most steroid-dependent patients need only low doses (<10 mg daily) and are, therefore, exposed to minimal steroid adverse effects.

As soon as the patient improves, usually after 2 weeks, azathioprine should be added to the corticosteroid treatment to taper steroids rapidly and limit the adverse effects associated with steroids. A low starting dose of azathioprine is recommended to limit adverse effects. Up to 5% of patients have azathioprine intolerance and develop marked symptoms such as fever, nausea and body pains, which resolve within 2 days of stopping treatment[140]. Mild nausea is even more common but improves with time and can be minimized initially by taking the drug after the main meal and using a low starting dose. 6-Mercaptopurine, which is a metabolite of azathioprine, at half the dosage of azathioprine may alleviate the gastrointestinal and other symptoms of intolerance and may be equally effective as an immunosuppressive agent[141]. Bone marrow toxicity associated

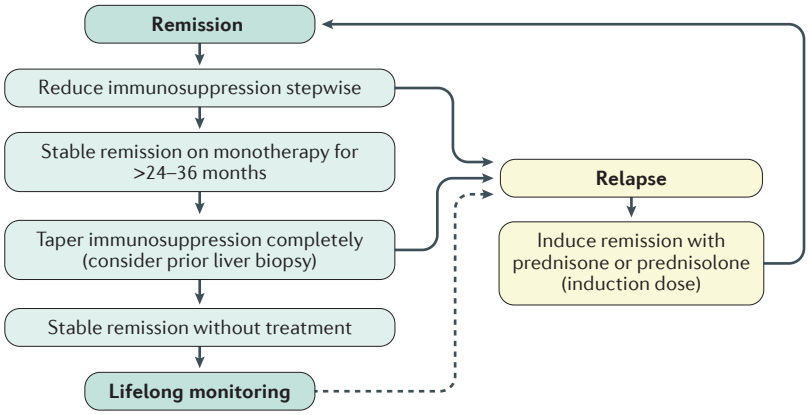

Figure 4 | **Follow-up of adults with AIH following remission.** Drug-free remission (with normal alanine transaminase and immunoglobulin G levels) of autoimmune hepatitis (AIH) is infrequent and cannot be achieved in the majority of patients. Accordingly, lifelong maintenance therapy (for which the lowest dose possible to achieve and maintain remission is the aim) or monitoring (every 3 months for the first year, then every 6 months) is usually required because reactivation of disease can develop at any time. In the few patients (10–20%) in whom it is possible to taper all immunosuppressive medication and who remain in stable drug-free remission, relapse remains possible (dashed line), even after many disease-free years; thus, lifelong monitoring is recommended. The longer the drug-free remission lasts, the less likely relapse becomes; however, cases of relapse after 20 years of drug-free remission have been observed. Adapted with permission from REF. 16, Elsevier.

with azathioprine is dose-dependent but also depends on the individual variability of azathioprine pharmacokinetics. Genetic testing for the rare mutations of the rate-limiting enzyme thiopurine *S*-methyltransferase (*TPMT*) can be used to avoid severe bone marrow toxicity in individuals at risk, but even patients without these *TPMT* mutations may develop bone marrow toxicity, whereas some carriers of the mutation tolerate the drug reasonably well[142]. With or without *TPMT* testing, the azathioprine dose should be increased stepwise with regular blood counts during the first 3 months of treatment until the optimum dose is reached, which is usually 1–2 mg per kg body weight. Because of the variability of azathioprine metabolism, it may be advisable to measure serum levels of its biologically active metabolites 6-mercaptopurine and 6-thioguanine during follow-up[143]. Measuring these metabolites can also be used to assess patient compliance. Patients with higher serum levels of 6-thioguanine are more likely to be in remission, suggesting that adapting the azathioprine dose on the basis of serum 6-thiohuanine levels can be helpful[143].

After achieving remission, most patients are keen to know whether it could be maintained without drugs[2,136] (FIG. 4). Unfortunately, <20% of patients can stop treatment successfully, and late relapses even years after cessation of therapy are not uncommon[144,145]. A trial of treatment withdrawal should be undertaken only after a minimum of 3 years of immunosuppressive therapy and only when full and stable remission has been achieved for the past 2 years of treatment. Patients with alanine transaminase levels in the lower half of the normal range and IgG levels <12 g per litre have a higher chance of successful treatment withdrawal than patients with values in the upper range of normal[146]. If an attempt at treatment withdrawal is undertaken, close monitoring for relapse should be maintained for the following 6–12 months to be able to treat a possible relapse early and effectively with low-dose transient steroid therapy and reinstitution of azathioprine. Long-term follow-up beyond 12 months is recommended as late relapses can occur.

Alternative drug treatments. Patients intolerant to azathioprine and patients not responding sufficiently to standard treatment may require alternative therapies. For this small group (3–5%) of patients, recommendations are based on experience and consensus rather than robust scientific data.

Patients intolerant to azathioprine probably fare best with mycophenolate mofetil as an alternative systemic immunosuppressant[16]. Mycophenolate mofetil is able to maintain ~80% of azathioprine-intolerant patients in stable remission with either low-dose prednisolone or without prednisolone[147]. However, mycophenolate mofetil is almost never effective in the few adult patients who do not achieve full remission on azathioprine; thus, mycophenolate mofetil is normally not advised as a second-line treatment for non-responders. In non-responders to azathioprine, 6-thioguanine levels should be checked to assess both compliance and aberrant pharmacodynamics[16,143]. If there is insufficient response despite adequate 6-thioguanine levels, various second-line drugs have been reported to be effective. Ciclosporin A and tacrolimus are effective in a large proportion of these patients but have considerable adverse effects and require regular monitoring[148]. Recently, biologicals such as anti-TNF (infliximab) and anti-CD20 (rituximab) have been used successfully in a small number of patients with refractory AIH[149,150]; the use of these agents should be restricted to specialized centres owing to potential very serious adverse effects.

Juvenile AIH

Juvenile AIH, which is more aggressive than adult AIH, should always be treated with immunosuppression (FIG. 5).

Standard of care. Juvenile AIH-1 and AIH-2 are treated similarly. Juvenile AIH responds well to immunosuppression, even in the presence of poor liver synthetic function, denoted by low albumin levels and coagulopathy and/or established cirrhosis[124]. Prednisolone is started at 2 mg per kg daily (maximum 60 mg daily) and is gradually decreased over 4–8 weeks in parallel to progressive normalization of transaminase levels to reach the minimal maintenance dose able to sustain normal transaminase levels, usually 5 mg daily. During the first 6–8 weeks, liver function tests are checked weekly to fine-tune treatment and avoid severe adverse effects associated with steroid use. The initial goal is to obtain an 80% reduction of baseline transaminase levels within 8 weeks of treatment. If progressive normalization of transaminase levels is not achieved, azathioprine is added at a starting dose of 0.5 mg per kg daily, which, in the absence of toxicity, is increased up to a maximum

of 2–2.5 mg per kg daily until remission is achieved (that is, normal transaminase and IgG levels, negative or very low titres of ANA (<1:10), SMA (<1:10) and anti-LKM1 antibodies (negative). Azathioprine is not recommended as first-line treatment because of its potential hepatotoxicity, particularly in severely jaundiced patients[124]. Normalization of transaminase levels may take several months[132].

Relapse on treatment affects ~40% of children with AIH, requiring a temporary increase of steroid dose. Often relapse is due to non-adherence, particularly in adolescents[151]. The risk of relapse is higher if steroids are administered on alternate days. Small daily doses are more effective in maintaining disease control, preventing the need for high-dose steroid pulses during relapses and do not ultimately affect growth[152].

Treatment is recommended for at least 3 years before considering cessation. Treatment withdrawal can then be attempted if liver function tests and IgG levels have been persistently normal, autoantibodies are either undetectable or detectable at very low titres over at least 12 months and a liver biopsy sample shows no inflammatory changes. Treatment withdrawal is successful in ~20% of individuals with AIH-1 but rarely in those with AIH-2 (REF. 132). Autoantibody titres and IgG levels correlate with disease activity[153].

Alternative drug treatments. Induction of remission has been reported using ciclosporin A alone for 6 months, followed by maintenance with low-dose prednisone and azathioprine[154], but whether this is better than standard treatment awaits evaluation in controlled studies. Induction of remission with budesonide doses used in adults is unsatisfactory in juvenile AIH, with a low remission rate after 12 months of treatment[155]. Large controlled studies are needed to establish the appropriate dose for children. In those 10% of patients who do not respond to standard immunosuppression or are intolerant to azathioprine, mycophenolate mofetil (20 mg per kg twice daily) has been successfully used[124]. In the case of persistent nonresponse, calcineurin inhibitors (ciclosporin A or tacrolimus) should be considered.

Autoimmune sclerosing cholangitis. In ASC, with early treatment, the parenchymal liver damage responds well to the same immunosuppressive schedule used for AIH with addition of ursodeoxycholic acid (15–20 mg per kg daily) with good medium-term and long-term survival. However, bile duct disease progresses in ~50% of patients, resulting in the need for liver transplantation in 20%[132]. Progression of liver disease is associated with poorly controlled inflammatory bowel disease.

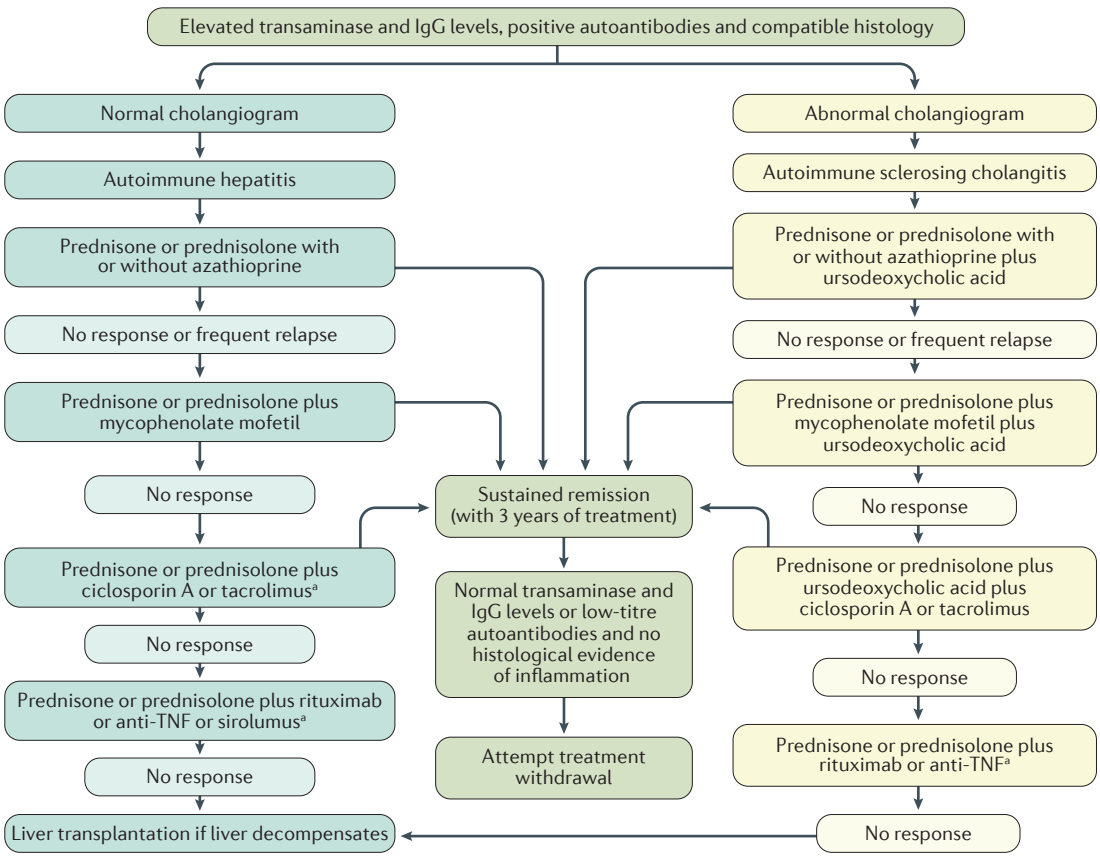

Figure 5 | **Treatment decision-making in children with autoimmune liver disease.** Cholangiography can be used to distinguish autoimmune sclerosing cholangitis from autoimmune hepatitis. Once this is established, different regimens can be pursued to achieve remission. IgG, immunoglobulin G; TNF, tumour necrosis factor. [a]Second-line and third-line treatments to be decided and monitored only in specialized paediatric hepatology centres.

Liver transplantation

In North America and in Europe, 4% of liver transplantations are performed for AIH[6]. Liver transplant is indicated in patients with AIH who develop fulminant hepatic failure (with encephalopathy) that is unresponsive to corticosteroids and, at the other end of the spectrum, in those (10–20%) who develop end-stage liver disease despite treatment[6,156–159]. End-stage liver disease requiring liver transplantation despite treatment develops in ~10% of children and adolescents with AIH and in ~20% of those with ASC within 15 years of diagnosis[123,132]. Recurrence of AIH and ASC following liver transplantation has been described as well as de novo AIH in patients not transplanted for autoimmune liver disease.

Recurrence of AIH, characterized by high transaminase levels, positive autoantibodies, interface hepatitis and response to steroids, affects 20–30% of transplanted patients and does not usually affect outcomes after liver transplant[160]. Recurrence of ASC is characterized histologically by fibrous cholangitis, fibro-obliterative lesions with or without ductopenia, fibrosis or cirrhosis and interface hepatitis; cholangiography can characterize diffuse biliary stricturing[161]. Before diagnosing recurrent ASC, other causes of bile duct damage after transplantation must be excluded, including ischaemic biliary insults (especially hepatic artery thrombosis), bacterial or fungal cholangitis and chronic ductopenic rejection[161]. Reported recurrence rates for ASC are 27–67%[162]. Recurrence of ASC, often associated with inflammatory bowel disease, leads to the need for re-transplantation in a high proportion of patients[160,162].

De novo AIH is characterized by chronic liver damage with interface hepatitis, high transaminase levels, high IgG levels and positive autoantibodies. De novo AIH occurs in 6–10% of patients transplanted for non-autoimmune liver disorders and has been reported mainly in young patients[163,164]. If de novo AIH develops, prednisolone and azathioprine using the same schedule used for classic AIH are highly effective and lead to excellent graft and patient survival, whereas standard anti-rejection treatment often fails, making early diagnosis of de novo AIH essential to avoid graft loss. Rapamycin is reportedly effective in difficult-to-treat patients with de novo AIH after liver transplantation[165]. To what extent the liver damage in de novo and recurrent AIH is the result of an autoimmune or an alloimmune attack to the liver remains to be established.

Quality of life

Chronic liver diseases have a considerable impact on health-related quality of life (HRQOL). This problem has been widely evaluated in patients with chronic cholestatic liver disease[166–168], chronic viral hepatitis[169,170] and nonalcoholic fatty liver disease[171,172]. In clinical practice, the overall well-being of patients with AIH is frequently affected, regardless of a good response to treatment and a fairly positive prognosis. However, studies evaluating the impact of AIH on HRQOL are limited (TABLE 3).

In one study, mental well-being was significantly reduced in patients with AIH compared with the general population and with patients with arthritis[173] (TABLE 3). Importantly, the presence of cirrhosis was not associated with impaired mental well-being in patients with AIH. Moreover, the frequency of depressive syndrome was more than double in AIH compared with the general population, and the scoring for a major depressive disorder was fivefold higher in AIH than in the general population. Anxiety assessment demonstrated that patients with AIH scored twice as high as the general population for moderate anxiety symptoms[173]. More importantly, they exhibit severe symptom levels of anxiety approximately fourfold more frequently than the general population[173]. The most important factors associated with depressive and anxiety symptoms were concerns related to chronic liver disease, including having or developing cirrhosis, shorter life expectancy and the need of liver transplantation.

Interestingly, psychological stress (defined as life events perceived as stressful) has been cited anecdotally as a potential factor for worsening of disease activity in AIH[174]. Chronic psychological stress might increase the levels of pro-inflammatory cytokines through activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system and ultimately lead to immune dysregulation[175,176]. Intensification of a pro-inflammatory response might have harmful effects in the liver tissue, particularly in patients susceptible to immune stimulation. A recent study showed an association between hepatocellular apoptosis, as determined by the cytokeratin levels, and HRQOL assessed by the Chronic Liver Disease Questionnaire[177,178]. One study evaluated the impact of psychological stress in patients with AIH and found that the frequency of major to moderate stress levels was significantly higher in patients with relapses than in patients with sustained remission[179]. These findings suggest that psychological stress favours relapse and that patients with AIH can benefit from strategies to reduce stress and promote psychological well-being.

Along the same line, patients with AIH with higher depressive and anxiety symptoms and avoidant relationship styles are more likely to be non-adherent to immunosuppressive therapy than those with AIH who score lower on these parameters[180]. These findings highlight that early recognition and treatment of anxiety and depression are important to improve treatment adherence and emphasize the need for formal evaluation of these factors, mainly in patients labelled non-responders[180].

HRQOL in children with AIH is also considerably impaired, and this seems to be associated with the presence of symptoms of end-stage liver disease and other general symptoms possibly related to adverse effects associated with immunosuppression, such abdominal pain, fatigue and mood changes[181]. Physical disfigurement secondary to steroids, including acne, can have serious psychosocial impact on teenagers. Studies have revealed acne to diminish adolescents' HRQOL and affect their global self-esteem[182]. The influence of steroids on mood and central nervous activity is also important to consider, as steroid use has been associated with depression in general[183] and in AIH[173].

Table 3 | **Studies evaluating health-related quality of life in AIH**

Study	Participant characteristics	Instrument	Findings	Factors associated with poor outcome
Schramm et al.[173]	103 individuals with AIH (77% in complete remission and 27% with cirrhosis) compared with the general population or individuals with inflammatory rheumatic diseases	12-Item Short-Form Health Survey	Mental well-being score was 46 ± 12[a] in those with AIH, 50 ± 9[a] in the general population ($P = 0.002$) and 50 ± 10[a] in those with inflammatory rheumatic diseases ($P = 0.003$)	None reported
		Patient Health Questionnaire-9	• Major depressive disorder: 11% in those with AIH versus 4% in the general population ($P < 0.001$) and 11% in those with inflammatory rheumatic diseases (P = NS) • Other depressive syndromes: 6% in those with AIH versus 3% in the general population ($P = 0.046$) and 9% in those with inflammatory rheumatic diseases (P = NS)	Female sex, steroid treatment and concerns regarding the consequences of their liver disease (including cirrhosis, shorter life expectancy and need for liver transplantation)
		Generalized Anxiety Disorder-7	• Moderate anxiety: 8% in those with AIH versus 4% in the general population ($P = 0.065$) • Severe anxiety: 8% in those with AIH versus 1% in the general population ($P = 0.006$)	Alcohol stigmatization and concerns regarding the consequences of their liver disease (including cirrhosis, shorter life expectancy and need for liver transplantation)
Srivastava et al.[179]	22 patients with AIH who have had >1 relapse versus 11 patients who showed sustained remission	Social Readjustment Rating Scale	Major to moderate stress: 68% of those with >1 relapse compared with 27% of those in sustained remission ($P = 0.06$)	Suboptimal response to treatment
Sockalingam et al.[180]	24 individuals with AIH who responded to treatment versus 24 non-responders	Generalized Anxiety Disorder-7	Anxiety symptoms: 21% of the non-responders versus 14% of the responders (P = NS)	Suboptimal response to treatment
		Patient Health Questionnaire-9	Depressive symptoms: 21% of the non-responders versus 11% of the responders ($P < 0.05$)	Suboptimal response to treatment
		Experiences in Close Relationships	Avoid score: 26 ± 12[a] in non-responders versus 20 ± 12[a] in responders ($P < 0.05$)	Adherence to treatment
Gulati et al.[181]	40 children with autoimmune liver diseases (16 AIH, 18 PSC and 6 AIH–PSC), compared with 40 healthy controls	PedsQL scale	PedsQL score: 72 ± 19[a] in those with autoimmune liver disease versus 84 ± 12[a] in healthy controls ($P = 0.002$)	Cirrhosis, abdominal pain, fatigue and psychological symptoms

AIH, autoimmune hepatitis; NS, not significant; PedsQL, Pediatric Quality of Life Inventory; PSC, primary sclerosing cholangitis. [a]Mean ± standard deviation.

Although clinicians treating patients with AIH usually focus on treatment outcomes such as biochemical disease remission, improving HRQOL should also be an important objective. Patients with AIH experience serious symptoms that considerably affect their well-being, including mood impairment, depression, anxiety, cognitive dysfunction and chronic fatigue. Appropriate attention should be paid to these aspects of AIH, and if they are present, appropriate counselling and treatment should be part of the management to address these concerns.

Outlook

Advances in our understanding of the epidemiology, pathophysiology, diagnosis and management of AIH and validation of these aspects in animal models and clinical trials promise to improve outcomes[184] (TABLE 4).

Pathogenetic insights

Hypothesis-free genome-wide association studies in different ethnic groups within the same and different countries and age groups will continue to identify genetic factors that influence susceptibility, clinical phenotype and outcomes[44]. A genetic polymorphism outside the *HLA* region has already been described; the *rs3184504*A* allele in the *SH2B3* gene may be associated with an increased adaptive immune response and disease severity[44]. Clarification of the genetic phenotype of AIH may enable individualized management strategies to develop and identify gene products that can be selectively targeted[185].

Epigenetic changes that might affect gene transcription and influence the occurrence, severity and outcome of AIH should be studied[54,186]. MicroRNAs miR-21 and miR-122 have already been shown to correlate with disease severity in AIH and may silence anti-inflammatory genes or derepress pro-inflammatory genes[186,187]. Clarification of the epigenetic changes associated with AIH might help explain differences in its occurrence in different ethnic and age groups.

Molecular mimicry between infectious and environmental agents and self-antigens will continue to be assessed in animal models and in the clinical setting[74]. Environmental factors that might trigger AIH (foreign antigens that resemble self-antigens) or induce epigenetic changes (pollutants, pharmaceuticals, diet and

Table 4 | **Anticipated advances in the diagnosis and management of AIH**

Research area	Anticipated advances	Precedents and progress
Pathogenetic insights	GWAS to identify non-*HLA* risk factors for AIH	Variant of *SH2B3* described
	Epigenetic changes account for some variations in occurrence and outcome of AIH	miR-21 and miR-122 increased in AIH
	Further molecular mimicry events are identified	Molecular mimicry induces epitope spread in animal model
	Disruptions in homeostatic mechanisms are expanded and manipulated	T cell immunoglobulin mucin proteins, galectins and PD1 implicated in immune-mediated disease
	Alterations in the intestinal microbiota are factored into pathogenesis	Dysbiosis and systemic lipopolysaccharides identified in AIH
	Vitamin D status is factored into pathogenesis	Vitamin D deficiency common in AIH
Diagnostic improvements	Biomarkers emerge that reflect therapeutic outcomes and suggest therapeutic targets	MicroRNAs, soluble PD1, anti-PD1, MIF and soluble CD163 are being assessed as biomarkers of treatment response
	Risk factors for poor outcome are clarified	Risk factor analyses are ongoing
	Surveillance protocols for hepatic and extrahepatic malignancies are updated	Hyperferritinaemia and low serum immunoglobulin levels predict treatment response
Therapeutic advances	Radiological tests demonstrate changes in hepatic fibrosis	MRE and TE reliable indicators of hepatic fibrosis in AIH
	Radiological tests demonstrate biochemical response and outcome	TE may reflect laboratory response
	Recombinant molecules and monoclonal antibodies continue to evolve; antioxidant and anti-fibrotic therapies emerge	Anti-TNF and anti-CD20 evaluated and anti-BAFF trial imminent
	Adoptive transfer of induced organ-specific T_{reg} cells is studied in animal models	Adoptive transfer of T_{reg} cells has been performed
	Probiotics, antibiotics and molecular interventions alter intestinal microbiota, block TLRs and/or strengthen intestinal barrier	Dysbiosis in AIH demonstrated
Reduce global disparities	Unrecognized genetic, epigenetic and environmental factors are investigated	Regional and ethnic disparities in occurrence and outcome demonstrated
	Disparities in outcome are evaluated for differences in medical resources, socio-economic status, cultural practices, patient compliance and follow-up mechanisms	Primary care access has improved outcome

AIH, autoimmune hepatitis; BAFF, B cell-activating factor; GWAS, genome-wide association studies; MIF, macrophage migration inhibitory factor; miR, microRNA; MRE, magnetic resonance elastography; PD1, programmed cell death protein 1; TE, transient elastography; TLR, Toll-like receptor; TNF, tumour necrosis factor; T_{reg}, regulatory T.

infections) should be scrutinized, and the aetiological associations between AIH and its environment should be better understood.

Disruption of the homeostatic mechanisms that modulate the innate and adaptive immune responses will continue to be investigated, and underevaluated or unassessed homeostatic pathways that have been implicated in other immune-mediated diseases should be evaluated in AIH. For example, the role of the T cell immunoglobulin mucin proteins[188], galectins[189] and the programmed cell death protein 1 and its ligands[190] constitute antigen-independent inhibitory mechanisms that may modulate the immune response in AIH. Investigations that describe the basis of self-sustained immune reactivity should be performed, and the therapeutic induction of T cell exhaustion should be explored as a possible management strategy[191].

The intestinal microbiota need to be further evaluated as a reservoir of microbial antigens and activated immune cells that can translocate to the systemic circulation and peripheral lymph nodes[64,192,193]. Dysbiosis has already been demonstrated in patients with AIH; lipopolysaccharides derived from Gram-negative bacteria have been detected in the systemic circulation and the expression of zona occludens 1 and occludin in patients with AIH is decreased[63,64]. Furthermore, female susceptibility to immune-mediated diabetes has been associated with sex-specific compositional changes in the intestinal microbiome of non-obese diabetic mice[194–196], and investigations of these sex differences may help explain the female predilection for immune-mediated diseases, including AIH.

Vitamin D deficiency (serum 25-hydoxyvitamin D_3 level of <30 μg per litre) has been found in 81% of Turkish patients with AIH[197], and 1,25-dihydroxyvitamin D_3 can regulate the expression of immune regulatory genes by binding to the vitamin D receptor, which can in turn activate the vitamin D response element within the gene[198]. Thus, studies evaluating the epigenetic effects of vitamin D deficiency in AIH are warranted, and the findings may further direct management strategies.

Diagnostic improvements

Several biomarkers are currently being evaluated to improve diagnosis and to monitor treatment response (TABLE 4). Preliminary studies have already indicated correlation between these biomarkers and indices of liver inflammation in AIH[93,187,199–203]. Some may predict treatment response (hyperferritinaemia and lower serum immunoglobulin levels)[204] and others may emerge as components of pivotal pathogenetic pathways that could become therapeutic targets[93,187,199–203].

Multivariate analyses should be refined to identify risk factors for poor outcome[205–207] and HCC associated with AIH[208], and surveillance protocols for hepatic and extrahepatic malignancies associated with AIH and its treatment should be updated[209].

Therapeutic advances

Magnetic resonance-based elastography[210] and ultrasound-based transient elastography[211] should undergo further evaluation to determine whether serial assessments can accurately demonstrate the progression or reversal of hepatic fibrosis. Furthermore, the usefulness of these non-invasive radiological tests in assessing the biochemical and histological responses to therapy and in predicting prognosis should be established[212]. These techniques might, in particular, facilitate the evaluation of interventions that have mainly anti-fibrotic actions (for example, angiotensin II inhibitors[213] and monoclonal antibodies against lysyl oxidase-like protein 2 (REF. 214)).

Targeted interventions may supplement or replace conventional immunosuppressive regimens as the principal pathogenetic pathways are defined and management strategies become individualized[215]. Recombinant molecules that impair lymphocyte activation (CTLA4 fused with immunoglobulin[216]) and monoclonal antibodies against cytokine pathways that affect lymphocyte differentiation and proliferation (antibodies to TNF[129] and antibodies to CD20 (REF. 150)) are indicative of the molecular advances that promise to change current paradigms of treatment[215]. B cell-activating factor (BAFF) is a cytokine expressed by T lymphocytes and DCs that modulates the differentiation, proliferation and survival of B cells; serum BAFF levels fluctuate with disease activity in patients with AIH, correlates with the serum levels of C-X-C motif chemokine 10 and improves during corticosteroid therapy[217,218]. Human monoclonal antibodies have been developed to neutralize BAFF activity[219], and an international trial of anti-BAFF therapy in AIH is imminent.

Pharmacological agents (such as cenicriviroc and maraviroc) that block the CC-chemokine receptor 2 (CCR2) and CCR5 chemokine receptors have reduced liver inflammation and hepatic fibrosis in animal models[220–224], and a phase IIb clinical trial of cenicriviroc in nonalcoholic steatohepatitis has demonstrated less inflammatory activity and a significant improvement in hepatic fibrosis[225]. Agents that reduce oxidative and nitrosative stresses (agonists of nuclear factor erythroid 2-related factor 2 (REF. 226), inhibitors of $NADP^+$ oxidases[227,228] and antagonists of TGFβ[229]) have also reduced liver inflammation and hepatic fibrosis in animal models of liver injury, and pan-caspase inhibitors have improved liver damage in murine models of non-alcoholic fatty liver disease[230]. The results of these studies have been encouraging, and they should generate similar studies in experimental models of AIH.

The adoptive transfer of T_{reg} cells, which has already had preliminary success in experimental AIH[231], should be evaluated further using induced, organ-specific T cell populations. T_{reg} cells can stimulate the generation of secondary T_{reg} cells by direct cell-to-cell contact with T_H0 cells[232]. These induced T_{reg} cells can in turn exist as memory cells that can be activated by antigen exposure. The induction of antigen-specific T_{reg} cells may be a mechanism by which to maintain a protracted immunosuppressive effect in patients with relapsing AIH.

Manipulations of the intestinal microbiota may also emerge as the role of the intestinal microbiome in shaping the autoimmune response in AIH is defined. Probiotics, antibiotics and molecular interventions that block Toll-like receptors or strengthen the intestinal mucosal barrier may be evaluated as adjunctive measures to reduce hepatic inflammation[192].

Global perspectives

Population-based epidemiological studies have shown increases in the incidence of AIH in Spain[22], Denmark[35] and the Netherlands[34], and the findings of a changing epidemiology suggest that unrecognized genetic, epigenetic and environmental factors are altering the risk burden of AIH[233]. Experiences in Singapore[234] and India[235] have described high frequencies of cirrhosis and poor survival, and the observations suggest that deficiencies in the early diagnosis and therapy of AIH are present. Disparities in the occurrence and outcome of AIH in different age groups, environments and ethnicities may reflect limited medical resources, low socio-economic status, various cultural beliefs, poor patient compliance and uncertain or disrupted follow-up strategies. These deficiencies must be identified and targeted by efforts to overcome individual and societal barriers that limit successful outcomes[233]. The importance of primary care access in improving outcome should drive efforts to strengthen health-care delivery in underperforming regions[236].

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Author contributions
Introduction (M.P.M.); Epidemiology (E.L.K.); Mechanisms/pathophysiology (D.V.); Diagnosis, screening and prevention (J.M.V. and G.M.-V.); Management (A.W.L. and G.M.-V.); Quality of life (A.J.M.-L.); Outlook (A.J.C.); Overview of Primer (D.V. and G.M.-V.).

Competing interests
M.P.M. received research grants and trial support from and serves as a consultant for Falk Foundation and Novartis Pharma. J.M.V. is a recipient of research grants from Gilead, Intercept, Novartis, Sundise and TaiwanJ and serves as a scientific adviser to BioIncept, Bristol-Myers Squibb, Gilead, Intercept, Novartis and Sundise. In addition, he is a co-author of "Immunosuppression in Liver Transplantation" for *Up-to-Date*. A.W.L. holds the patent on SLA/LP diagnostic testing, but all revenues from this patent go to the charitable YAEL foundation supporting patients and research in autoimmune liver diseases. G.M.-V., D.V., A.J.C., E.L.K. and A.J.M.-L. declare no competing interests.

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